Wld Rev. Nutr. Diet., vol. 28, pp. 112–142 (Karger, Basel 1978)

Biochemistry and Physiology of Magnesium

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I. Introduction

Magnesium is one of the most plentiful elements on earth; in the vertebrate, it is the fourth most abundant cation. Magnesium is associated with so many different biological processes that this involvement suggests that it has some single fundamental role (4). It is the purpose of this review to summarize the current knowledge of the biochemistry and physiology of magnesium.

II. Biochemistry of Magnesium

A. The Role of Magnesium in Photosynthesis

1. Chloroplast

One of the greatest triumphs of early evolution was the invention of a means to harness the energy of the sun which is transmitted as light to drive energy-requiring synthetic processes. This process in higher plants occurs in an especially organized subcellular organelle, the chloroplast. The chloroplast is an organized set of membranes, crowded with water-insoluble lipid and containing

the central pigment chlorophyll. Chlorophyll is the *magnesium* chelate of porphyrin.

2. Chlorophyll

It is chlorophyll which produces the oxygen and the foods for all other forms of life on earth. The excess production of oxygen soon made the oxidation of organic compounds thermodynamically favorable. Under these new conditions, the desired thermodynamically uphill reactions would be the photoreduction of the oxidized organic compounds, including carbon dioxide. It is just these photoreactions which are favored by chelating a dipositive closed shell metal ion into the porphyrin ring. *Mauzerall* (94) hypothesizes that the purpose of the ionically bound magnesium in the vacant hole in the porphyrin ring is to stabilize the structure so that it would undergo perfectly reversible one-electron oxidations. The redox potential of chlorophyll correlates very well with the electronegativity of the central magnesium ion. With photoactivation, the chelated magnesium makes the excited state a powerful reductant and stabilizes the resulting cation. Why magnesium rather than some other metal in the photosynthetic pigments? *Fuhrhop and Mauzerall* (47) suggest that if the aim of the biological system is a minimum redox potential combined with maximum stability in a protonic solvent, then magnesium is a good minimax solution to the requirements.

3. Regulation of Photosynthesis by Magnesium

One can imagine that the chlorophyll molecule harvests light in the manner of a lightmeter. The light quantum activates the chlorophyll molecule, i.e. an electron moves from the π orbitals to the exterior of an atomic shell and then is ejected, leaving behind a chlorophyll-free radical. This terminates the true photochemical event, in which a light quantum is transmuted into a high-energy electron. *Lin and Nobel* (79) observed an increase in the concentration of chloroplast Mg^{++} *in vivo* caused by illuminating the plant, the first direct evidence indicating that changes in magnesium level actually occur in the plant cell. This extra magnesium in the chloroplasts enhanced the photophosphorylation rate. Thus, the increase in magnesium in chloroplasts may be a regulatory mechanism whereby light controls photosynthetic activity.

The energy of electrons is used to produce the adenosine triphosphate (ATP) which, together with reduced nicotinamide adenine dinucleotide (NADPH), drives the formation of carbohydrates from CO_2. Therefore, the chloroplast is a transducer which converts the electromagnetic energy from the sun into the chemical energy of ATP. This transduction does not occur in the absence of the chelated magnesium.

The chloroplast is located physically in the granum. The granum possesses a lamellar structure which is compatible with the existence of an interface

between hydrophilic and hydrophobic phases, in which the chlorophyll molecule could be completely accommodated in a closely packed or monomolecular layer. From this characteristic lamellarity evolves the concept of a unit membrane held together with the assistance of magnesium. Magnesium could stiffen lipoprotein membranes by bridging neighboring carboxylate groups (66). Chlorophyll functions in photosynthesis by virtue of its ability to produce and to maintain a charge separation in the highly ordered lamellar structure of the chloroplast.

4. A View of Photosynthesis

The entire photosynthetic process can be viewed as the capture of the energy of photons in the form of high-energy electrons, followed by a stepwise passage of electrons down an energy gradient in a structured membrane held together by the coordinating properties of the magnesium atom. This model is essentially the unifying concept first proposed by *Szent-Györgi* (124); it is now modified to explain the role of magnesium.

The subsequent synthetic process may be summarized as follows: $6CO_2 + 6H_2O + 18$ ATP + 12 NADPH $\rightarrow C_6H_{12}O_6 + 18$ ADP + 18 Pi + 12 NADP + $6O_2$. ATP and chemical reducing power operate to produce carbohydrate via common intermediates which require twelve separate enzymes. All enzyme reactions that are known to be catalyzed by ATP show an absolute requirement for magnesium.

B. The Role of Magnesium in Oxidative Phosphorylation

In the absence of sunlight, plants rely on stored chemical energy to maintain life. This stored energy is released by oxidative phosphorylation, a process which occurs in the mitochondrial membrane of both plants and animal cells. The primary function of all mitochondria is to couple phosphorylation to oxidation. ATP, the main fuel of life, is produced in oxidative phosphorylation. All enzyme reactions that are known to be catalyzed by ATP show an absolute requirement for magnesium. These reactions encompass a very wide spectrum of synthetic processes.

So fundamental and widespread are the reactions involving ATP, that it must influence practically all processes of life. Many enzymes are activated by the magnesium cation; this group includes all those utilizing ATP or catalyzing the transfer of phosphate. ATP is known to form a magnesium complex, with Mg^{++} binding usually to the phosphate moiety. Magnesium has a single divalent state and does not form highly stable chelates with organic complexes, as do the transitional metals. It is perhaps this quality which allows it to act as a bridge in a large number of chemical reactions not requiring redox reactions, but resulting in transfer of organic groups from one molecule to another. When organic phosphate takes part in a reaction, magnesium is usually its inorganic cofactor. All partners in reactions known to be dependent on ATP are capable of chelating

with magnesium. The effect of magnesium chelation in such reactions is to lower the free energy of activation of the rate-determining step.

The ATP molecule is usually depicted as existing in a linear configuration, with the purine and the phosphate ends separated by the pentose. *Szent-Györgi* (125) has suggested that the spacial configuration of the ATP molecule is such that it could function as a transformer as well as a storage battery. The phosphate chain can touch the purine ring; magnesium can form a very stable quadridentate chelate connecting the two ends of the ATP molecule, and energy in the form of electrons can now pass from the phosphate to the purine. The magnesium may not only actually connect the two ends of the molecule, but it may also make one single, unique electronic system of the phosphate chain and the purine with common nonlocalized electrons which could transport energy.

C. The Mitochondrion

The role of sunlight, chlorophyll, and magnesium in the primary synthetic process on earth have already been discussed; in photosynthesis, carbon dioxide and water are synthesized into carbohydrate, and oxygen is released. In the absence of sunlight, plants rely on stored chemical energy to maintain life. This stored energy is released by oxidative phosphorylation, a process which occurs in the mitochondrion of both plant and animal cells. The biosynthesis of ATP coupled to the oxidation of substrate is known as oxidative phosphorylation and takes place in the mitochondrial membrane. The primary function of all mitochondria is to couple phosphorylation to oxidation. The transduction is the conversion of chemical energy from the bond energies of certain metabolites to the bond energies of ATP. Whereas phosphorylation in the chloroplast is light-dependent, phosphorylation in the mitochondrion is dependent not on light but on oxygen. Whereas photosynthesis combines carbon dioxide and water and evolves oxygen, oxidative phosphorylation does just the reverse. It requires oxygen and evolves carbon dioxide and water, thus completing the carbon cycle on earth and returning the electrons to ground state.

ATP, the main fuel of life, is produced in both photosynthesis and oxidative phosphorylation. In both cases, ATP is produced by an electric current, i.e. the energy released by 'dropping' electrons.

The mitochondrion represents a general blueprint that is characteristic of all membrane systems; in fact, it is characteristic of all the energy-transforming systems of the cell (56). The basic design of the mitochondrion is copied in all other systems in the cell that have to do with the transformation or use of energy. Under the electron microscope, the mitochondrion, just like the chloroplast, is seen to consist of a lamellar membrane. The inner membrane forms invaginations (cristae). The intermembrane and intercristal spaces are thought to be continuous and to form a central compartment. The intermembrane compartment of rat liver mitochondria contains high molecular weight compounds, most

likely proteins, which form complexes with magnesium ions (22). The matrix, which is surrounded by the folded inner membrane, comprises the second compartment, and the entire mitochondrion is thought to be a two-compartment system. The cristae contain a strictly regulated respiratory chain along which electrons are transferred by the difference in redox potentials. Along this respiratory chain, the oxidation-reduction energy is converted into phosphate bond energy in the form of ATP. The optimum concentration of magnesium for the process appears to be 10^{-4} to 10^{-5} *M*. The respiratory enzymes – cytochromes and flavoproteins – which sequentially release the energy of the electrons, may be embedded in the mitochondrial membranes that are structurally organized into respiratory units. The oxidizing enzymes in the inner mitochondrial membrane are assembled asymmetrically in a way that gives rise to a vectorial movement of protons. *Racker* (106) feels that this proton current is the driving force in the production of biologically useful energy.

The traditional concept of a mitochondrion is that of small, discrete, intracellular organelles, relatively free in the cytoplasm. Recent serial section studies indicate that in the yeast (65) and in the rat liver (23) there is but one mitochondrion per cell, consisting of a single branching tubular structure.

Magnesium is present inside the mitochondrial membrane at a concentration of about 1 nmol/mg protein and plays an essential regulatory role in the maintenance of membrane integrity; the presence of magnesium on a number of membrane sites appears to be necessary to maintain the impermeability of the mitochondrial inner membrane (21). Specific pathways for electrophoretic penetration of monovalent cations are present in the inner membrane of the mitochondrion; Mg^{2+} bound by a limited number of high-affinity sites in or near these pathways can control monovalent cation permeability (134). The mitochondrion can be made to swell and contract experimentally. Although swelling can be caused by a large variety of different chemical agents, it is significant that only ATP together with magnesium can cause contraction. ATP is always split during contraction of swollen mitochondria.

A rapid swelling of heart and liver mitochondria can be produced in rats fed a magnesium-deficient diet for 10 days. whereas no significant decrease in the magnesium content of the mitochondrion results. ATP reverses the swelling of mitochondria from heart and liver of magnesium-deficient rats.

Life could have been no more than an experiment of nature until protoorganisms developed dependable machinery to perform two basic functions: (a) generate energy in a form usable for the organisms' various requirements (ATP), and (b) reproduce themselves. It is of considerable theoretical interest that all forms of life on earth have basically the same system for these purposes. They are summed up in the familiar initials ATP and DNA (deoxyribonucleic acid). The relationship between ATP and magnesium has already been discussed. We shall discuss next the involvement of magnesium in the biochemistry of DNA.

D. Magnesium and DNA

During the past 20 years, scientists have obtained substantial understanding of how information is stored and replicated in DNA molecules, how it is passed on to RNA molecules and finally to proteins, and how the three-dimensional structure of proteins depends upon the linear arrangement of the constituent amino acids. This information storage in molecular structure and its subsequent readout is dependent upon the presence of magnesium in optimal concentration (74). The rather complicated three-dimensional structures assumed by some polymers are a consequence of their primary sequence. The interactions of these to form even more complicated multicomponent complexes are also determined by their chemistry.

One of the most important chemical constituents of the cell is DNA, which is almost exclusively confined to the cell nucleus. DNA is the carrier of genetic information.

Much of the magnesium in the cell nucleus is combined with those phosphoric groups of DNA which are not occupied by histone. The chemical factors that control the variable activity at the sites along a chromosome are largely unknown. There is a suggestion that the sites along the DNA chain at which the phosphoric acid groups are combined with histone are inactive and, conversely, that those at which they are combined with magnesium are active. The physical integrity of the DNA helix appears to be dependent upon magnesium. There is evidence to suggest that Mg^{++} is necessary as an intermediate complexing agent during cell duplication and during the formation of ribonucleic acid (RNA) on a double-stranded DNA template.

Both magnesium and ATP are involved in the synthesis of nucleic acids. Since sections of the chromosomes in the nucleus are held together by calcium and magnesium, it seems likely that changes in the concentration of magnesium in the medium might determine the degree of chromosomal aberration. There is evidence that variations in the concentration of magnesium *in vivo* exerts control on DNA synthesis.

E. Magnesium and the Ribosome

Ribosomes are of universal occurrence in microorganisms, higher plants, and animals. The principal and probably the only function of the ribosome is the biosynthesis of protein. The rate of protein synthesis is proportional to the number of ribosomes present. Ribosomes require magnesium ions in order to maintain their physical stability (66); they dissociate into smaller particles when the magnesium concentration becomes low (140). An optimum intracellular concentration of magnesium is required for the integrity of the macromolecules necessary for RNA synthesis (34). The physical size of the RNA aggregates is controlled by the concentration of magnesium, and polypeptide formation cannot proceed unless magnesium concentration is optimal (137). Mg^{++} probably acts to stabilize a favorable protein conformation (30).

F. Discussion

There is very little doubt that magnesium is essential for life on earth. The exact function of magnesium in the chlorophyll molecule, as well as in maintaining the structural integrity of the granum, is conjectural; however, it seems possible that magnesium, because of its inherent atomic composition is, in this particular situation, able to capture and transmit energy more efficiently than any other element. Moreover, the magnesium atom is able to hold reacting groups together and to thus maintain the physical configurations that are optimal either for the transfer of energy in the form of excited electrons or for the transmutation of energy into ATP. The one fundamental property of magnesium upon which all of these photosynthetic processes depends is *chelation.* It seems that the capture, conversion, storage, and utilization of solar energy are all dependent upon a chelating function which is unique to, and specific for, the magnesium atom.

Two of the basic functions of solar energy in living cells are *genetic transcription* and *protein synthesis.* Recent studies in molecular biology have established that interrelations exist among the three major biologic macromolecules: DNA, RNA, and proteins. Genetic information stored in DNA is transcribed into messenger RNA, which in turn translates that information into amino acid sequences in the newly synthesized protein. At literally every turn in these processes, magnesium plays a vital role. The physical integrity of the DNA helix appears to be dependent upon magnesium. The physical size of the RNA aggregates is controlled by the concentration of magnesium, and polypeptide formation cannot proceed unless magnesium concentration is optimal. Magnesium appears to play a central role in the coordinate control of growth and metabolism in animal cells (110).

Rasmussen (108) has recently discussed the role of calcium in the 'closed-loop' feedback system necessary for the mediation of hormonal action; he predicts that it is likely that Mg^{++} will prove to be another divalent cation with a messenger function as complex as that of calcium. This messenger function for magnesium may involve chemical binding to establish physical proximity of reacting groups.

III. Physiology of Magnesium

A. Normal Distribution and Turnover of Magnesium in Man

1. Body Content

The limited data available from analysis of human carcasses indicate that the magnesium content of the human body ranges between 22.7 and 35.0 mEq/kg wet weight of tissue (135). Extrapolations from tissue analyses performed on

victims of accidental death indicate that the body content of magnesium for a man weighing 70 kg would be on the order of 2,000 mEq (24 g) (112).

89% of all the magnesium in the body resides in bone and muscle. Bone contains about 60% of the total body content of magnesium at a concentration of about 90 mEq/kg wet weight. Most of the remaining magnesium is distributed equally between muscle and nonmuscular soft tissues. Of the nonosseus tissues, liver and striated muscle contain the highest concentration, 14–16 mEq/kg. Approximately 1% of the total body content of magnesium is extracellular. The levels of magnesium in serum of healthy people are remarkably constant, remaining on the average of 1.7 mEq/l, and varying less than 15% from this mean value (130). The distribution of normal values for serum magnesium is identical in men and women and remains constant with advancing age (71). Approximately one third of the extracellular magnesium is bound nonspecifically to plasma proteins. The remaining 65% which is diffusible or ionized, appears to be the biologically active component. The ratio of bound to unbound magnesium, as well as the total serum levels, is remarkably constant. The magnesium content of erythrocytes varies from 4.4 to 6.0 mEq/l (19).

2. Intake

The average American ingests daily between 20 and 40 mEq of magnesium; magnesium intakes of from 0.30 to 0.35 mEq/kg/day are thought to be adequate to maintain magnesium balance in normal adult (69). A daily intake of 17 mEq (0.25 mEq/kg) may meet nutritive requirements provided that the individual remains in positive magnesium balance. *Schroeder et al.* (112) called attention to the theoretic relationship of dietary magnesium deficiency to serious chronic diseases, including atherosclerosis. The estimated daily requirements for a child is 12.5 mEq (150 mg) (36). The greater importance of magnesium in childhood is suggested by the relative ease with which deficiency states are produced experimentally in young animals as compared with adult animals (36).

Some common foods can be ranked in order of decreasing mean concentrations of magnesium, as follows: nuts, 162 mEq/kg; cereals, 66; sea foods, 29; meats, 22; legumes, 20; vegetables, 14; dairy products, 13; fruits, 6; refined sugars, 5, and fats, 0.6. This order differs when the concentrations are ranked on the basis of the caloric values of the foods, as follows: vegetables, legumes, sea foods, nuts, cereals, dairy products, fruit, meat, refined sugars, and fats. Noteworthy is the very small contribution of fats and refined sugars to the total intake of magnesium. These two, the major sources of caloric energy, are virtually devoid of magnesium (112).

3. Absorption

When a tracer dose of ^{28}Mg was administered orally to 26 subjects, fecal excretion within 120 h accounted for 60–80% of the administered dose (1). The

concentration of radioactivity in the plasma was maximal at 4 h, but the actual increase in serum magnesium concentration was negligible. When ^{28}Mg was injected intravenously into a normal human subject, only 1.8% of the radioactivity was recovered in the stool within 72 h (5). The fecal magnesium appears to be primarily magnesium from material that is not absorbed by the body rather than magnesium secreted by the intestine. Ingested magnesium appears to be absorbed mainly by the small intestine (112). The factors controlling the gastrointestinal absorption of magnesium are poorly understood.

4. Secretion

There undoubtedly is considerable secretion of magnesium into the intestinal tract from bile and from pancreatic and intestinal juices. This secretion is followed by almost complete reabsorption. Parotid saliva contains about 0.3 mEq/l (75) and pancreatic juice about 0.1 mEq/l of magnesium. The concentration of magnesium in other secretions varies considerably. The observation that hypomagnesemia can occur in patients suffering from large losses of intestinal fluids suggests that intestinal juices contain enough magnesium to deplete the serum when magnesium is not reabsorbed by the colon.

Studies are just beginning on the role played in the transport of divalent cations by biochemical changes in the cells of the intestinal mucosa (87). Further investigations may show that the cells of the intestinal mucosa, like those in the kidney and elsewhere in the body, may depend in part upon metabolic activity for the uptake and release of calcium and magnesium.

5. Excretion

Most of that portion of the magnesium which is *absorbed* into the body is excreted by the kidney; fecal magnesium represents largely the unabsorbed fraction. In subjects on a normal diet, one third or less of the *ingested* magnesium (5–17 mEq) is excreted by the kidney. After the intravenous injection of a tracer dose of ^{28}Mg in 12–16 mEq of stable magnesium, the daily urinary excretion of magnesium in 8 normal subjects ranged between 6 and 36 mEq (5). Urinary excretion increased as the parenteral dose was increased. The maximal renal capacity for excretion is not known, but it is probably quite high, perhaps greater than 164 mEq/day (130).

The diffusible magnesium in plasma is filtered by the glomeruli and is reabsorbed by the renal tubules, probably by an active process, although the control mechanisms are not known. There is some evidence that magnesium may be secreted by the renal tubule (46). Both the mercurial and the thiazide diuretics increase excretion of magnesium, calcium, potassium, and sodium.

Magnesium excretion also occurs in sweat (35). When men are exposed to high temperature for several days, from 10 to 15% of the total output of magnesium is recovered in sweat. Acclimatization does not occur, as in the case for

sodium and potassium. Under extreme conditions, sweat can account for 25% of the magnesium lost daily; this factor would be important when the intake of magnesium is low.

6. Magnesium Conservation on a Low-Magnesium Diet

It is primarily the ionic fraction of the magnesium in plasma which appears in the glomerular filtrate. Any protein-bound magnesium which is filtered is probably returned to the circulation via lymph. The excretion of magnesium may be greater than normal in renal diseases associated with heavy proteinuria.

Magnesium clearance, corrected for protein binding, increases as a linear function of serum magnesium concentration and approaches the inulin clearance at high plasma levels of magnesium. There normally appears to be almost maximal tubular reabsorption of magnesium (32).

In spite of the probability of diets being low in magnesium under certain circumstances, magnesium deficiency does not occur in human beings with healthy kidneys. The explanation for this clinical observation appears to be that renal mechanisms are efficient enough to conserve all but about 1 mEq of magnesium/day. Fecal losses are minimal (17).

7. Abnormal Magnesium Levels in the Blood

Values lower than 1.1 mEq/l have been obtained in patients with congestive heart failure, cirrhosis, or renal failure after hemodialysis. All values higher than 2.0 mEq/l were found in patients with renal failure before therapy (1).

B. The Plasma Clearance and Tissue Uptake of Magnesium

1. Early Studies

Mendel and Benedict (98) reviewed much of the early literature on the absorption and excretion of magnesium. These investigators showed quite clearly that rapid renal excretion of magnesium followed the subcutaneous injection of various magnesium salts, whereas intestinal excretion was minimal. *Hirchfelder and Haury* (64), however, reported that in seven normal adults, 40–44% of an injected dose of magnesium appeared in the urine within 24 h. *Tibbetts and Aub* (128), by means of classic balance techniques, studied the excretion of magnesium in normal subjects; they found that individuals on an oral intake of 49–74 mEq/day excreted 41–66 mEq, of which slightly over one half was in the stools. *Smith et al.* (118) studied the excretion of magnesium in dogs after the intravenous administration of $MgSO_4$ and concluded that the magnesium distributed itself throughout the extracellular fluid during the first 3–4 h; during subsequent hours, some of the ion appeared to be segregated from the extracellular fluid and not excreted.

2. Tracer Studies in Human Beings

The introduction of the radioactive isotope of magnesium, ^{28}Mg, for clinical studies in 1957 made possible determination of the 'exchangeable' pool in human subjects. When nine normal subjects were given intravenous infusions of 12–30 mEq of magnesium tagged with ^{28}Mg, the material was very rapidly cleared from the extracellular fluid (5). The concentration of radioactivity in plasma and urine was too low to follow beyond 36 h. Within a few hours, the volume of fluid available for the dilution of this ion, as calculated from the plasma concentration of ^{28}Mg, exceeded the volume of total body water.

The clearance curves in general showed a rapid phase during the first 4 h, a subsequent more gradual decline up to about 14 h, and a slow exponential slope thereafter. Biopsies of tissues contained concentrations of ^{28}Mg in liver, appendix, fat, skin, and subcutaneous connective tissue which could not be attributed solely to the extracellular components of these tissues. All of these observations suggested that ^{28}Mg rapidly entered cells of the soft tissues and that 70% or more of the infused magnesium was retained in the body for at least 24 h.

Of interest is the observation that the 24-hour urinary excretion of stable magnesium following the infusion of ^{28}Mg approximated the amount of non-radioactive magnesium infused, whereas only 20% of the ^{28}Mg infused was recovered. Previous investigators without the benefit of the radioisotopic data have assumed that most of the infused magnesium was rapidly excreted by the kidney. The additional isotopic data indicate that the infusion of fairly large amounts of magnesium results in a compensatory renal excretion of the body store of magnesium and that the material excreted is probably not the ions that were administered.

Serial external surveys of radioactivity over the entire body revealed the maximal distribution of radioactivity at the end of infusion over the right upper quadrant of the abdomen. This finding suggests initial concentration of magnesium in the liver. At 18 h, the specific activity in bile was equal to that of serum. This equilibration of the infused ^{28}Mg had occurred earlier in bile than in any other tissue or fluid available for study (5).

After about 18 h, the specific activities in plasma and urine showed only a slight gradual increase, suggesting that the infused material had equilibrated with the stable magnesium in a rather labile pool and that further exchange was occurring very slowly in a less labile pool. The size of this labile pool in normal subjects ranged between 135 and 397 mEq (2.6–5.3 mEq/kg of body weight). Since the body content of magnesium is estimated to be 30 mEq/kg, it appears that less than 16% of the total body content of magnesium is measured in the ^{28}Mg exchange technique.

The results of the external survey and the tissue analyses suggest that the labile pool of magnesium is contained primarily in connective tissue, skin, and

the soft tissues of the abdominal cavity (such as the liver and intestine) and that the magnesium in bone, muscle and red cells exchanges very slowly.

In another study, *Silver et al.* (117) followed the turnover of magnesium for periods up to 90 h after ^{28}Mg was injected intravenously into human subjects. Even at 90 h, only one third of the body's magnesium had reached equilibrium with the isotope. The results confirmed the impression that the gastrointestinal absorption of magnesium is very limited. Graphic analysis of urinary ^{28}Mg curves in terms of exponential components yielded a slow component with a half-time of 13–35 h, which accounted for 10–15% of the injected dose, and two more rapid components with half-time of 1 and 3 h each, accounted for 15–25% of the injected dose. The large fraction remaining – about 25–50% of the body's total – had a turnover rate of less than 2% per day. Because approximately 25–50% of the total body content exchanges at a turnover rate of less than 2% per day, this isotopic dilution method, used so successfully with sodium and potassium, cannot be employed to quantitate the total body content of magnesium in man. In rabbits, however, the exchangeable magnesium value at 24 h agrees well with the total carcass content of magnesium (7). During starvation, the renal excretion of magnesium amounts to 61.7 mEq/kg of weight loss (2).

3. Magnesium Equilibration in Bone

The reactivity of the skeleton, as measured by isotopic exchange, declines with age (24). The exchange of ^{28}Mg, expressed as bone/serum-specific activity, is much more rapid in younger animals than in older ones. ^{28}Mg accumulates in the bones of young rats about twice as fast as in the bones of adult rats (76).

The exchange of ^{28}Mg in cortical bone occurs much more rapidly in young rats than in old ones. The stable magnesium content of bone increases with age and varies inversely with the water content of bone. ^{28}Mg studies in lambs indicate that the magnesium reserve in bone is mobilized during dietary magnesium deficiency (95).

4. ^{28}Mg Compartmental Analysis in Man

Avioli and Berman (15) used a combination of metabolic balance and ^{28}Mg turnover techniques in order to develop a mathematical model for magnesium metabolism in man. The data thus derived were subjected to compartmental analysis using digital computer techniques.

After the intravenous administration of ^{28}Mg, the decline in the specific activity of plasma or urine can be expressed as the sum of several exponential terms by the method of graphic analysis. On the basis of such analyses, *Silver et al.* (117) defined in man three exchangeable magnesium compartments with half-times of 38, 3, and 1 h. *MacIntyre et al.* (86) described three exchangeable magnesium compartments containing 7.3, 24.4, and 98.7 mEq of magnesium. *Zumoff et al.* (141) obtained similar data.

Multicompartmental analysis indicates that in man there are at least three exchangeable magnesium pools with varied rates of turnover: compartments 1 and 2, exemplifying pools with a relatively fast turnover, together approximating extracellular fluid in distribution; compartment 3, an intracellular pool containing over 80% of the exchanging magnesium with a turnover rate of one half that of the most rapid pool; and compartment 4, which probably accounts for most of the whole-body magnesium. Only 15% of whole-body magnesium, averaging 3.54 mEq/kg body weight, is accounted for by relatively rapid exchange processes (15).

C. Gastrointestinal Absorption

1. Daily Absorption in Man

In normal individuals on regular diets, the average daily absorption of magnesium from the gastrointestinal tract is 0.14 mEq/kg, an amount approximately 40% of the size of the extracellular pool. The rate of entry of magnesium into the intracellular pool would be approximately 0.0058 mEq/kg/h if one assumes that absorption occurs continuously throughout the day. This rate of entry is approximately 1% of the rate of removal of magnesium from the extracellular pool by all routes (132).

2. Factors Affecting Absorption

No single factor appears to play a dominant role in the absorption of magnesium as does vitamin D in the absorption of calcium. Several studies using ^{28}Mg suggest that the absorption of magnesium in man is influenced by the load presented to the intestinal mucosa (6, 55). On an ordinary diet containing 20 mEq of magnesium, 44% of the ingested radioactivity was absorbed per day. On a low-magnesium diet (1.9 mEq/day), 76% was absorbed. On a high-magnesium diet (47 mEq/day), absorption was decreased to 24%.

Absorption begins within an hour of ingestion and continues at a steady rate for 2–8 h; it is minimal after 12 h. In man, absorption throughout the small intestine is fairly uniform, but little or no magnesium is absorbed from the large bowel (55).

3. Site of Absorption

Evidence from a variety of animals suggests that the small intestine is the main site of magnesium absorption, but that the pattern of absorption varies with the species studied (42, 55). Absorption from the large intestine is negligible in the rabbit (7). In male albino rats, more than 79% of the total absorption of ^{28}Mg takes place in the colon, and excretion of endogenous magnesium occurs predominatly in the proximal gut (33). Both magnesium and calcium are

bound to phosphate and to nonphosphate-binding material of an unknown nature in the ileal contents of ruminating calves (119), and hence are rendered nonultrafiltrable.

There appears to be an interrelationship between the absorption of magnesium and calcium in the proximal part of the small intestine in the rat (8). The suggestion has been made that there is a common mechanism for transporting calcium and magnesium across the intestinal wall (62, 83).

4. The Role of Ionic Magnesium

At the present time, there is no unequivocal evidence that magnesium is actively transported across the gut wall (3). It seems reasonable to assume that the net amount of dietary magnesium absorbed is directly related to the intake and to the time available for absorption of the magnesium from the small intestine. Therefore, apart from a small effect from the difference in potential across the wall of the small intestine, the concentration of *ionic* magnesium in the digest at the absorption site must be the main factor controlling the amount absorbed in a given time (119).

D. Renal Excretion

1. Control of Body Content

The kidney is the major excretory pathway for magnesium once it is absorbed into the body (98). In subjects on a normal diet, this renal excretion amounts to one third or less of the 5–17 mEq of magnesium which is ingested every day. The mean daily excretion of magnesium in the urine of 12 normal men on an unrestricted diet was 13.3 ± 3.5 mEq (130). Following the intravenous injection of a tracer dose of ^{28}Mg in 12–16 mEq of stable magnesium, the daily urinary excretion of magnesium in eight normal subjects ranged between 6 and 36 mEq (6). Urinary excretion of magnesium increased as the parenteral dose was increased

Metabolic balance studies in 27 subjects on a self-selected diet of normal composition showed a close positive correlation between the level of dietary intake and the magnesium excretion in both the urine and the feces (61). These results suggest that the absorption of magnesium from the intestinal tract is a poorly controlled process which is determined largely by the dietary intake of the element. The kidney must therefore be the organ principally responsible for regulating the total body content of magnesium. When dietary intake of magnesium is increased or decreased, urinary excretion of magnesium is increased or decreased respectively without any significant change in the plasma level of magnesium.

2. Effect of Dietary Restriction of Magnesium

Retention of magnesium by the kidney occurs rapidly in response to a restriction in the dietary intake (17, 43). This is why it is so difficult to produce magnesium depletion in the adult without some source of abnormal loss from the body.

Diurnal variations in the urinary excretion of calcium and magnesium have been demonstrated in patients in a metabolism ward (25). A reduction in the excretion of calcium, magnesium, sodium, and creatinine occurs at night. There are slight but constant diurnal variations in the serum concentration of calcium and magnesium with the values being lower in the morning than in the evening. Diet and physical activity appear to play the dominant roles in this diurnal fluctuation, but there also might be an associated rhythmicity in the function of the parathyroid gland.

3. Mechanism of Renal Excretion

The mechanism of excretion of magnesium by the mammalian kidney is still unclear (92). It could involve glomerular filtration and partial reabsorption of the filtered material by the renal tubules, or the filtered material could be completely reabsorbed and the excreted magnesium appear by tubular secretion, as is believed to occur with potassium. Tubular secretion of magnesium undoubtedly occurs in the aglomerular fish (20), but stop-flow studies with radioactive magnesium in dogs have produced conflicting evidence about secretion of magnesium by the tubules (50, 104). In the rabbit, the renal excretion of magnesium appears to be essentially glomerular; the tubular wall appears to be impermeable to magnesium throughout its length (109).

4. A Possible Renal Threshold

The amount of magnesium that is filtered at the glomerulus in an adult human is about 9.6 mEq/h, assuming a glomerular filtration rate of 130 ml/min, a total plasma magnesium concentration of 1.6 mEq/l and an ultrafiltrable fraction comprising 75% of the total. The mean rate of magnesium excretion in the urine (about 0.33 mEq/h) therefore represents only 3.5% of the filtered load. Moreover, the whole range of excretion observed under physiologic conditions in man can be explained if the tubular reabsorption of magnesium varies between 91 and 99% of the amount filtered at the glomerulus. In the rat (14), sheep (138), and cattle (122), there is evidence for the existence of a renal threshold for excretion of magnesium at a value close to the lower limit of the normal blood level. There is reduction in net tubular reabsorption of magnesium above a total serum magnesium concentration of 1.2–1.4 mEq/l; this could be due to either a decrease in the maximum capacity for tubular reabsorption or an increase in tubular secretion of magnesium.

5. Tubular Secretion

The possibility of secretion of magnesium by the renal tubules has been investigated under conditions of magnesium loading (61). At serum concentrations above 6.2 mEq/l, the amount excreted exceeded twice the filtered load, thus demonstrating tubular secretion of magnesium beyond any likely experimental error. The response to the administration of 2,4-dinitrophenol suggested that magnesium is also secreted by the tubules under physiologic conditions.

All the available evidence in the rat until recently have been consistent with a mechanism for magnesium excretion which involves reabsorption of the filtered material, with the excreted magnesium derived chiefly by tubular secretion. This secretion only appears to commence when the magnesium concentration in serum exceeds a critical value which is close to the lower limit of the normal range. However, studies with the stop-flow techniques did not find magnesium secretion in acutely magnesium-loaded rats undergoing mannitol or sulfate diuresis (9).

In the dog (93), magnesium excretion, like sodium and calcium excretion, is determined by filtration and reabsorption alone without evidence for tubular secretion. There is a maximal tubular reabsorptive capacity (Tm) for magnesium of approximately 11.5 μEq/min/kg body weight. The parathyroid hormone may directly enhance tubular reabsorption of magnesium.

E. Homeostasis

We do not understand yet the physiologic mechanisms which are responsible for maintaining the plasma magnesium concentration at a constant level (84). Both calcitonin (81) and parathormone may be involved. Nevertheless, animals and human beings on an adequate intake of magnesium do remain in magnesium balance, and the two chief regulatory sites appear to be the gastrointestinal tract and the kidney.

1. Effects of Parathyroid Hormone

There is considerable evidence for the hypothesis that the parathyroid hormone may help to control the concentration of plasma magnesium through a negative feedback mechanism (49, 60, 85).

Magnesium deficiency in the intact rat is accompanied by hypercalcemia and hypophosphatemia, provided the parathyroid glands are intact. The concentration of ionic calcium in plasma is elevated. In the absence of the parathyroid gland, magnesium-deficient rats do not develop hypercalcemia or hypophosphatemia. Moreover, parathyroidectomized animals with magnesium deficiency develop a concentration of ionized calcium in plasma that is lower than that observed in parathyroidectomized rats on a normal diet (52, 111).

These observations help to establish a relationship between an apparent

increased function of the parathyroid gland and magnesium deficiency (111). Recent studies suggest that magnesium depletion may result in impaired synthesis or release of parathyroid hormone in man, or both (13, 31, 123). Parathyroid hormone responsiveness in hypomagnesemic patients may, at least in part, be dependent upon the adequacy of intracellular magnesium stores (101).

2. Effects of Hypermagnesemia

If parathyroid regulation is influenced by the concentration of magnesium in plasma, hypermagnesemia should diminish parathyroid gland activity (12). This hypothesis was tested in intact and chronically parathyroidectomized rats which were nephrectomized to eliminate the urinary excretion of calcium as a variable in the study. Isotonic magnesium chloride was administered subcutaneously to the experimental animals and normal saline was administered to the controls. A significant decrease in the concentration of ionic calcium was observed in the magnesium-treated animals with the intact parathyroid glands. In contrast, magnesium-treated parathyroidectomized animals failed to develop a significant change in the concentration of ionic calcium in comparison to saline-treated parathyroidectomized controls. These observations suggest that hypermagnesemia may inhibit parathyroid gland activity. The results are consistent with the hypothesis that the parathyroid regulatory mechanism which is involved in calcium homeostatis is modified by alterations in the concentration of plasma magnesium (51).

3. Perfusion Studies

The influence of the plasma magnesium concentration on parathyroid gland function was evaluated in goats and in a sheep by perfusion of the isolated parathyroid gland with whole blood of varying magnesium concentration (26). The concentration of parathyroid hormone in venous plasma from the gland was estimated by a specific radioimmunoassay. In each animal, the concentration of parathyroid hormone in the effluent plasma *diminished* when the concentration of magnesium was raised; the concentration of hormone *increased* when the concentration of magnesium was lowered. The response of the parathyroid hormone concentration to changes in plasma magnesium concentration occurred rapidly within minutes. Magnesium appeared to have a specific influence on the rate of release of parathyroid hormone.

4. Studies in Organ Culture

Sherwood et al. (113) recently developed an organ culture system utilizing normal bovine parathyroid tissue. Studies with this system provide direct evidence that the release of parathyroid hormone is inversely proportional to both the calcium and the magnesium ion concentrations. These two cations are equipotent in blocking hormone release.

5. Relationship between Bone and Extracellular Magnesium

Magnesium deficiency in the rat has been shown repeatedly to cause lowering of the magnesium concentration in bone (91). The observation of a close direct relationship between the magnesium concentration in the plasma and the femur of magnesium-deficient rats, calves, and man (10) supports the view that the skeleton provides the magnesium reserve in the body and suggests that there exists an equilibrium between the magnesium of the plasma and the bone. Recent clinical studies indicate that bone and extracellular fluid magnesium and the major magnesium pools in man increased during magnesium excess and decreased during magnesium depletion (11). This equilibrium is apparently independent of enzymatic activity and must, therefore, be physicochemical in nature. The fact that the equilibrium is dependent upon the concentration of magnesium in both the medium and the bone suggests that the relationship between bone and extracellular fluid magnesium is analogous to the ionization of a poorly dissociated salt, with the magnesium in bone corresponding to the undissociated salt.

6. Effects of Parathyroid Extract *in vitro*

Parathyroid extract increases the rate of magnesium loss from either fresh or boiled bone *in vitro* in a magnesium-low medium containing 50% bovine serum; however, the extract has no effect in a protein-free medium. These observations are consistent with the hypothesis that the physicochemical action of parathyroid preparations may involve the binding of divalent cations by a parathyroid-albumin complex (54, 91). This phenomenon in dead tissue, which may partially explain an important biologic function, certainly is not in accord with current concepts of the mechanism of hormonal action.

F. Magnesium Deficiency in Man

1. The Clinical Syndrome

For many years, there was doubt about the existence of a pure magnesium deficiency state in man. Now it is established that there is such a condition (44, 129). It is characterized by the following features: (1) spasmophilia (41), gross muscular tremor, choreiform movements, ataxia, tetany and, in some instances, predisposition to epileptiform convulsions (58); (2) hallucinations, agitation, confusion, tremulousness, delirium, depression, vertigo, muscular weakness, and an organic brain syndrome (57); (3) a low serum magnesium concentration associated with a normal serum calcium concentration and a normal blood pH; (4) a low-voltage T wave in the electrocardiogram (27), low-voltage PQRS complexes, and a short fixed P-R interval (16); (5) a positive Chvostek and Trous-

seau sign; and (6) prompt relief of the tetany when the serum magnesium concentration is restored to normal (129). *Durlach* (40) recognizes the presence of other manifestations of clinical magnesium deficiency, such as phlebothrombosis, constitutional thrombasthenia and hemolytic anemia, an allergic or osseous form of the deficiency, and oxalate lithiasis.

2. Experimental Production of a Pure Magnesium Deficiency

It is difficult to achieve a significant magnesium depletion in normal individuals by simple dietary restriction because of the exceedingly efficient renal and gastrointestinal mechanisms for conservation. The urinary magnesium in normal individuals falls to trivial amounts within 4–6 days of magnesium restriction (18, 43). In spite of these conservatory mechanisms, *Dunn and Walser* (39) did induce in two normal subjects deficits approaching 10% of the total body content of magnesium by infusing sodium sulfate and adding calcium supplements to the magnesium-deficient diet. The concentration of magnesium in plasma and erythrocytes fell moderately. Because the muscle magnesium content remained normal, the presumption was that bone was the source of the loss. No untoward clinical effects were noted.

Randall et al. (107) reported data suggesting that total body depletion of magnesium may result in psychiatric and neuromuscular symptoms. Administration of magnesium by the parenteral route or in the diet was associated with clinical improvement which occasionally was dramatic.

The best study to date of magnesium deficiency in man is that recently reported by *Shils* (114–116). Seven subjects were placed on a magnesium-deficient diet containing 0.7 mEq of magnesium/day. The concentration of magnesium in plasma declined perceptibly in all subjects within 7–10 days. Urinary and fecal magnesium decreased markedly, as did urinary calcium. At the height of the deficiency, the plasma magnesium concentration fell to a range of 10–30% of the control values, while the red cell magnesium declined more slowly and to a smaller degree. All male subjects developed hypocalcemia; the one female patient did not. Marked and persistent symptoms developed only in the presence of hypocalcemia. The serum potassium concentration decreased, and in four of the five subjects in whom the measurement was made, the ^{42}K space was decreased. The serum sodium concentration was not altered significantly. Three of the four subjects with the severest symptoms also had metabolic alkalosis.

A positive Trousseau sign which occurred in five of the seven subjects was the most common neurologic sign observed. Electromyographic changes, which were characterized by the development of myopathic potentials, occurred in all five of the patients tested. Anorexia, nausea, and vomiting were frequently experienced. When magnesium was added to the experimental diet, all clinical and biochemical abnormalities were corrected.

3. Clinical Conditions Associated with Depletion of Magnesium

Magnesium deficiency can occur in congestive heart failure, after diuresis, with furosemide, ethacrynic acid and mercurials, and with digitalis intoxication, diabetic acidosis, acute and chronic alcoholism, delirium tremens, cirrhosis, malabsorption syndromes, protracted postoperative cases, open heart surgery, the diuretic phase of acute tubular necrosis, and with primary hypoparathyroidism, primary aldosteronism, juxtaglomerular hyperplasia, and pancreatitis (68).

a) Fasting. Prolonged fasting is associated with a continued renal excretion of magnesium (38). After 2 months of fasting, the deficit in some subjects may amount to 20% of the total body content of magnesium. Despite evidence for depletion of magnesium in muscle, the concentration of magnesium in plasma remains unchanged. The excess acid load presented for excretion to the kidney and the absence of intake of carbohydrate might be factors contributing to the persistent loss of magnesium. The magnitude of the excretion of magnesium parallels the severity of the acidosis. The ingestion of glucose decreases the urinary loss of magnesium.

b) Excess loss from the gastrointestinal tract. Persistent vomiting or prolonged removal of intestinal secretions by mechanical suction coupled with the administration of magnesium-free intravenous infusions can induce clinical magnesium deficiency (48, 72).

c) Surgical patients. There are postoperative changes in magnesium metabolism in patients undergoing a variety of operations involving a moderate degree of trauma (59). A lowered serum magnesium concentration is observed on the day after operation in 56% of the patients, but it is usually corrected by the second or third postoperative day. Surgery is followed by a negative magnesium balance of days' duration and similar changes are observed after dietary restriction in normal subjects. However, the magnitude of the magnesium loss following surgery is minimal and usually does not result in symptomatic magnesium deficiency (73, 82, 103).

d) Gastrointestinal disorders. The intestinal tract plays a major role in magnesium homeostasis. The rate of transport of magnesium across the intestine appears to be slower than that of calcium and directly proportional to intestinal transit time (87). Malabsorption of magnesium, therefore, occurs in conditions in which intestinal transit is abnormally rapid or in which the major absorbing site, the distal small intestine, has been resected.

Hypomagnesemia is associated frequently with *malabsorption* due to a variety of causes. In general, there appears to be a correlation between the degree of hypomagnesemia and the severity of the underlying disease. The increased fecal loss of magnesium that has been demonstrated in this disorder may be due to steatorrhea (53). In acute pancreatitis, hypomagnesemia may occur due in part to deposition of this cation in areas of fat necrosis (63).

e) Acute alcoholism. The mean serum magnesium value in patients with delirium tremens in one study was 1.53 ± 0.27 mEq/l. In alcoholics without delirium tremens, it was 1.89 ± 0.22 mEq/l. In the control group of 157 non-alcoholics, the mean serum magnesium value was 1.84 ± 0.18 mEq/l. There was a tendency for the lowest serum magnesium levels to coincide with the highest values for serum glutamic oxalacetic transaminase (105). Hypomagnesemia occurs frequently in patients with chronic alcoholism with and without delirium tremens. Patients exhibiting alcohol withdrawal signs and symptoms (100) have low serum and cerebrospinal fluid levels of magnesium, low exchangeable magnesium levels (88, 99), a lowered muscle content of magnesium (70, 77), and conservation of magnesium following intravenous loading (96). A transient decrease in serum magnesium may occur during the withdrawal state even though prewithdrawal levels are normal. An ethanol-induced increase of magnesium in the urine occurs only when the blood alcohol level is rising. It does not persist once the subject has established high blood alcohol levels. However, in the presence of hypomagnesemia and delirium tremens, sudden death can occur as a result of cardiovascular collapse, infection, and hyperthemia (102). The red cell concentration of magnesium is abnormally low in all patients with delirium tremens, whereas the plasma concentration is abnormally low in only 58% of them (120). Intracellular fluid levels of magnesium as reflected in the erythrocyte correlate better with clinical symptoms and signs than do extracellular fluid levels. The predominant factor accounting for magnesium depletion in acute alcoholism is most likely an inadequate intake of magnesium, but another factor may be increased excretion of magnesium in the urine and feces (37, 97).

Independent of the phenomena described above, an abrupt and significant fall in serum magnesium levels may occur following cessation of drinking. This acute fall in serum magnesium level is associated with a transient decrease in concentration of other serum electrolytes and with respiratory alkalosis (139) and coincides with the onset of neuromuscular hyperexcitability that characterizes the withdrawal state (100). Hypomagnesemia appears to be directly related to the syndrome of alcoholic encephalopathy; adequate treatment with magnesium reverses the syndrome (121). A kinetic analysis of radiomagnesium turnover was performed in a group of partially repleted alcoholic subjects. Despite the continued presence of hypomagnesemia and of decreased urinary excretion of magnesium, there was little evidence of continued depletion of magnesium in the extracellular space or in the tissue pools (131).

f) Cirrhosis. The magnesium content of the liver tissue per unit weight is decreased in cirrhosis (136). This decrease appears to be due mainly to the substitution of parenchymal tissue of high magnesium content with connective tissue of low magnesium content. There is a good relationship between histological changes (extent of fibrosis and degree of infiltration of inflammatory cells) and decrease of the magnesium concentration per number of cells. The actual

changes in the concentration of magnesium in the parenchymal cells of the cirrhotic liver appear to be negligible.

Patients with cirrhosis may have clinical features consistent with magnesium deficiency in the presence of a normal serum magnesium value but with a low skeletal muscle magnesium content and a normal bone and erythrocyte magnesium content (78).

g) Cardiovascular disorders. It was recognized but not widely appreciated as early as 1952 that magnesium deficiency occurs in congestive heart failure (67), and that hypomagnesemia follows the administration of mercuhydrin (90). Cardiac glycosides may induce magnesium deficiency; magnesium deficiency is frequently associated with cardiac arrhthymias such as ventricular tachycardia and arterial or ventricular fibrillation (68).

h) Hypomagnesemia as a cause of persistent hypokalemia. Of considerable clinical interest is the recent recognition that hypokalemia may be secondary to magnesium deficiency and may be resistant to treatment unless the underlying magnesium deficiency is corrected (133). Since hypokalemia is so prevalent, a high index of suspicion is necessary to detect the underlying magnesium deficiency.

IV. Diagnosis

In many patients, the clinical symptoms and signs, although non-specific, accompanied by a low serum magnesium concentration confirm the diagnosis. However, a normal serum magnesium level does not exclude magnesium deficiency.

Since serum magnesium is regulated largely by renal control of urinary magnesium secretion, urinary output of the element has been used as an index of magnesium deficiency (61). *Caddell* (28) has described a magnesium load test in infants up to 6 months of age. A 56-hour test measured cation and creatinine excretion before and after an intramuscular load of 0.49 mEq Mg/kg of body weight. This approach has been extended to postpartum American women (29). An intravenous test load of 0.4–0.5 mEq Mg/kg of estimated lean body weight was administered and the net retention calculated. *Thoren* (127) has used an intravenous dose of 0.25 mmol of Mg/kg of body weight; more than 80% of this dose should be excreted in the urine within 24 h if tissue reserves are adequate.

V. Therapy

In patients with the clinical symptoms and signs of magnesium deficiency, the deficit of magnesium is on the order of 1–2 mEq/kg of body weight. Since

less than one half of the administered magnesium is usually retained in the body, the required therapeutic dose is 2–4 mEq/kg which can be administered parenterally over a 4-day period. In order to administer the dose safely, one should first determine the adequacy of renal function, then monitor the plasma levels of magnesium during therapy (45).

Flink (45) recommends, an initial loading dose of 49 mEq (6.0 g of $MgSO_4$ in 1,000 ml of solution containing 5% glucose) given intravenously over a period of 3 h, followed by additional doses of 49 mEq every 12 h.

Another suggested regimen is the intravenous administration of 98 mEq on the first day (2.0 g, 16.3 mEq, every 2 h for three doses and then every 4 h for four doses), followed by 33–49 mEq/day in divided doses for 4 days (45).

For the treatment of arrhythmia, *Iseri et al.* (68) administer 10–15 ml of a 20% magnesium sulfate solution, given intravenously over 1 min, followed by a slow 4- to 6-hour infusion of 500 ml of a 2% magnesium sulfate in 5% dextrose water. A second infusion of magnesium sulfate may be necessary should the arrhythmia recur.

VI. Summary and Comments

Almost seven decades have passed since *Richard Willstatter* demonstrated the central position of the magnesium atom in the chlorophyll molecule. Although much has been learned since concerning the photosynthetic process, the exact function of the magnesium atom in this process still eludes us. That magnesium is essential for photosynthesis is an established fact. There is recent evidence to suggest that magnesium may play a role in the regulation of the photosynthetic processes.

Chlorophyll is a component of the chloroplast which is located physically in the granum which possesses a lamellar structure conductive to charge separation; the granum is the locus for photosynthesis. What is the role of magnesium at this interface of chemistry and physics to molecular biology? What about the properties of water with its low-energy bonds as emphasized by *Szent-Györgi* (126)? Can polarized water be as important as lipid in providing the living cell with its selective surface barrier (80)? Can all of the functions of magnesium be explained solely on the basis of the coordinating properties of the magnesium atom?

In the synthetic processes which follow the capture of solar energy, ATP plays a vital role. It is significant that all enzyme reactions which are known to be catalyzed by ATP have an absolute requirement for magnesium; so fundamental and widespread are the reactions involving ATP that it must influence practically all processes of life.

Is the mitochondrion a single large branching tubular structure *in vivo* and are the small intracellular organelles artifacts of preparation; what is the role of magnesium in this living organelle? Recent attempts to use computer graphics and computer analysis of serial section electron micrographs may supply further insight into these problems which involve detailed studies of the tertiary structure and the spacial interrelationships of terribly complex molecules.

Energy originally derived from the sun is used by living organisms for genetic transcription and protein synthesis. It appears that magnesium plays a vital role in all of these processes: the physical integrity of the DNA helix is dependent upon magnesium; the physical size of the RNA aggregates is controlled by the concentration of magnesium; and polypeptide formation is magnesium-dependent. How to explain this all-pervasive role of magnesium?

Concerning the physiology of magnesium, the first obvious fact is that most of it is located within cells. This differential concentration is on the order of 10:1, intracellular/extracellular, in the soft tissues of the body. Is metabolic energy required for the maintenance of this state, or can this be explained as due primarily to physicochemical adsorption? Can the symptoms and signs of magnesium deficiency be explained simply on the basis of the coordinating properties of the magnesium atom?

Bone contains the highest concentration of magnesium of any tissue in the body. Does this concentration require the expenditure of metabolic energy? How exactly are the parathyroid hormone and calcitonin involved in this process?

These are questions begging further studies.

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