Magnesium and the Gastrointestinal Tract

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Zusammenfassung

Die Übersicht gibt eine kritische Analyse des gegenwärtigen Wissenstandes über Zusammenhänge zwischen Magnesium und dem Gastrointestinaltrakt auf Grund von Daten aus der Literatur und eigener Ergebnisse. Nur wenig ist bekannt über Mg-Wirkungen auf sekretorische und motorische Vorgänge im Gastrointestinaltrakt, und nichts ist bekannt über gastrointestinale Mechanismen der Mg-Homeostase. Im Gegensatz zur Magensekretion und intestinalen Motilität ist eine beträchtliche Anzahl von Daten publiziert worden über den Mechanismus der Mg-Absorption durch die Darmmucosa, insbesondere im Hinblick auf chemische Faktoren oder physiologische Bedingungen, die die Absorption entweder fördern oder hemmen. Die diskutierten Faktoren und Bedingungen schließen ein: die Natur des Mg-Salzes, die Diät, die Stoffwechsellage, den Einfluß von Ionen, den Einfluß von Bestandteilen der Nahrung und verschiedene Chemikalien sowie die Orte von Absorption und Sekretion.

Schlüsselwörter:
Magnesium, Gastrointestinaltrakt, Magensekretion, intestinale Motorik, Absorption, Exkretion, Wiederkäuer

Summary

This review provides a critical analysis of the current state of our knowledge of magnesium and the gastrointestinal tract. We have examined the literature and our own data for information pertaining to magnesium and its role in gastrointestinal function. Actually little is known about the effects of magnesium on gastrointestinal secreto-motor activities and nothing is known about gastrointestinal mechanisms of magnesium homeostasis. Unlike gastric secretion and intestinal motility, a sizable amount of information has been published concerning the mechanism of magnesium absorption across the intestinal mucosa especially with respect to chemical factors or physiological conditions which influence absorption by either enhancement or inhibition. The factors and conditions discussed include nature of the magnesium salt, dietary intake, host conditions, the effect of ions, the influence of dietary constituents and various chemical agents, and sites of absorption and secretion.

Keywords:
magnesium, gastrointestinal tract, gastric secretion, intestinal motor activities, absorption, excretion, ruminants.

Résumé

Cette revue présente une analyse critique de l'état actuel de nos connaissances sur le magnésium et le tractus gastrointestinal. Nous avons examiné la littérature et nos propres données pour l'information concernant le Mg et son rôle dans la fonction gastro-intestinale. En fait, les connaissances sur les effets du Mg sur les activités secrétrices et motrices gastro-intestinales sont réduites et rien n'est connu en ce qui concerne les mécanismes gastro-intestinaux de l'homéostase du Mg. En opposition à la secrétion gastrique et à la motilité intestinale, une quantité appréciable d'informations a été publiée en ce qui concerne le mécanisme de l'absorption du Mg à travers la muqueuse intestinale, en considérant spécialement les facteurs chimiques et les conditions physiologiques qui présentent une influence sur l'absorption, en l'accroissant ou en l'inhibant. Les facteurs et les conditions discutés comprennent la nature du sel de Mg, la consommation avec le régime, les conditions de l'hôte et les effets des ions, l'influence des constituants du régime et de divers agents chimiques, et les sites de l'absorption et de la secrétion.

Mots clefs:
magnésium, tractus gastro-intestinal, secrétion gastrique, activités motrices intestinales, absorption, secrétion, ruminants.

A review of the literature which has appeared in the last 50 years reveals the somewhat remarkable fact that observers have apparently been content to remain satisfied with the general idea that the gastrointestinal tract serves merely as a conduit for magnesium intake, excretion, and conservation. Magnesium deficiency is viewed mostly in terms of defective intake, whether by malabsorption, or failure of conservation. Little attention has been paid to the fact that *Cassidy* and *Tidball* [21] have shown that the gastrointestinal tract in six species (including man) contains quite high concentrations of this element. Other workers have obtained data in agreement with this [17, 80, 120]. The subcellular distribution of magnesium within the gastrointestinal tract has also been studied. Two groups of workers have provided a comprehensive picture of the distribution of calcium and magnesium in subcellular fractions obtained from rat tissues [91] and the canine intestinal mucosa [22].

Experimental evidence obtained under controlled laboratory conditions suggests that gastrointestinal motor activity and, to some degree secretory performance are affected by chronic magnesium deficiency [140]. In rats two general consequences of magnesium deficiency have been noted: a massive release of histamine into the blood and an apparent nervous hyperreactivity [131]. Thus, it seems reasonable to examine gastrointestinal dysfunctions which may be classified in these categories.

According to *Kraeuter* and *Schwartz* [70] during chronic magnesium deficiency in the rat, blood histamine concentrations increase 4—5 fold by 14 days but reach control values in 30 days from the onset of the deficient diet. Histamine is a potent stimulant of gastric acid secretion in man, dogs, and guinea pigs. Yet, published results from our own laboratories [140] indicate that early or late stage magnesium deficiencies in rats are not associated with elevations in titratable

gastric acid output. This is understandable for two reasons: rat gastric acid secretion is relatively refractory to histamine [43, 69, 75] and the rat gastric mucosa contains a histaminase [66] which is not found in other species. However, these differences simply make the rat a poor model because the inferences from these observations cannot be extended to guinea pigs, dogs, or humans.

The alternative to studying the effects of magnesium deficiency on gastric secretory function is to observe the effects of magnesium administration. Magnesium is known to inhibit the stimulatory effect of calcium on certain secretory systems, probably as a competitive effect [33] and it has been demonstrated that magnesium can inhibit calcium-induced acid secretion in humans [8]. This inhibitition appears to involve an effect of magnesium directly upon the parietal cell [23]. However, magnesium inhibition appears to be only significant in the case of calcium-induced gastric acid secretion. Magnesium does not appear to exert an inhibitory effect upon basal gastric acid secretion or secretion stimulated by pentagastrin or histamine [106]. The preceding experiments demonstrate that a limited amount of information has been obtained on a number of aspects of magnesium metabolism and gastric acid secretion. On the other hand, considerable ignorance remains on the effects of magnesium or magnesium deficiency with respect to other gastrointestinal secretory activity.

Studies of neuromuscular transmission have shown that magnesium ion inhibits the release of acetylcholine [131]. We have shown an increased level of spontaneous motor activity in the small intestine and acetylcholine-hyperreactivity of strips of small intestine taken from rats that were made magnesium deficient either by diet [72] or by radiation [139]. These phenomena were not seen in either the intact colons or colonic muscle strips taken from the same rats. Interestingly enough, the spiral colons of magnesium-deficient sheep have been reported to be atonic [15].

It has been shown that increased magnesium concentrations inhibit the contractile responses to serotinin of isolated strips of guinea pig ileum and rabbit mesenteric artery and vein [45]. These data were interpreted to indicate that this inhibition was of a non-competitive nature. A simple hypothesis of calcium-magnesium competition for membrane receptor sites as an explanation for altered membrane sensitivity to various agents or contractile mechanism responses has not gained even a modicum of acceptance.

Experiments have been conducted with glycerinated skeletal and smooth muscles to determine the effects of both calcium and magnesium on their contractile mechanisms [92]. The necessity of calcium as an activator of the skeletal muscle contractile mechanism and the potentiating effect of magnesium are well known. At least one author [92] has succeeded in eliciting magnesium-induced contractile activities in glycerinated canine jejunal smooth muscle under calcium free conditions. However, the mechanism of tension production may not be entirely the same as that when normal calcium is present in the system. The physiological significance of *Nakahata's* [92] observation is not known. One might add also that alterations in membrane behavior associated with neurotransmitter release or membrane responses to neurotransmitters may be systems which are more sensitive to ambient magnesium concentrations (and possibly easier to observe experimentally) than the contractile mechanisms themselves. In any event, we have come to the conclusion that a great opportunity exists to develop information relating to the effects of magnesium on gastrointestinal motor activities as well as the role of the gastrointestinal tract in magnesium homeostasis. There is certainly a need to determine the mechanisms which control the intracellular and extracellular concentrations of this ion.

In considering magnesium absorption, one is confronted with an extremely difficult problem. The uptake of this ion has been very extensively studied, but highly divergent views still prevail regarding the nature of its absorption from the gastrointestinal tract. From the standpoint of absorption the mode in which magnesium is combined is important. Magnesium absorption studies have employed chloride, sulfate, acetate, citrate, nitrate, trisilicate, hydroxide, ocide, lactate, and gluconate moieties. In most studies, sulfate is commonly used despite the fact that chloride is most likely to be the associated anion once dietary magnesium has entered the duodenum. On the other hand, because of the cathartic effect of sulfate, chloride is frequently favored for isotope studies. It appears that the rate at which magnesium is absorbed from the gastrointestinal tract depends to a large extent upon the form in which it is ingested. There are experimental indications that magnesium chloride is absorbed much faster than magnesium sulfate [29]. Also, absorption of magnesium from the intestine is greater when the associated anion is acetate [47]. Other soluble organic magnesium salts from which the metal may be absorbed readily are magnesium oxide, lactate, and gluconate [6]. However, the consensus is that those forms of magnesium that are equally dissociated in the intestinal tract appear to have equal abilities to raise serum magnesium concentrations [6, 115, 142].

Behavioral studies have failed to produce evidence that the feeding behavior of animals is a significant specific controller of magnesium intake. In fact, there is no evidence that an appetite for magnesium exists either in humans or animals. *Elmslie* and *Steenbock* [36] found that excessive amounts of magnesium salts given to rats render the diet unpalatable, resulting in a lower food intake. This is also borne out by the fact that magnesium-deficient rats will shun a magnesium-containing diet even to the point of death. The apparent abhorrence for magnesium is not unique, as potassium-deficient rats similarly have no appetite for diets containing potassium [121]. For the most part, it

is still uncertain whether the absorption of magnesium is regulated by the needs of the body or absorbed independently of body requirements [19]. According to Chutkow [24], the quantity of magnesium absorbed in the normal rat greatly exceeds the animal's requirements and has no upper limit. Unfortunately, there is no accepted theory of magnesium homeostasis that embodies control of absorption, equilibrium between mobile and storage compartments and excretion.

Magnesium absorption is influenced by factors which could be expected to affect the absorption of any substance: starvation, vomiting, and diarrhea [52], and reduction of absorbing capacity by virtue of intestinal resection and fistulae [7, 40, 47, 65, 81, 118], radiation damage [83, 95, 136, 138, 147], or interference from luminal contents [13]. Diabetes [86] and biliary atresia [67] result in reduced magnesium absorption. In summary, host conditions that influence the absorption of magnesium from the intestine can be classified according to the mechanism of action: (1) loss or destruction of absorbing surface, (2) loss of the availability of the ion, (3) loss of the ion, and (4) pathological states.

No evidence exists in nonruminants to suggest that age is a determining factor in magnesium absorption. *Chutkow* [26] did not find any substantial depression in magnesium absorption with aging of the rat, although aging has been associated with quantitative changes in magnesium uptake in ruminants. Studies with young calves indicate that after the first 2 to 5 weeks of life the large intestine rapidly loses its ability to absorb magnesium; thereafter, the primary site of absorption is the small intestine [127].

The advent of the germ-free rat soon resulted in experiments to determine whether it could be inferred that the absence of bowel flora affected the intestinal absorption of magnesium. It was concluded that the absorption of magnesium in germ-free animals was greater than in ordinary controls, although it could not be concluded that the resulting plasma concentrations were different [109]. According to Reddy et al. [109], the increased magnesium absorption in germ-free animals was not a generalized phenomenon because the germ-free conditions did not markedly affect phosphorus absorption. No morphological changes were obvious in the lining epithelia of the intestines of the germ-free rats, but the cells of the ileum and jejunum showed increases in the contents of brush-border proteins such as Ca^{2+}— ATPase, Mg^{2+}— ATPase, alkaline phosphatase, and mucosal calcium-binding protein [110, 111]. Inasmuch as the increase in magnesium absorption in these germ-free rats was accompanied by an increase in calcium absorption, it was concluded that the increases in these protein complexes were probably associated with the increases in ion absorptions [110, 111].

Species differences in the rate at which food traverses the gastrointestinal tract may make comparisons and interpretations of magnesium-absorption data difficult [27]. Such variations alter the duration of contact between the luminal magnesium and the absorptive surfaces in any given segment of the bowel and, assuming that the mineral enters the cells in an ionic form, modify the interaction of magnesium with those intraluminal factors that may change the chemical state of magnesium rendering it unavailable for absorption [27]. Experiments with calves older than 2 months of age suggest that the rate of intestinal mass propulsion may have a strong influence on the intestinal absorption of magnesium [128]. Thus, *Smith* [129] showed a strong positive linear correlation between small intestinal transit time and percentage of magnesium absorbed. Transit times increased when calves were fasted and decreased when they were fed magnesium chloride rather than milk. Oral or intramuscular administration of an anticholinergic agent (propantheline bromide) to calves resulted in an increase in magnesium absorption regardless of whether they were fed milk or magnesium chloride [129]. Similar work has not been done with nonruminants. However, it is known that, in the rat, transit times are reduced when the animals are made hypomagnesemic by a low-magnesium diet [140]. Therefore, there is a reason to ask whether magnesium deficiency might be systematically associated with magnesium malabsorption, at least in calves (which would demonstrate a curious form of positive feedback in a biological system).

It has been suggested that several ions, including potassium, sodium, phosphate, calcium, and magnesium itself, affect magnesium absorption. The magnesium ion concentration in the lumen of the rat intestine influences magnesium absorption by that organ [24]. *Chutkow* [24] reported that magnesium absorption is depressed for at least 7 to 8 hours after the passage of a large amount of intraluminal magnesium. According to the results of *in vitro* experiments, the magnesium effect is also specific. Thus, increasing the concentration of mucosal magnesium ion intensifies transport in the lower jejunum and ileum but not in the upper jejunum [115]. Contrary to what was expected from observations by *Tansy* et al. [140], magnesium deficiency in the rat might not augment further magnesium deficiency as a regenerative process. *MacIntyre* and *Robinson* [78] noted an adaptive (but transient) increase in intestinal magnesium uptake of rats made deficient by diet, although, this increased uptake was probably not due to hypomagnesemia or hypophosphotemia *per se.* In the early stages, the increased uptake was probably due to a low magnesium concentration in the lumen, which was reversible if magnesium was administered by gavage. As the deficiency progressed by continued deprivation, the acute administration of the ion could no longer abolish the increased uptake. It is unlikely that the difference between the early and late stages could be due to the luminal existence of some residual dietary magnesium inasmuch as the early stages were defined at least 8 days after the beginning of the hypo-

magnesemia regimen [78]. Unfortunately, there is no information dealing with differences in transit times. It cannot confidentially be expected, therefore, that the relationship between transit time and absorption efficiency previously noted for normomagnesemic calves would apply to hypomagnesemic rats, especially since the rat appears to be critically dependent upon magnesium [132]. It has been reported that relatively high concentrations of luminal magnesium are required by rats for absorption [96, 97]; however, saturation has also been reported to occur [14, 47]. Texter's statement that "the major regulator of absorption is the quantity of magnesium in the intestinal lumen rather than the nutritional requirements of the animal" might apply to rats [143]. Certainly an affirmation of this statement would place a burden on any subsequent model purporting to reflect a homeostatic mechanism for serum magnesium.

From results of their own experiments and those of *Schacter* and *Rosen* [117], *Alcock* and *MacIntyre* [4] hypothesized that the apparent inhibition of calcium transport by magnesium ion indicated that these ions shared a common transport mechanism. As with any popular theory, this hypothesis provided the basis for numerous experiments designed to demonstrate it, to refute it, or to demonstrate its consequences [16, 19, 31, 55, 85, 89, 128]. Several years later the very genesis of the common carrier hypothesis was criticized by *Clark* [28] on the basis of the relationship of the reported experimental preparations of *Alcock* and *MacIntyre*'s studies [4] to a "physiological" state. *Clark* [28] published data which showed that oral magnesium administration could either promote or inhibit calcium absorption in the normomagnesemic rat, depending upon the dietary calcium state. Magnesium facilitated calcium absorption in the normocalcemic rat and inhibited it in the hypocalcemic rat. *Urban* [146] has since demonstrated that each ion is absorbed at its highest rate in different segments of the rat intestine. Subsequent observations [5] of interferences with magnesium absorption by calcium have been interpreted as indicating that calcium alters the permeability of a membrane to magnesium [145]. The critical demonstration of true competitive inhibition, in which the inhibition of one ion is dependent upon the concentration of the other, has never been made to these authors' knowledge in the case of the intestinal absorption of these ions. Indeed, the current literature now abounds with evidence that militates against the notion of a common transport mechanism [14, 86].

High levels of dietary phosphorus have been reported to be associated with decreases in the magnesium absorption rate in guinea pigs to the extent that the animals enter a state of negative magnesium balance [100, 101]. Conversely, rats placed on a low phosphorus ration showed an enhanced ability to absorb an ingested load of magnesium [32]. It is well established that a relationship exists between sodium concentration and rate of magnesium transport. This has been shown in segments of small intestine from rats [116]. The same relationship holds *in vivo* [51]. According to *Hanson* and *Jones* [51], the magnesium uptake and resulting magnesium content of the primary feathers appear to be heavily dependent upon sodium intake in Canadian geese. Neither potassium nor nitrogen have been associated in the literature with reports of augmentation of magnesium intake in ruminants. Both may have an inhibitory effect [53, 134], although it has been suggested that potassium may exert a more dominant effect [87, 90, 94]. Quantitation sufficient to assign relative magnitudes to these effects or to infer actual inhibition via some other mechanism is lacking.

Mass balance studies with human subjects indicated that, on the average, subjects maintained on high-protein diets absorb more calcium and magnesium than did subjects on a low-protein diet. On the average, increasing protein intake resulted in a net intake of more milliequivalents per day of magnesium than of calcium [82]. Similar data have not been reported for other nonruminant species. It has also been reportet that plant constituents such as crude protein appear to affect the absorption of isotopic magnesium from the digestive tract of sheep [134] and cattle [63]. Interestingly enough, the apparent availability of magnesium decreases as the crude protein concentration of the herbage increases. It has been reported that when the crude protein content of fresh herbage given to cattle is progressively increased from 14 to 26 percent, the apparent availability of magnesium decreased from 20 to 10 percent [63]. Furthermore, in sheep given dried forage, an increase in dietary crude protein from 16 to 27 percent also decreased the availability of magnesium from 24 to 16 percent [134]. These observations have led some to suggest that the availability of magnesium in pasture containing high concentrations of crude protein may be considerably reduced; however, other workers have recently obtained contradictory data. *Grace* and *McCrae* [46] increased the level of dietary protein from 16.5 to 21.5 percent by means of casein supplements and reported no effect on the apparent availability of isotopic magnesium or on the net absorption of magnesium from the digestive tract of sheep given dried grass. They found that a protein supplement had no effect on the extent or sites of magnesium absorption, but altering the feeding regimen changed the proportion of net absorption of magnesium in the stomach and intestinal regions. It is not clear what factors operated to bring about these divergent results.

There are numerous reports that suggest relationships between magnesium absorption and the influence of carbohydrates [2, 42, 73, 80, 102], lactose in particular. Dietary lactose has been reported to increase dietary magnesium uptake in the chicken, rat, and human [68, 80]. Glucose has been reported to depress magnesium absorption in the rat intestine, an effect that can be reversed by 2,4-dinitrophenol [5]. Although

the lactose effect on magnesium absorption may be due to changes in intestinal permeability [153], the mechanism(s) whereby lactose and glucose affect the absorption of this metal remains unknown. A reduction in fat intake by human subjects on fixed-magnesium diets was associated with diminished magnesium excretion and increases in serum concentrations of this ion [13]. Fat loading produced a negative magnesium balance. It has also been reported that if a resected patient was kept on a constant magnesium intake merely by reducing the fat intake, a rise in the level of serum magnesium would occur [118]. No data indicating the role fat plays in magnesium homeostasis with respect to absorptive and excretory processes have been published.

Magnesium absorption is enhanced by the presence of several chemically dissimilar substances in the intestinal tract. The data on some of these agents, however, are too scanty to merit lengthy discussions. Specific hormones such as growth hormone [82], aldosterone [49], vasopressin [76], calcitonin [19, 76], and parathormone [19, 62, 76, 78] have been shown to influence magnesium absorption from the gut. Parathormone has been reported to enhance the absorption of magnesium throughout the small intestine of the rat in a response that takes 24 hours to develop [78]. However, the opposite response has also been reported for thyroparathyroidectomized sheep where commercial parathyroid preparation was reported as producing a sharp reduction in the rate of magnesium absorption from *Thiry-Vella* loops [19]. The intravenous administration of calcitonin was reported to reduce magnesium absorption by *Thiry-Vella* loops in sheep with intact parathyroids [19]. A reduction in the magnesium content of the intestinal mucosal cells was reported to be associated with the administration of aldosterone to guinea pigs [116]. The authors suggested that aldosterone exerts this effect by limiting the uptake of magnesium by the cell rather than by increasing its efflux.

Most researchers agree that the administration of vitamin D is probably associated with enhanced magnesium absorption in the cat [50], chicken [154], baby pig [85], and rat [55, 84]. The magnitude of the vitamin D response to magnesium in the rat varies from indications of limited degree to rough equality with the calcium response [67, 84]. The situation with ruminants may be different, since Smith [126] was unable to conclude that vitamin D administration to milk-fed calves of any age was associated with significant changes in net magnesium absorption. Enhanced absorption of both calcium and magnesium has been reported for rats treated with antibiotics such as chloramphenicol or neomycin provided that they were on high-carbohydrate diets — 60 percent galactose or glucose [54]. Although no mechanism has been proposed to account for these observations, prior data reported for germ-free rats suggest that any treatment that will alter the composition of the intestinal flora may exert an indirect but significant influence upon calcium and magnesium absorption. Metabolic inhibitors such as cyanide, fluoracetate, and iodoacetate have been reported to increase the efflux and reduce the influx of magnesium in the intestinal walls of guinea pigs [116].

Considerable material has been published purporting to describe the effects of irritants, poisons, and autonomic drugs on magnesium absorption. The appropriate references are included for the sake of completeness but it is doubtful whether the observations reported have any functional significance. The increased absorption of magnesium provoked by aspirin and sodium salicylate in humans [155], as well as by ginger and alcohol in dogs [156], is probably due to irritation of the gastric mucosa. The most bizarre observation concerning magnesium absorption is that in fevered animals such absorption appears to be poor unless the animals vomit. It then seems be much better than in normal animals on the same dose but not vomiting [141, 156]. Conceivably, the same irritation which reflexively produces vomiting also augments absorption of magnesium. In rabbits, acute arsenic poisoning caused by sodium arsenite raises the absorption rate of magnesium sulfate [60]. It is reasonable to assume that this facilitated absorption occurs because of lesions produced in the mucous membranes of the gastrointestinal tract, even though there is some reason to believe that renal magnesium excretion is impaired. Another aspect is the ability of parasympathomimetics to influence magnesium absorption. The intramuscular injection of physostigmine, neostigmine, or acetylcholine has been reported to cause an elevation in serum magnesium [142]. In all instances, the effect was attributed to acetylcholine, presumably through the production of intracellular damage. This damage may be due to a direct acetylcholine effect on cellular permeability or to an acute circulatory insufficiency, with anoxia of the tissues resulting from the fall in blood pressure. However, it had been established much earlier [98] that even severe degrees of anoxia had no effect on magnesium absorption in the small intestine. For that matter, anemic anoxia produced by pronounced hemorrhage does not appear to change the intestinal permeability to magnesium [148]. Conflicting results concerning the effects of anticholinesterases on magnesium absorption have been displayed. *Jensen-Holm* [59] reported parenteral neostigmine to be ineffective in altering the absorption of orally or rectally administered magnesium sulfate in rabbits. He reported later, though, that if neostigmine was given orally or if paraoxon was injected subcutaneously, then intestinal magnesium absorption was greatly accelerated [61]. No reason was given for the discrepancies.

The sites of magnesium absorption from the gastrointestinal tract are somewhat dependent upon the animal species. However, magnesium can be absorbed throughout the gastrointestinal tract of all animals at some

point in their life cycle. To the best of the authors' knowledge, there are no published data on magnesium absorption from the oral cavity, although evidence of gastric magnesium absorption has been reported [155]. In nonruminants, magnesium absorption is said to occur throughout the small intestine, with the greatest absorptive activity in the ileum and the least in the duodenum [24, 55, 115]. Previous reports also suggest that the small intestine is the major site of isotopic magnesium absorption in the rabbit [1] and man [1, 47]. Nevertheless, in the rat [24], rabbit [59], and human [34, 37, 93, 108], there is ample evidence substantiating magnesium absorption in the large intestine. The reason that isotopic magnesium is taken up by the rat colon [25, 55] but not by the rabbit [1] or human colon [47] was not considered by the authors and still remains a mystery.

The rat may be a special case in that, while considerable absorption takes place in the ileum, more than 70 percent of the total absorptive activity occurs in the cecum and ascending colon [25]. According to *Chutkow* [25], this is because food moves relatively rapidly through the small intestine and then pools in the proximal colon for several hours, thereby allowing sufficient time for completion of absorption. *Chutkow* was of the opinion that differing absorptive capacities of various sites could depend upon intestinal transit rates in these regions, factors that can be expected to be species-specific [27].

At least one more recent report has appeared [146] which advances a reason for questioning current concepts regarding the sites of highest absorptive capacity in various species. Those studies which simply report intestinal absorptive rates do so by assigning values on the basis of the performance of the entire gut [24—27]. Such values are not specific measures of absorptive performance per unit weight of a defined intestinal segment [146].*Urban* and *Schedl* [146] pointed out that when performance is expressed in these latter terms, *in vivo* magnesium absorption in the rat becomes significantly greater in the duodenum than in the terminal ileum. Subsequent work using *in vitro* everted sacs made from specific segments was able to show a proximal-distal absorptive gradient that was in agreement with these similar observations made *in vivo* [5]. This was followed by work using comparative balance and isotope dilution techniques in chickens, which indicated that absorption of both dietary and endogenous magnesium was greatest in the duodenum and jejenum [48].

Aside from these studies, there is little information on magnesium absorption in rodents or other animals despite their extensive use in magnesium-deficiency studies. Therefore, in order to obtain more information on intestinal magnesium absorption, it will be necessary to refer to studies of ruminants, realizing that many of the observed differences may be the result of significant species variation. While the considerable attention devoted to magnesium absorption in ruminants resulted in a lot of published data, a void exists with respect to relating (and interpreting similarities or differences in) observations in ruminants and nonruminants because of the structural and functional differences in digestive apparatus. In the ruminant, four distinct stomach compartments are present. The first two, rumen and reticulum, are storage pouches where vegetable food is kneaded to a more workable pulp by the action of muscular walls. The pulp is then subjected to the action of microorganisms that break down complex plant materials and manufacture useful organic substances, some of which are absorbed in the rumen. The animal regurgitates the "cud" for chewing or rumination and then sends it by a bypass to the omasum, where there is further physical breakdown, and finally to the true stomach, the abomasum [112]. According to *Romer* [112], here alone are found the three types of epithelium proper to the mammalian stomach; it now becomes obvious that the three preceding compartments are not part of the original stomach, but essentially elaborations of the lower end of the esophagus.

In 1929, *Sjollema* and *Seekles* [123] first reported a physiological magnesium-deficiency in adult cattle and sheep. Much difficulty is encountered in grazing cattle on lush late winter and early spring natural grasses, oats, or wheat due to the disease referred to as "grass staggers" or "grass tetany". This condition has been reported in many parts of the world, including Holland, Great Britain, Ireland, Norway, New Zealand, Australia, South Africa [30], and Japan [90]. The disease occurs mainly in lactating cows shortly after calving, but it has also been encountered in dry cows, steers, calves, and ewes. Symptoms suggest that the disease is associated with a disturbance in mineral metabolism. Hypomagnesemia is the most common feature of grass tetany in cows [11, 124]. Magnesium is of particular importance in cattle and sheep nutrition because, except in very young calves [125—127], it appears to be poorly absorbed from normal diets [12, 38, 113], and clinical deficiency sometimes occurs under normal management conditions. In retrospect, it would appear that this veterinary malady has done more to advance our knowledge of gastrointestinal magnesium absorption than any other factor.

It was reported in 1956 by *Stewart* and *Moodie* [133] that some magnesium absorption can be demonstrated from the rumen to the cecum of sheep if the concentration of luminal magnesium ion is sufficiently high. The principle site of absorption appeared to be the small intestine, in terms of both the rate of absorption and the minimum level of luminal magnesium at which absorption could be demonstrated [133]. The rumen apparently serves as a significant site of absorption when the magnesium content rises above normal dietary levels, as with supplemented diets [20]. However, the midthird of the small intestine remained the chief contender as the primary absorption site (complete with rate limitation) as determined by *in vivo* studies [20],

thus supporting a similar contention based on earlier *in vitro* works [39]. Although the reticulo-rumen and duodenum are quite acidic [57, 79, 104] and are known to be permeable to magnesium [18], there is no significant uptake of dietary magnesium from these regions in the sheep [18, 20, 135]. The acidity of the digesta passing through the duodenum and upper jejunum of the sheep probably maintains the dietary magnesium in an ionized form, which favors absorption from the remaining small intestine. These areas act as important sites of magnesium absorption only after the diet is supplemented with magnesium.

Subsequently, it was reported that the colon [114] and forestomach [10], specifically, are significant sites of absorption of magnesium when its local concentration is high. Recent studies reported that a substantial amount of ingested isotopic magnesium is absorbed before it reaches the duodenum [10]. *Ben-Ghedalia* and co-workers concluded that inasmuch as the rumen epithelium appears to be impermeable to magnesium [104] and no net absorption of magnesium occurs in the abomasum [20], it is possible that the omasum is the site of magnesium absorption in the Awassi ram [10].

Although dietary magnesium can be absorbed from both the small and large intestine in young calves, for some undetermined reason large intestinal absorption decreases markedly with age [127, 128], even if the calf is magnesium deficient [129]. It has been estimated that the 40 to 70 percent of the magnesium escaping absorption in the small intestine, which would normally be absorbed in the large intestine, represents a loss of about 25 to 40 percent of the dietary intake [128]. This apparent loss of absorptive function by the large bowel is believed to be the major factor responsible for the onset of the "grass staggers" [128]. Even in young calves of similar age, a wide variation in magnesium utilization exists. Analysis of the published data indicates that the calf-to-calf difference in ability to absorb dietary magnesium up to the end of the small intestine ranges from 9 to 44 percent of intake [128]. The variance in magnesium absorption between calves of like age is attributed to the inherent dissimilarity in their small intestinal motor activities [130]. Increased net absorption of magnesium has been found to accompany the decreased transit time obtained after oral or intramuscular administration of the anticholinergic drug propantheline bromide or magnesium chloride solutions to milk-fed calves [129]. It is interesting to note that no associated variations in absorption of other minerals were observed in any of these studies. It seems plausible, therefore, that differences in transit time may also be responsible for the considerable variation found between adult cattle in their ability to utilize dietary magnesium. This could explain the slight but wide animal-to-animal variations in susceptibility to clinical hypomagnesemia.

Most authors agree that the principal locale of observed magnesium excretion in the rat [24, 115], chicken [48], sheep [46, 104], and cattle [20] is the duodenum and upper jejunum. However, the relative contributions of duodenal and biliary secretions to the total duodenal excretion have not yet been established. Inasmuch as preceding citations have indicated that the control of excretory processes may constitute the chief mechanism of magnesium homeostasis, the role of the sites and mechanisms of excretion should be the subject of extensive research efforts.

The consensus remains that the most significant site of magnesium absorption is the small intestine. This is true for adult ruminants [20, 39, 46, 103, 104, 122, 127, 133] and nonruminants [1, 5, 47, 48, 55, 115, 146] when the luminal magnesium concentration approximates dietary levels. The great proportion of magnesium absorption by the large intestine of young calves is not eventually transferred to the small intestine, but simply lost, thus reflecting a net reduction in the calf's ability to absorb magnesium. Certainly the ability (or lack of it) of a variety of exogenous agents to influence magnesium absorption represents little more than an interesting curiosity because magnesium deficiency is not a significant endemic condition. Short-term alterations in intestinal transit time can also be shown to influence magnesium absorption, but as in the case of other luminal contents (including flora), the average result is simply not a significant hypomagnesemia.

Currently available information suggests that all approaches to date have indicated that magnesium homeostasis may be an almost exclusive function of the control of excretion rather than of absorption. However, this logical approach and the experimental data generated in its image are necessarily open-loop and follow from ignorance of the fact that closed-loop thinking need not necessarily be circular. In the absence of any accepted body of fact and opinion concerning a conservation mechanism, therefore, there is currently no valid reason to exclude absorption as the principal controller of magnesium homeostasis. When it is recalled that the principal site of magnesium excretion is the duodenum, and the principal site of absorption is the small intestine: then, in a fashion similar to regulation of water balance by the kidney, magnesium homeostasis could very well result from the regulation of magnesium absorption. The data are not sufficient to accept or reject such a contention because the experiments were never designed to do so in the first place. But the experience of hypomagnesemia associated with radiation damage of the small intestines of rats, humans, and other species strongly suggests that reabsorption is certainly an important factor in a conservation mechanism which must by definition be included in a regulatory mechanism. Thus, magnesium must continue to hold its sinister record in the annals of physiology as the most ubiquitous ionabout which almost nothing is known concerning either its conservation or its regulation and control.

Although the major intestinal sites of absorption in the

various species have been defined, there seems to be no general agreement on the basic physiological mechanism controlling the transport of magnesium across the gut wall. A review of the literature indicates that there is a paucity of reports devoted to the results of investigations of the mechanism of magnesium transport across the intestinal mucosa. Some of the earliest studies suggested that the intestinal absorption of magnesium involved active transport [115], facilitated diffusion [20], and passive diffusion [5, 99, 122]. As was pointed out earlier with the hypothesis of a common calcium-magnesium transport system, none have withstood the test of time. A common criticism of some of these studies is that a demonstration of loss of luminal magnesium content and/or gut tissue magnesium accumulation is not necessarily conclusive evidence of normally operating transport mechanisms. This is particularly true when an unfortunate choice of luminal perfusates might in fact result in an alteration of the properties of cell membranes.

The definitive work on intestinal absorption of magnesium in the rat must be credited to *Behar* [9] whose carefully collected and thorough data indicated that magnesium transport in the rat small intestine and colon can probably be attributed to a sodium-dependent solvent drag mechanism. Under normal circumstances, this mechanism is adequate to insure the transport of magnesium against a net electrochemical gradient measured from the mucosal to the serosal sides. This work was definitive because it not only reported lumen-to-plasma fluxes but also tissue accumulation. Thus, the replacement of luminal sodium by mannitol or choline resulted in a decrease in the rate of magnesium transport and a rise in tissue magnesium content. At the time of *Ebel* and *Günther's* [35] review on magnesium metabolism was written, *Behar's* data reported in 1974, constituted the last authoritative word on the subject.

During the past 20 years, numerous reviews [35, 44, 56, 58, 77, 105, 119, 144, 149—152], monographs [41], and texts [3, 157], have treated the general subject of magnesium metabolism, and in all cases the treatment of gastrointestinal tract functions has ranged from non-existant to scanty. The majority of studies are both species and organ specific and exist in a universe of understanding which is devoid of general theories of either transport or homeostasis as controlled processes. This state of affairs probably exists because of the material abundance of magnesium. Magnesium-deficiency syndromes present a negligible epidemiological challenge to social and economic systems and a restricted and easily eliminated threat to the economics of animal husbandry.

Magnesium is so ubiquitious and its many roles are so well understood and accepted that little incentive has existed to define the mechanisms of transport let alone of gastrointestinal homeostasis. A limited attempt was made to fill this void [137]. Since that time, conditions have not significantly improved with respect to the availability of mechanistic evidence of general or specific applicability because of persistent differences in objectives, hypotheses tested, experimental protocol, and reduction and interpretation of data. Therefore, this contribution provides a comprehensive review of published information, but it does not provide the sorely needed answers to the important questions alluded to earlier.

References

[1] *Aikawa, J. K.:* Gastrointestinal Absorption of ^{28}Mg in Rabbits. Proc. Soc. Exp. Biol. Med. **100**, 293—295 (1959).

[2] *Aikawa, J. K., Rhoades, K. L., Harmes, D. R., Reardon, J. Z.:* Magnesium Metabolism in Rabbits Using ^{28}Mg as a Tracer. Amer. J. Physiol. **197**, 97—101 (1959).

[3] *Aikawa, J. K.:* The Relationship of Magnesium to Disease in Domestic Animals and in Humans, 1st ed., Charles C. Thomas, Illinois, p 1—145 (1971).

[4] *Alcock, N., MacIntyre, I.:* I. Interrelation of Calcium and Magnesium Absorption. Clin. Sci. **22**, 185—193 (1962).

[5] *Aldor, T. A. M., Moore, E. W.:* Magnesium Absorption by Everted Sacs of Rat Intestine and Colon. Gastroenterology **59**, 745—753 (1970).

[6] *Barbour, H. G., Winter, J. E.:* Magnesium Absorption in Dogs and Its Effect Upon the Metabolism of Calcium. J. Pharmacol. Exp. Ther. **43**, 607—620 (1932).

[7] *Barnes, B. A., Cope, O., Gordon, E. B.:* Magnesium Requirements and Deficits: An Evaluation in Two Surgical Patients. Ann. Surg. **152**, 518—533 (1960).

[8] *Barreras, R. F., Donaldson, R. M.,* Jr: Effects of Induced Hypercalcemia on Human Gastric Secretion. Gastroenterology **52**, 670—674 (1967).

[9] *Behar, J.:* Magnesium Absorption by the Rat Ileum and Colon. Amer. J. Physiol. **227**, 334—340 (1974).

[10] *Ben-Ghedalia, D., Tagari, H., Zamwel, S., Bondi, A.:* Solubility and Net Exchange of Calcium, Magnesium and Phosphorus in Digesta Flowing Along the Gut of the Sheep. Br. J. Nutr. **33**, 87—94 (1975).

[11] *Blakemore, F., Stewart, J.:* Some Observations on Several Outbreaks of So-Called Lactation Tetany in Cattles. Rep. Inst. Anim. Path., Cambridge **3**, 159—168 (1932/33).

[12] *Blaxter, K. L., McGill, R. F.:* Magnesium Metabolism in Cattle. Vet. Rev. and Annotations **2**, 35—55 (1956).

[13] *Booth, C. C.:* The Metabolic Effects of Intestinal Resection in Man. Postgrad. M. J. **37**, 725—728 (1961).

[14] *Brannan, P. G., Vergne-Marini, P., Pak, C. Y. C., Hull, A. R., Fordtran, J. S.:* Magnesium Absorption in the Human Small Intestine. Results in Normal Subjects, Patients with Chronic Renal Disease, and Patients with Absorptive Hypercalciuria. J. Clin. Invest. **57**, 1412—1418 (1976).

[15] *Bueno, L., Fioramonti, J., Geuz, E., Raissiguier, Y.:* Gastrointestinal Hypomotility in Magnesium-Deficient Sheep. Can. J. Anim. Sci. **60**, 293—301 (1980).

[16] *Bunce, G. E., Chiemchaisri, Y., Phillips, P. H.:* Effect of Certain Dietary and Physiologic Factors Upon the Mg Deficiency Syndrome. J. Nutr. **76**, 23—29 (1962).

[17] *Burch, G. E., Lazzara, R. K., Yun, T. K.:* Concentration of Magnesium in Tissues of the Dog. Proc. Soc. Exp. Biol. Med. **118**, 581—584 (1965).

[18] *Care, A. D.:* British Veterinary Association Conference on Hypomagnesaemia, London, pp. 34—35 (1960).
[19] *Care, A. D., Keynes, W. M.:* The Role of Parathyroid Hormones in the Absorption of Calcium and Magnesium from the Small Intestine. Proc. Roy. Soc. Med. **57**, 867—868 (1964).
[20] *Care, A. D., Van't Klooster, A. T.:* In Vivo Transport of Magnesium and Other Cations Across the Wall of the Intestinal Tract in Sheep. J. Physiol. (Lond.) **177**, 174—191 (1965).
[21] *Cassidy, M. M., Tidball, C. S.:* Calcium and Magnesium Contents of Gastrointestinal Tissue in Six Species. Am. J. Physiol. **217**, 674—679 (1969).
[22] *Cassidy, M. M., Goldner, A. M., Tidball, C. S.:* Subcellular Localization of Calcium, Magnesium, and Protein in Canine Intestinal Mucosa. Am. J. Physiol. **217**, 680—685 (1969)
[23] *Christiansen, J., Rehfeld, J. F., Stadil, F.:* Interaction of Calcium and Magnesium on Gastric Acid Secretion and Serum Gastrin Concentration in Man. Gastroenterology **68**, 1140—1143 (1975).
[24] *Chutkow, J. G.:* Metabolism of Magnesium in the Normal Rat. J. Lab. Clin. Med. **63**, 80—99 (1964).
[25] —*:* Sites of Magnesium Absorption and Excretion in the Intestinal Tract of the Rat. J. Lab. Clin. Med. **63**, 71—79 (1964).
[26] —*:* Studies on the Metabolism of Magnesium in the Magnesium-Deficient Rat. J. Lab. Clin. Med. **65**, 912—926 (1965).
[27] —*:* Effect of Magnesium Deficiency on Location of the Intestinal Absorption of Magnesium in Rats. Proc. Soc. Exp. Biol. Med. **123**, 836—840 (1966).
[28] *Clark, I.:* Relation of Magnesium Ions to Calcium and Phosphate Absorption. Nature (Lond.) **207**, 982—983 (1965).
[29] *Cohen, H.:* Purgative Action of Magnesium Salts. Quart. J. Med. **19**, 249—256 (1926).
[30] *Colby, R. W., Frye, C. M.:* Effect of Feeding Various Levels of Calcium, Potassium and Magnesium to Rats. Amer. J. Physiol. **166**, 209—212 (1951).
[31] *Cramer, C. F., Dueck, J.:* In Vivo Transport of Calcium from Healed Thiry-Vella Fistulas in Dogs. Amer. J. Physiol. **202**, 161—164 (1962).
[32] *Day, H. G., McCollum, E. V.:* Mineral Metabolism, Growth and Symptomatology of Rats on Diet Extremely Deficient in Phosphorus. J. Biol. Chem. **130**, 269—283 (1939).
[33] *Douglas, W. W., Rubin, R. P.:* The Mechanism of Catecholamine Release from the Adrenal Medulla and the Role of Calcium in Stimulus-Secretion Coupling. J. Physiol. (Lond.) **167**, 288—310 (1963).
[34] *Duthie, H. L., Watts, J. M., Dedombal, F. T., Goligher, J. C.:* Serum Electrolytes and Colonic Transfer of Water and Electrolytes in Chronic Ulcerative Colitis. Gastroenterology. **47**, 525—530 (1964).
[35] *Ebel, H., Günther, T.:* Magnesium Metabolism: A Review. J. Clin. Chem. Clin. Biochem. **18**, 257—270 (1980)
[36] *Elmslie, W. P., Steenbock, H.:* Calcium and Magnesium Relations in Animals. J. Biol. Chem. **82**, 611—632 (1929)
[37] *Fawcett, D. W., Gens, J. P.:* Magnesium Poisoning Following Enema of Epsom Salt Solution. J. A. M. A. **123**, 1028—1029 (1943)
[38] *Field, A. C., Jennie, W., McCallum, E., Butler, E. J.:* Studies on Magnesium in Ruminant Nutrition. Balance Experiments on Sheep with Herbage from Fields Associated with Lactation Tetany and from Control Pastures. Brit. J. Nutr. **12**, 433—436 (1958)
[39] *Field, A. C.:* British Veterinary Association, Report of Conference on Hypomagnesemia. London, p. 13 (1960)
[40] *Fletcher, R. F., Henly, A. A., Sammon, H. G., Squire, J. R.:* A Case of Magnesium Deficiency Following Massive Intestinal Resection. Lancet **1**, 522—525 (1960)
[41] *Flink, E. B., Jones, J. E.:* The Pathogenesis and Clinical Significance of Magnesium Deficiency. Ann. N. Y. Acad. Sci. **162**, 705—984 (1969)
[42] *Forbes, G. B.:* In: Mineral Metabolism. Comar, *C. L, Bronner, F.* (eds). Academic Press, New York, p. 29 (1962)
[43] *Friedmann, M. H. F.: Histamine Ineffective in the Rat as a Gastric Secretory Stimulant. Proc. Soc. Exp. Biol. Med.* **54**, 42—44 (1943)
[44] *Gitelmann, H. J., Welt, L. C.:* Magnesium Deficiency. Ann. Rev. Med. **20**, 233—242 (1969)
[45] *Goldstein, S., Zsotér, T. T.:* The Effect of Magnesium on the Response of Smooth Muscle to 5-Hydroxytryptamine. Br. J. Pharmac. **62**, 507—514 (1978)
[46] *Grace, N. D., Macrae, J. C.:* Influence of Feeding Regimen and Protein Supplementation on the Sites of Net Absorption of Magnesium in Sheep. Br. J. Nutr. **27**, 51—55 (1972)
[47] *Graham, L. A., Caesar, J. J., Burgen, A. S. V.:* Gastrointestinal Absorption and Excretion of ^{28}Mg in Man. Metabolism 9, 646—659 (1960)
[48] *Guenter, W., Sell, J. L.:* Magnesium Absorption and Secretion Along the Gastrointestinal Tract of the Chicken. J. Nutr. **103**, 875—881 (1973)
[49] *Hanna, S., MacIntyre, I., Harrison, M., Fraser, R.:* The Syndrome of Magnesium Deficiency in Man. Lancet **2**, 172—175 (1960)
[50] *Hanna, S.:* Influences of Large Doses of Vitamin D on Magnesium Metabolism in Cats. Metabolism **10**, 735—743 (1961).
[51] *Hanson, H. C., Jones, R. L.:* The Biogeochemistry of Blue, Snow, and Ross' Geese, Southern Illinois University Press, Carbondale-Edwardsville, 207—210 (1976).
[52] *Harris, I., Wilkinson, A. W.:* Magnesium Depletion in Children. Lancet **1**, 735—736 (1971).
[53] *Head, M. J., Rook, J. A. F.:* Hypomagnesemia in Dairy Cattle and its Possible Relationship to Ruminal Ammonia Production. Nature (Lond.) **176**, 262—263 (1955).
[54] *Heggeness, F. W.:* Effect of Antibiotics on the Gastrointestinal Absorption of Calcium and Magnesium in the Rat. J. Nutr. **68**, 573—582 (1959).
[55] *Hendrix, J. Z., Alcock, N. W., Archibald, R. M.:* Competition Between Calcium, Strontium, and Magnesium for Absorption in the Isolated Rat Intestine. Clin. Chem. **9**, 734—744 (1963).
[56] *Henzel, J. H., Deweese, M. S., Ridenhour, G.:* Significance of Magnesium and Zinc Metabolism in the Surgical Patient. I. Magnesium. Arch. Surg. **95**, 974—990 (1967).
[57] *Hogan, J. P., Phillipson, A. T.:* The Role of Flow of Digesta and Their Removal Along the Digestive Tract of Sheep. Brit. J. Nutr. **14**, 147—195 (1960).
[58] *Imbert, J.:* Le Rôle Biologique du Magnésium. Rev. Fr. Gastroenterol. **88**, 41—55 (1973).
[59] *Jensen-Holm, J.:* Effects of Different Hypertonic Solutions on the Absorption of Magnesium from the Rabbit Colon. Arch. Int. Pharmacodyn. **140**, 105—114 (1962).
[60] —*:* Effects of Sodium Arsenite on the Intestinal Absorption of Magnesium in Rabbits. Acta Pharmacol. et Toxicol. **20**, 109—112 (1963).
[61] —*:* Effects of Cholinergic Agents on Intestinal Absorption of Magnesium by Rabbits. Acta Pharmacol. et Toxicol. **20**, 97—108 (1963).
[62] *Jones, K. H., Fourman, P.:* Effects of Infusions of Magnesium and Calcium in Parathyroid Insufficiency. Clin. Sci. **30**, 138—150 (1966).
[63] *Kemp, A., Hart, M. C.:* Grass Tetany in Grazing Milking Cows. Netherlands, J. Agric. Sci. **5**, 4—10 (1957).

[64] *Kessner, D. M., Epstein, F. H.:* Effect of Magnesium Deficiency on Gastrointestinal Transfer of Calcium. Proc. Soc. Exp. Biol. Med. **122**, 721—725 (1966).

[65] *Kinney, J. M., Goldwyn, R. M., Barr, J. S., Moore, F. D.:* Loss of the Entire Jejunum and Ileum, and the Ascending Colon. J. A. M. A. 179, 153—155 (1962).

[66] *Kobayashi, Y., Ivy, A. C.:* Histamine Metabolizing Activity of the Stomach and Intestine of the Rat. Am. J. Physiol. **196**, 835—836 (1959).

[67] *Kobayashi, A., Utsunomiya, T., Ohbe, Y., Nagashima, Y.:* Intestinal Absorption of Calcium and Magnesium in Hepatobiliary Disease in Infancy. Arch Disease Childhood **49**, 90—96 (1974).

[68] *Kobayashi, A. T., Kawai, S., Ohbe, Y., Nagashima, Y.:* Effects of Dietary Lactose and a Lactose Preparation on the Intestinal Absorption of Calcium and Magnesium in Normal Infants. Am. J. Clin. Nutr. **28**, 681—683 (1975).

[69] *Komarov, S. A., Shay, H., Rayport, M., Fels, S. S.:* Some Observations on Gastric Secretion in Normal Rats. Gastroenterology **3**, 406—413 (1944).

[70] *Kraeuter, S. L., Schwartz, R.:* Blood and Mast Cell Histamine Levels in Magnesium-Deficient Rats. J. Nutr. **110**, 851—858 (1980).

[71] *Krawitt, E. L.:* Effect of Dietary Magnesium Deficiency on Calcium Transport by the Rat Small Intestine. Proc. Soc. Exp. Biol. Med. **141**, 569—572 (1972).

[72] *Landin, W. E., Kendall, F. M., Tansy, M. F.:* Metabolic Performance and GI Function in Magnesium-Deficient Rats. J. Pharm. Sci. **68**, 978—983 (1979).

[73] *Lengemann, F. W.:* The Site of Action of Lactose in the Enhancement of Calcium Utilization. J. Nutr. **69**, 23—27 (1959).

[74] *Lifshitz, F., Harrison, H. C., Harrison, H. E.:* Intestinal Transport of Calcium and Phosphate in Experimental Magnesium Deficiency. Proc. Soc. Exp. Biol. Med. **125**, 19—23 (1967).

[75] *Lin, T. M., Alphin, R. S., Henderson, F. G., Chen, K. K.:* 3-β-Aminoethyl — 1, 2, 4-Triazole, a Potent Stimulant of Gastric Secretion. J. Pharmacol. Exp. Therap. **134**, 88—94 (1961).

[76] *MacIntyre, I., Boss, S., Troughton, V. A.:* Parathyroid Hormone and Magnesium Homeostasis. Nature (Lond.) **198**, 1058—1060 (1963).

[77] *MacIntyre, I.:* Magnesium Metabolism. Advances in Int. Med. **13**, 143—154 (1967).

[78] *MacIntyre, I., Robinson, C. J.:* Magnesium and the Gut: Experimental and Clinical Observations. Ann. N. Y. Acad. Sci. **162**, 865—873 (1969).

[79] *Magee, D. F.:* An Investigation into the External Secretion of the Pancreas in Sheep. J. Physiol. (Lond.) **158**, 132—143 (1961).

[80] *Marcus, C. S., Wasserman, R. H.:* Ca and Mg Levels in Gastrointestinal Mucosa of Fed, Fasted and Lactose-Treated Rats. J. Appl. Physiol. **21**, 1063—1067 (1966).

[81] *Mayo, H. W., Duggan, J. J.:* Postcolectomy Enteritis. Ann. Surg. **157**, 92—96 (1963).

[82] *McCance, R. Z., Widdowson, E. M., Lehmann, H.:* Effect of Protein Intake on Absorption of Calcium and Magnesium. Biochem. J. **36**, 686—691 (1942).

[83] *McHargue, J. S., Roy, W. R.:* Effect of Ultraviolet Irradiation on Magnesium Content of Rats Receiving Reflekted Sunlight and Uniform Stock Ration. Amer. J. Physiol. **92**, 651—655 (1930).

[84] *Meintzer, R. B., Steenbock, H.:* Vitamin D and Magnesium Absorption. J. Nutr. **56**, 285—294 (1955).

[85] *Miller, E. R., Ullrey, D. E., Zutaut, D. L., Hoefer, J. A., Luecke, R. W.:* Mineral Balance Studies with the Baby Pig: Effects of Dietary Vitamin D_2 Level Upon Calcium, Phosphorus and Magnesium Balance. J. Nutr. **85**, 255—259 (1965).

[86] *Miller, D. L., Schedl, H. P.:* Effects of Diabetes on Intestinal Magnesium Absorption in the Rat. Amer. J. Physiol. **231**, 1039—1042 (1976).

[87] *Moore, W. F., Fontenot, J. P., Webb, K. E., Jr.:* Effect of Form and Level of Nitrogen on Magnesium Utilization. J. Anim. Sci. **35**, 1046—1053 (1972).

[88] *Morehead Jr., R. M., Kessner, D. M.:* Effects of Mg Deficiency and Parathyroidectomy on Gastrointestinal Ca Transport in the Rat. Amer. J. Physiol. **217**, 1608—1613 (1969).

[89] *Mraz, F. R.:* Intestinal Absorption of ^{45}Ca and ^{89}Sr as Affected by Ca, Sr and Mg. Poultry Science **52**, 1208—1209 (1973).

[90] *Murakami, D., Naito, Y., Sato, K.:* Studies on Grass Tetany in Cattle. I. Studies of Grass-Tetany in the Sotoyama Pasture. Jap. J. Vet. Sci. **34**, 323—330 (1972).

[91] *Murdoch, J. A., Heaton, F. F.:* Subcellular Distribution of Metals (Sodium, Potassium, Calcium and Magnesium) in Rat Liver, Kidney and Intestinal Mucosa. Comp. Biochem. Physiol. **26**, 121—128 (1968).

[92] *Nakahata, N.:* Magnesium Dependent Contraction of Glycerinated Smooth Muscle. Pflügers Arch. **382**, 133—136 (1979).

[93] *Neuwirth, I., Wallace, G. B.:* On Use of Magnesium as an Aid in Anesthesia. J. Pharmacol. Exp. Ther. **35**, 171—175 (1929).

[94] *Newton, G. L., Fontenot, J. P., Tucker, R. E.:* Effects of High Dietary Potassium Intake on the Magnesium Metabolism by Sheep. J. Anim. Sci. **35**, 440—443 (1972).

[95] *Nichini, F., Tansy, M. F., Kendall, F. M.:* Serum Magnesium Fall in Radiation Induced Gastrointestinal Symptomatology. Radiology **108**, 413—415 (1973).

[96] *Nordio, S., Donath, A., Macagno, F., Gatti, R.:* Chronic Hypomagnesemia with Magnesium-Dependent Hypocalcemia I. A New Syndrome with Intestinal Magnesium Malabsorption. Acta. Paediat. Scand. **60**, 441—448 (1971).

[97] —, —, —, —: Chronic Hypomagnesemia with Magnesium-Dependent Hypocalcemia. II. A Study of the Relationship Between Magnesium, Calcium and Strontium. Acta Paediat. Scand. **60**, 449—455 (1971).

[98] *Northup, D. W., Vanliere, E. J.:* Effect of Anoxemia on Absorption of Magnesium Sulphate from Small Intestine. Arch. Internat. Pharmaco. et de Therap. **62**, 175—178 (1939).

[99] *Nunn, Jr., A. S., Ellert, M. S.:* An Effect of Penetrating Ions on Magnesium Efflux from Rat Small Intestine *In Vitro*. Biochem. Biophys. Acta **135**, 973—978 (1967).

[100] *O'Dell, B. L., Morris, E. R., Pickett, E. E., Hogan, A. G.:* Diet Composition and Mineral Balance in Guinea Pigs. J. Nutr. **63**, 65—77 (1957).

[101] *O'Dell, B. L., Morris, E. R., Regan, W. O.:* Magnesium Requirements of Guinea Pigs and Rats. Effects of Calcium and Phosphorous and Symptoms of Magnesium Deficiency. J. Nutr. **70**, 103—110 (1960).

[102] *Outhouse, J., Smith, J., Twomey, I.:* Relative Effects of Certain Saccharides and Vitamin D as Mineral Metabolism of Rats. J. Nutr. **15**, 257—268 (1938).

[103] *Perry, S. C., Cragle, R. G., Miller, J. K.:* Effect of Ration Upon the Intestinal Distribution of Ca, Mg. Na, K. and N in Calves. J. Nutr. **93**, 283—290 (1967).

[104] *Phillipson, A. T., Storry, J. E.:* The Absorption of Calcium and Magnesium From the Rumen and Small Intestine of the Sheep. J. Physiol. (Lond.) **181**, 130—149 (1965).

[105] *Pleshchitser (Gor'kii) A. la.:* Biological Role of Magnesium. Clin. Chem. **4**, 429—450 (1968).

[106] *Puscas, I., Nadaban, F., Voicu, L., Lerintiu, A., Kovacs, T., Blaj, St., Turi, Z., Orban, I.:* Magnesium and Gastric Acid Secretion. Acta Hepato-Gastroenterol. **24**, 33—37 (1977).

[107] *Rasmussen, H., Ogata, E.:* Parathyroid Hormone and the Reaction of Mitochondria to Cations. Biochemistry 5, 733—745 (1966).
[108] *Rector, J. M.:* Synergistic Analgesia, Clinical Observations. Amer. J. Surg. **36**, 114—119 (1922).
[109] *Reddy, B. S., Pleasants, J. R., Wostmann, B. S.:* Effect of Intestinal Microflora on Calcium, Phosphorus and Magnesium Metabolism in Rats. J. Nutr. 99, 353—362 (1969).
[110] *Reddy, B. S.:* Calcium and Magnesium Absorption: Role of Intestinal Microflora. Federation Proc. **30**, 1815 (1971).
[111] —*:* Studies on the Mechanism of Calcium and Magnesium Absorption in Germ Free Rats. Arch. Biochem. Biophys. 149, 15—21 (1972).
[112] *Romer, A. S.:* The Vertebrate Body. 3rd ed. W. B. Saunders Co., Philadelphia, p. 1—475 (1962).
[113] *Rook, J. A. P., Balch, C. C., Line, C.:* Magnesium Metabolism in the Dairy Cow. I. Metabolism on Stall Rations. J. Agr. Sci. **51**, 189—198 (1958).
[114] *Rook, J. A. F.:* Production Disease in Farm Animals. *Payne, J. M., Hibbitt, K. G., Sansom, B. F.* (eds.). Bailliere Tindall, London p. 14 (1972).
[115] *Ross, D. B.:* In Vitro Studies on the Transport of Magnesium Across the Intestinal Wall of the Rat. J. Physiol. (Lond.) **160**, 417—428 (1962).
[116] *Ross, D. B., Care, A. D.:* The Movement of $^{28}Mg^{2+}$ Across the Cell Wall of Guinea-Pig Small Intestine *In Vitro*. Biochem. J. **82**, 21P (1962).
[117] *Schacter, D., Rosen, S. M.:* Active Transport of ^{45}Ca by the Small Intestine and its Dependence on Vitamin D. Amer. J. Physiol. **196**, 357—362 (1959).
[118] *Scheiner, E., Shils, M. E., Vanamee, P.:* Malabsorption Following Massive Intestinal Resection. Am. J. Clin. Nutrition **17**, 64—72 (1965).
[119] *Schroeder, H. A., Nason, A. P., Tipton, I. H.:* Essential Metals in Man. Magnesium. J. chron. Dis. **21**, 815—841 (1969).
[120] *Schwartz, M., Kashiwa, H. K., Jacobson, A., Rehm, W. S.:* Concentration and Localization of Calcium in Frog Gastric Mucosa. Am. J. Physiol. **212**, 241-246 (1967).
[121] *Scott, E. M., Verney, E. L., Morissey, P. D.:* Self Selection of Diet, Appetites for Sodium, Chloride and Sodium Chloride, J. Nutr. **41**, 187—201 (1950).
[122] *Scott, D.:* Factors Influencing the Secretion and Absorption of Calcium and Magnesium in the Small Intestine of the Sheep. Quart. J. Exp. Med. **50**, 312—329 (1965).
[123] *Sjollema, B., Seekles, L.:* Over de Stoornissen Derminerale Stofwisseling by Kalf-en kopziekte. Tijdschr. Diergeneesk. **56**, 979—982 (1929).
[124] *Sjollema, B.:* Nutritional and Metabolic Disorders in Cattle. Nutr. Abst. Rev. **1**, 621—632 (1932).
[125] *Smith, R. H.:* Calcium and Magnesium Metabolism in Calves: Plasma Levels and Retention in Milk-Fed Calves. Biochem. J. **67**, 472—481 (1957).
[126] —*:* Calcium and Magnesium Metabolism in Calves. 2. Effect of Dietary Vitamin D and Ultraviolet Irradiation on Milk-Fed Calves. Biochem. J. **70**, 201—205 (1958).
[127] —*:* Calcium and Metabolism in Calves. 3. Endogenous Faecal Excretion and Absorption of Magnesium. Biochem. J. **71**, 306—311 (1959).
[128] —*:* The Exchange of Certain Inorganic Ions and Water in the Alimentary Tract of the Milk-Fed Calf. Biochem. J. **83**, 151—163 (1962).
[129] —*:* Small Intestine Transit Time and Magnesium Absorption in the Calf. Nature (Lond.) **1968**, 161—162 (1963).
[130] —*:* Passage of Digesta Through the Calf Abomasum and Small Intestine. J. Physiol. (Lond.) **172**, 305—320 (1964).
[131] *Solounias, B. M., Schwartz, R.:* The Effect of Magnesium Deficiency on Serum Aldosterone in Rats Fed Two Levels of Sodium. Life Sci. **17**, 1211—1218 (1976).
[132] *Starling, E. H.:* Principles of Human Physiology. 12th ed. *Lovatt Evans, Sir. C.* (ed). Lea and Febiger, Philadelphia, p. 1—1233 (1956).
[133] *Stewart, J., Moodie, E. W.:* The Absorption of Magnesium From the Alimentary Tract of Sheep. J. Comp. Path. **66**, 10—21 (1956).
[134] *Stillings, B. R., Bratzler, J. W., Marriott, L. F., Miller, R. C.:* Utilization of Magnesium and Other Minerals by Ruminants Consuming Low and High Nitrogen-Containing Forages and Vitamin D. J. Anim. Sci. **23**, 1148—1151 (1964).
[135] *Storry, J. E.:* Studies on Calcium and Magnesium in the Ruminant in Relation to the Aetiology of Grass Tetany, Ph. D. Thesis, University of Aberdeen (1960).
[136] *Tansy, M. F., Nichini, F. M., Baker, H. W., Chryzanowski, J.:* Association of Low Serum Magnesium Concentrations with Severity of Gastrointestinal Symptomatology in the Irradiated Patient. J. Surg. Res. **11**, 213—216 (1971).
[137] *Tansy, M. F.:* Intestinal Absorption of Magnesium. In: *Skoryna, S. C., Waldron-Edward, D.* (eds). Intestinal Absorption of Metal Ions and Radionuclides. Pergamon Press, New York, p. 193—210 (1971).
[138] *Tansy, M. F., Kendall, F. M., Nichini, F. M.:* Role of Magnesium in the Acute Intestinal Radiation Death in the Rat. Journal of International Research Communications, November (1973).
[139] *Tansy, M. F., Friedman, M. H. F.:* Hypophysectomy-Induced Inhibition of Augmented Acetylcholine Responses of the Rat Bowel Following Adrenalectomy and/or Whole Body Irradiation. Rad. and Environm. Biophys. **16**, 101—106 (1979).
[140] *Tansy, M. F., Landin, W. E., Salkin, L.:* Alterations in Gastrointestinal Function in the Magnesium-Deficient Rat. In: *Cantin, M., Seelig, M. S.* (eds). Magnesium in Health and Disease. Spectrum Publications Inc., New York—London, p. 137—143 (1980).
[141] *Taylor, W. F., Winter, J. E.:* Studies in Absorption and Excretion of Magnesium. J. Pharmacol. Exp. Ther. **35**, 435—439 (1929).
[142] *Terkildsen, T.:* Effect of Physostigmine, Neostigmine and Acetylcholine on Serum Magnesium Concentration. Chr. Acta. Pharmacol. et Toxicol. **8**, 385—390 (1952).
[143] *Texter, E. C., Laureta, H. C., Chou, C. C.:* Vascular Factors in Metal Ion Absorption. In: *Skoryna, S. C., Waldron-Edward, D.* (eds). Pergamon Press, New York, p. 383—394 (1971).
[144] *Thorén, L.:* Magnesium Metabolism. Progr. Surg. **9**, 131—156 (1971).
[145] *Tidball, C. S.:* Magnesium and Calcium as Regulators of Intestinal Permeability. Amer. J. Physiol. **206**, 243—246 (1964).
[146] *Urban, E., Schedl, H. P.:* Net Movements of Magnesium and Calcium in the Rat Small Intestine *In Vivo*. Proc. Soc. Exp. Biol. Med. **132**, 1110—1113 (1969).
[147] *Vallee, B. L., Wacker, W. E. C., Ulmer, D. D.:* The Magnesium-Deficiency Tetany Syndrome in Man. New Eng. J. Med. **262**, 155—161 (1960).
[148] *Vanliere, E. J., Northup, D. W., Stickney, J. C., Richard, R. E.:* Effect of Anemic Anoxia on Absorption of Isotonic Magnesium Sulfate From Small Intestine. Proc. Soc. Exp. Biol. Med. **64**, 62—64 (1947).
[149] *Wacker, W. E. C., Vallee, B. L.:* The Magnesium Deficiency Tetany Syndrome in Man. Borden's Review of Nutrition Research **22**, 51—71 (1961).
[150] *Wacker, W. E. C., Parisi, A. F.:* Magnesium Metabolism. New Eng. J. Med. **278**, 658—663 (1968).
[151] —, —*:* Magnesium Metabolism. New Eng. J. Med. **278**, 712—717 (1968).

[152] —, —: Magnesium Metabolism. New Eng. J. Med. **278**, 772—776 (1968).
[153] *Wasserman, R. H., Comar, C. L.:* Carbohydrates and Gastrointestinal Absorption of Radiostrontium and Radiocalcium in the Rat. Proc. Soc. Exp. Biol. Med. **101**, 314—317 (1959).
[154] *Wasserman, R. H.:* Studies on Vitamin D_3 and the Intestinal Absorption of Calcium and Other Ions in the Rachitic Chick. J. Nutr. **77**, 69—80 (1962).
[155] *Winter, J. E., Richey, C. H.:* Human Absorption of Magnesium With and Without Aspirin and Other Adjuvants. J. Pharmacol. Exp. Ther. **42**, 179—183 (1931).
[156] —; —: Magnesium Absorption in Dogs. J. Pharmacol. Exp. Ther. **41**, 245—254 (1931).
[157] *Wiseman, G.:* Absorption From the Intestine. Academic Press, New York, p. 1—564 (1964).