PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 176, 8–13 (1984)

# Magnesium Sulfate-Induced Water Secretion in Hamster Small Intestine[1] (41834)

MARK REICHELDERFER,[2] BARBARA PERO, VILJA LORENZSONN, AND WARD A. OLSEN

*Gastroenterology Research Laboratory, William S. Middleton Memorial Veterans Hospital, 2500 Overlook Terrace, Madison, Wisconsin 53705, and Department of Medicine, Center for Health Sciences, University of Wisconsin, Madison, Wisconsin 53706*

*Abstract.* We studied possible mechanisms of magnesium sulfate ($MgSO_4$)-induced diarrhea. *In vivo* perfusion of hamster small intestine with an isotonic electrolyte solution containing 50 m*M* $MgSO_4$ produced nearly three times as much fluid secretion as did a solution containing an equiosmotic amount of mannitol. We found that magnesium was absorbed at a faster rate than mannitol under these conditions, suggesting that differences in solute permeability do not explain the differences in secretory rates. Magnesium ion rather than sulfate appeared largely responsible for the effect as replacement of sulfate with chloride did not diminish the response. $MgSO_4$ perfusion of a proximal intestinal segment did not affect water transport in an isolated distal segment suggesting that release of cholecystokinin or alterations in serum levels of other hormones were not responsible. Intestinal permeability, morphology, and cyclic nucleotide levels were normal after $MgSO_4$ perfusion. Thus, $MgSO_4$-induced diarrhea cannot be explained by the usual mechanisms, and additional processes responsible for intestinal secretion must exist.

Magnesium salts have been widely used as cathartics since the early 17th century when the $MgSO_4$-rich water from a spring in Epsom, England was found to have a laxative effect (1). The mechanism of action of $MgSO_4$ is uncertain. Because magnesium is poorly absorbed, these compounds have been assumed to be osmotic cathartics (2, 3). Recent work, however, suggests that magnesium-induced intestinal secretion may not be accounted for solely by osmotic forces (4). In fact, decreased water and sodium absorption in rat jejunum has been reported as a consequence of elevated magnesium concentrations in blood (5). The purpose of our work, therefore, was to reexamine the role of osmotic forces in the effect and to also study some of the more recent suggestions that the secretory effect is mediated by release of cholecystokinin (CCK) (6), or changes in the serum levels of parathormone or calcitonin (5). We also examined other possible mechanisms including altered cyclic nucleotide metabolism and mucosal damage.

**Methods.** We studied male Syrian golden hamsters (Sprague–Dawley, Madison, Wisc.) weighing 100 to 150 g, using a modification of an *in vivo* perfusion technique (7). Nonfasting animals were anesthetized with 100 mg/kg of intraperitoneal pentobarbital sodium, and the abdomen opened in the midline. The small bowel was rinsed with warm saline and cannulated with polyethylene tubing distal to the hepaticopancreatic pedicle and proximal to the ileocecal junction. Solutions contained 20 $\mu$Ci/l of [$^{14}$C]polyethylene glycol, (PEG, mol wt 4000, sp act 0.5 $\mu$Ci/mg, New England, Boston, Mass.) as a nonabsorbable marker of net water flux (8), and were infused at 0.7 to 0.8 ml/min with a peristaltic perfusion pump (Polystaltic Model 2-6100, Buchler Instruments, Fort Lee, N.J.). The solutions were maintained at 38°C in a water bath and the animals kept warm with an overhead lamp. Experimental and control animals were perfused simultaneously.

The test solutions contained $MgSO_4$ at 12.5, 25, and 50 m*M* concentrations with corresponding control solutions containing mannitol at 15, 30, and 60 m*M* (11, 10, and 10 animals in each group at each comparison level, respectively). At each concentration level, $MgSO_4$ and mannitol contributed equal numbers of osmotic particles as measured by freezing point depression (osmometer model

[1] This study was supported by NIH grant AM 13927 and the Veterans Administration.

[2] To whom reprint requests should be addressed at William S. Middleton Memorial Veterans Hospital.



0037-9727/84 $1.50

3D, Advanced Instruments, Inc., Needham Heights, Mass.). Additional perfusions with 120 and 200 m*M* mannitol were also carried out (10 and 8 animals, respectively) to evaluate the effects of high concentrations of poorly absorbed solute. We also compared $MgSO_4$ with $MgCl_2$ at 50 m*M* concentrations to determine whether the magnesium or the sulfate ion was most important in eliciting secretion. In addition to $MgSO_4$ or mannitol, the solutions contained KCl and $NaHCO_3$ at 4 and 12 m*M* concentrations, respectively. Osmolality was adjusted to between 285 and 290 mOsm/kg by addition of NaCl. The pH of all solutions was adjusted to between 7.85 and 7.95 to allow us to compare our results with previous studies from our laboratory (7).

It should be emphasized that the design of these experiments allowed us to compare the effects of $MgSO_4$ with those of another relatively impermeant substance, mannitol, at concentrations chosen to provide similar osmotic loads of poorly absorbed solute. Measured total osmolality ($MgSO_4$ or mannitol plus the other solutes) was also similar between test and control solutions. In order to maintain a physiological osmolality we reduced the sodium concentration of our solutions as we increased the concentration of poorly absorbed solute (for example, the solutions containing the highest concentrations of $MgSO_4$ or mannitol had a sodium concentration of 107 m*M*). It is important to point out that the sodium concentrations of the mannitol and $MgSO_4$ solutions were identical for each comparison as shown in Table I.

Preliminary experiments indicated that a steady state of fluid movement was reached within the first 30 min of perfusion; consequently perfusates were collected from the distal cannula during each of the next two 20-min periods. Additional pentobarbital was given as needed through the perfusion period to maintain anesthesia. At the end of the perfusion, the animals were sacrificed, and the perfused segments removed and dried to constant weight at 100°C. Perfusion collections were centrifuged at 1000*g* for 10 min to remove debris. Two-hundred-microliter aliquots of supernatants and infusion solutions were then mixed with 15 ml of Aquasol (New England Nuclear), and radioactivity measured with a liquid scintillation spectrometer (Tri-Carb 3300, Packard Instruments, Downers Grove, Ill.) with an efficiency of 65–80%. Counts were converted to disintegrations per minute (dpm) by means of an automatic external standard and a card programmable calculator (Model 1266, Monroe Instruments, Orange, N.J.).

TABLE I. CONCENTRATIONS OF $MgSO_4$, MANNITOL, NaCl, AND TOTAL SOLUTE IN SOLUTIONS[a]

| $MgSO_4$ solutions | | | Mannitol solutions | | |
|---|---|---|---|---|---|
| $MgSO_4$ (m*M*) | NaCl (m*M*) | Osmolality (mOsm/K) | Mannitol (m*M*) | NaCl (m*M*) | Osmolality (mOsm/K) |
| 12.5 | 129 | 289 | 15 | 129 | 292 |
| 25 | 122 | 289 | 30 | 122 | 289 |
| 50 | 107 | 288 | 60 | 107 | 291 |

[a] All solutions contained KCl 4 m*M* and $NaHCO_3$ 12 m*M*.

Water transport for each of the two 20-min collection periods was calculated, averaged, and expressed per gram of dry tissue weight. The following formula was used: Net flux = perfusion rate $(1 - [PEG]_i/[PEG]_0)$ where $[PEG]_i$ and $[PEG]_0$ are $^{14}C$ concentrations in the infusion solutions and perfusion collections, respectively. Positive values indicate absorption and negative values secretion.

Magnesium and mannitol absorption from 50 and 60 m*M* solutions, respectively, was measured in two 20- to 25-min collection periods as the ratio of amount infused to amount recovered. The two results were averaged and expressed as percentage recovered. Magnesium concentrations were measured by atomic absorption spectrometry (Model 372, Perkin-Elmer Corporation, Norwalk, Conn.) and mannitol as DPMs of $^{14}C$ with inclusion of 20 $\mu$Ci [$^{14}C$]mannitol (sp act 45 mCi/mmole, New England Nuclear). The latter experiments did not include [$^{14}C$]PEG, and the isotope was counted as described above.

*Split gut perfusions.* $MgSO_4$-induced release of a gastrointestinal hormone such as CCK (6) which has secretory properties is an attractive possible mechanism of action of magnesium cathartics. Since in most species CCK cells are found in highest concentration in the proximal intestine (9, 10), we studied the effects of $MgSO_4$ perfusions of proximal intestine on the rates of fluid absorption in the distal bowel using a split gut preparation. We

divided the entire small intestine into two segments which were perfused simultaneously at 0.7 to 0.9 ml/min. The first segment included the duodenum and proximal one-third of the rest of the small intestine and was perfused with either the 50 m*M* $MgSO_4$ solution or a control solution consisting of 137 m*M* NaCl, 4 m*M* KCl, and 12 m*M* $NaHCO_3$. Osmolality and pH of the solutions were adjusted as described above. The distal segment, consisting of the remaining small intestine, was perfused with the control solution containing 20 $\mu$Ci/l of [$^{14}$C]PEG. After steady-state conditions were reached, 20-min collections of distal segment perfusate were treated as above and rates of net water transport calculated.

*Intestinal permeability.* Permeability was assessed by measuring intestinal clearance of intravenously administered inulin as previously described (7). We injected 25 $\mu$Ci of [$^{14}$C]inulin (mol wt 6000, sp act 1.9 $\mu$Ci/mg, New England Nuclear) into the inferior vena cava of hamsters with subsequent ligation of both renal pedicles. The small intestine was then perfused with the 50 m*M* $MgSO_4$ or 60 m*M* mannitol solutions (omitting [$^{14}$C]PEG). After a 30-min equilibration period, four 15-min collections were made since previous experiments had demonstrated constant plasma concentrations of the isotope from 20 to 90 min after injection. Twenty-microliter aliquots of plasma and 200-$\mu$l aliquots of collected samples were mixed with 150 $\mu$l of Soluene TM 100 (Packard Instruments Co., Inc.) and the isotope counted as above. Clearance was calculated as follows: Clearance = $(VC)/P$ where $V$ is collection volume, $C$ is $^{14}$C concentration in collected sample and $P$ is $^{14}$C concentration in plasma. Mean clearance of the four collections was calculated and expressed per gram dry tissue weight.

*Morphology.* We used lanthanum permeability and binding as a means of assessing mucosal damage in previous studies of the effects of bile salts and fatty acids on hamster small intestine (7, 11). We therefore perfused the small intestine with lanthanum hydroxide after 60 min of perfusion with either 50 m*M* $MgSO_4$ or 60 m*M* mannitol and prepared the tissue for light and electron microscopy as described previously (7, 11).

*Cyclic nucleotides.* To measure the effect of $MgSO_4$ on mucosal cyclic AMP levels we perfused the animals for 60 min with either the 50 m*M* $MgSO_4$ or the 60 m*M* mannitol solution. The intestine was then quickly removed and rinsed in ice cold 0.05 *M* Tris buffer, pH 7.5, containing 8 m*M* theophylline. The gut was everted over a glass rod, rinsed again with buffer, and scraped with a glass slide over ice. The scrapings were weighed and deproteinized as follows. Boiling 0.05 *M* potassium phosphate buffer, pH 7.5, containing 8 m*M* theophylline was added to the scrapings (approximately 1 ml/150 mg) and the mixture boiled for 10 min, homogenized with a Polytron homogenizer (Brinkman Instruments, Inc., Westbury, N.Y.) at setting No. 4 for 10 sec and then 15 sec, and centrifuged at 2000*g* for 20 min at 4°C. The pellet was assayed for total protein content (12) and the supernatant stored at −20°C. The supernatant was subsequently thawed, centrifuged again at 2000*g* for 10 min, and assayed for cyclic AMP by a competitive binding method (13, 14) using an assay kit (Amersham, Arlington Heights, Ill.). The results were expressed as picomoles per milligram of mucosal protein. Total elapsed time between removal of intestine to addition of boiling buffer did not exceed 60 sec.

To determine effects on cyclic GMP levels, we perfused animals and prepared mucosal scrapings as described for the cyclic AMP studies. The scrapings were then frozen with liquid nitrogen and weighed. Total elapsed time to freezing was less than 60 sec. Ice-cold 6% trichloracetic acid was then added at 1 ml/100 mg of tissue, and the mixture homogenized at 4°C as above. The mixture was then divided into two aliquots. To the second aliquot we added 1.5 pmole of cGMP/0.3 ml of assay sample as an internal standard. Each aliquot was then centrifuged at 4°C at 2000*g* for 15 min. The pellet was assayed for total protein content (12). The supernatant was extracted with ether and evaporated to dryness under a stream of nitrogen at 70°C in a warm water bath. The residue was redissolved in 1.6 m*M* sodium acetate buffer and frozen at −20°C. The supernatant was subsequently thawed and centrifuged at 2000*g* for 10 min before measurement of cGMP by a competitive binding technique (15, 16) using a kit from Becton Dickinson, Orangeburg, New York. The percentage recovery was calculated by dividing the differences of the resulting amounts of cGMP by the known amount (1.5 pmole) added to the second aliquot. Mucosal

cGMP was then determined by dividing by the percentage recovery and expressed as picomoles per milligram of mucosal protein.

**Results.** We found a dose related increase in water secretion with both $MgSO_4$ and mannitol as shown in Fig 1. At the lowest concentrations studied, mean net water fluxes were similar, approximating 0. Higher concentrations resulted in increasing fluid secretion, particularly with $MgSO_4$; a 50 m*M* $MgSO_4$ solution produced nearly three times the rate of secretion of the equivalent mannitol solution. These results confirm the observation that $MgSO_4$-induced secretion is not simply related to the presence of a poorly absorbed solute. In fact, as the figure shows, the secretion induced by very high concentrations of mannitol (120 and 200 m*M*) did not approach that seen with 50 m*M* $MgSO_4$. We also considered the possibility that the effective osmotic pressure of $MgSO_4$ might be greater than mannitol because the intestine might be less permeable to $MgSO_4$; thus, the effect of $MgSO_4$ would be greater even though measured osmolality was the same. Our results suggest, however, that permeability to $MgSO_4$ is less, not greater, than to mannitol: we found that 12.5 ± 1.4% (SEM) of Mg was absorbed as compared to 7.0 ± 1.0% of mannitol (eight perfusions each), $P < 0.01$.

The magnesium rather than the sulfate ion appears largely responsible for the secretory effect. We found no significant difference in secretory rates between 50 m*M* $MgSO_4$ and 50 m*M* $MgCl_2$ (129 ± 17 (SEM) ml/min/g dry wt × $10^3$ in eight perfusions compared to 212 ± 49 in nine experiments, respectively).

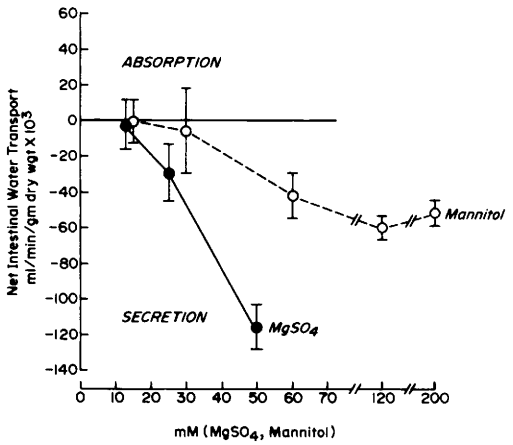


FIG. 1. Effects of $MgSO_4$ and mannitol on intestinal water transport. $MgSO_4$ resulted in a statistically significant increase in fluid secretion as compared to the mannitol control at the 50 m*M* concentration ($P < 0.001$), but the differences at the lower concentrations were not significantly different. Means ± SEM are shown.

TABLE II. EFFECT OF $MgSO_4$ ON MUCOSAL CYCLIC NUCLEOTIDE CONCENTRATIONS[a]

| | Cyclic AMP[b] | Cyclic GMP[b] |
|---|---|---|
| 50 m*M* $MgSO_4$ | 4.93 ± 0.62 (7) | 4.43 ± 1.19 (11) |
| 60 m*M* Mannitol | 4.30 ± 0.29 (6) | 2.80 ± 0.41 (10) |

[a] Mean ± SEM are shown. Number of animals are given in parentheses.
[b] Expressed as picomoles/mg of mucosal protein.

We found that fluid absorption from distal bowel was not affected by perfusion of the proximal segment with $MgSO_4$. Mean distal absorption was 30 ± 17 (SEM) ml/min/g dry wt × $10^3$ for 12 proximal $MgSO_4$ perfusions and 44.1 ± 11 for 12 proximal electrolyte solution perfusions.

Fifty-millimolar $MgSO_4$ did not increase mucosal levels of either cAMP or cGMP in comparison to mannitol perfusion (Table II) and did not significantly alter inulin clearance (Table III). Previously reported effects of sodium ricinoleate on inulin clearance are shown for comparative purposes (7); we used an 8 m*M* concentration of fatty acid because it resulted in comparable rates of fluid secretion. Intestinal villi were morphologically intact on both light and electron microscopy, although intercellular spaces in the distal one-half of villi appeared more dilated after $MgSO_4$. Lanthanum binding was similar after $MgSO_4$ and mannitol perfusions and did not differ from our findings after saline perfusions (11).

**Discussion.** We chose concentrations of $MgSO_4$ that are likely to be found after therapeutic doses of the agent: for example, the relatively low dose of 5 g of $MgSO_4 \cdot 7H_2O$ in 200 ml of water is 101 m*M* in concentration. We found that concentrations much less than that produced significantly more water secretion than did equiosmotic mannitol, suggesting that the secretory effects of $MgSO_4$ are not explained by its osmotic activity alone. Furthermore, the differences between $MgSO_4$ and mannitol do not appear to be explainable by differences in intestinal permeability to the

TABLE III. EFFECT OF $MgSO_4$ ON CLEARANCE OF INULIN[a]

| | 50 m*M* $MgSO_4$ | 60 m*M* Mannitol | Saline[c] | 8 m*M* Na ricinoleate[c] |
|---|---|---|---|---|
| Inulin clearance[b] | 4.1 ± 1.5 (3) | 2.0 ± 0.2 (4) | 2.9 ± 0.5 (10) | 35.9 ± 8.6 (5) |

[a] Mean ± SEM are shown. Number of animals are given in parentheses.
[b] Expressed as μl/min/g dry weight.
[c] Data reported previously (7).

two substances. If the reflection coefficient for $MgSO_4$ were higher than for mannitol (i.e., $MgSO_4$ less permeable), more fluid would be secreted in response to $MgSO_4$ even if osmotic concentrations as measured by freezing-point depression were identical because the *effective* osmotic pressure of $MgSO_4$ would be higher (17). Our finding of minimal absorption of mannitol is consistent with previous reports that it is close to an impermeate solute with theoretical and effective osmotic pressures equal in human intestine, i.e., a reflection coefficient of 1.0 (17, 18). $MgSO_4$ is unlikely therefore to be less permeate than mannitol, and, in fact, our study demonstrates that it is more readily absorbed. Our perfusion results with high mannitol concentrations also support our belief that the osmotic pressure of $MgSO_4$ does not explain the secretory response. Even a 30-fold increase in mannitol concentration did not result in secretion at anywhere near the rate found with 50 m*M* $MgSO_4$. In fact, it did not significantly increase the rate over that found with 60 m*M* mannitol suggesting that maximal osmotic responses were achieved at the latter concentration.

Our studies also exclude the possibility that $MgSO_4$-induced secretion is the result of a sodium diffusion gradient as others have suggested (19). The suggestion was that the lower intraluminal sodium concentration, the result of replacement of NaCl by $MgSO_4$, might lead to movement of NaCl (and water) into the lumen. Since sodium concentrations were identical between each $MgSO_4$ solution and the corresponding mannitol solution, that suggestion is untenable.

Our study also demonstrates that the secretory effect of $MgSO_4$ is largely related to the magnesium ion rather than the poorly absorbed sulfate ion since $MgCl_2$ resulted in a response at least as great we found with $MgSO_4$. This finding is, of course, consistent with the notion that osmotic factors are unimportant in the effect, although it is at variance with a study in man where $MgSO_4$ was found to produce more secretion than $MgCl_2$ (19). We do not know the reason for the discrepancy between the two studies.

We explored several other possible mechanisms that might mediate magnesium-induced intestinal secretion. Our first thought was that intraluminal magnesium might release a duodenal hormone, especially CCK, into the circulation (20). Since CCK in pharmacologic doses, at least, affects intestinal fluid transport (21, 22), CCK or some other hormone might mediate the magnesium effect (6). A related hypothesis is that the fluid secretion is mediated by either an increase in serum calcitonin or a decrease in parathormone from magnesium absorption (6). We tested these hypotheses by dividing the small intestine into two isolated segments; if either were correct, proximal magnesium perfusion would have been expected to alter fluid transport in the isolated distal segment, but it did not. These results are consistent with those reported by others. Studies in man have shown that magnesium is a relatively weak stimulus to CCK release (19, 23) and studies in dogs have shown that stimulation of CCK release by a potent stimulant (sodium ricinoleate) does not affect fluid transport in a second isolated intestinal loop (24). It is conceivable, of course, that $MgSO_4$ stimulates release of a hormone from the ileum rather than from the proximal intestine or that a secretory effect of a hormone might be observable only in the jejunum. If either possibility were correct, we would not have detected it in our experiment, but both possibilities seem very unlikely.

We considered two other possibilities which might explain the $MgSO_4$ effect: intestinal mucosal damage (as appears related to the intestinal secretion found with fatty acids and bile salts (7, 11)) and altered levels of cyclic nucleotides (involved in the regulation of in-

testinal secretion (25–28)). We were unable to demonstrate significant changes by either light or electron microscopy, however, and mucosal levels of cyclic nucleotides did not change with $MgSO_4$. Thus our study has demonstrated that the mechanism of $MgSO_4$-induced secretion depends upon the presence of the magnesium but not the sulfate ion and is independent of both osmotic factors and the usual mediators of intestinal secretion.


1. Soper HW. The story of magnesium sulphate with special reference to its use in biliary drainage. Amer J Med Sci **169**:398–407, 1925.
2. Binder HJ, Donowitz M. A new look at laxative action. Gastroenterology **69**:1001–1005, 1975.
3. Donowitz M. Current concepts of laxative action: Mechanisms by which laxatives increase stool water. J Clin Gastroenterol **1**:77–84, 1979.
4. Wanitschke R, Ammon HV. Effects of magnesium sulfate on transit time and water transport in the human jejunum. Gastroenterology **70**:949, abstr, 1976.
5. DiBona GF, Swain LL. Effect of hypermagnesia on rat jejunal sodium and water transport. Amer J Physiol **231**:1771–1776, 1976.
6. Harvey RF, Read AE. Saline purgatives act by releasing cholecystokinin. Lancet **2**:185–187, 1973.
7. Cline WS, Lorenzsonn V, Benz L, Bass P, Olsen WA. The effects of sodium ricinoleate on small intestine function and structure. J Clin Invest **58**:380–390, 1976.
8. Miller DL, Schedl HP. Total recovery studies of nonabsorbable indicators in the rat small intestine. Gastroenterology **58**:40–46, 1970.
9. Polak JM, Bloom SR, Rayford PL, Pearse AGE, Buchan AMJ, Thompson JC. Identification of cholecystokinin-secreting cells. Lancet **2**:1016–1018, 1975.
10. Bryant MG, Bloom SR. Distribution of the gut hormones in the primate intestinal tract. Gut **20**:653–659, 1979.
11. Gullikson GW, Cline WS, Lorenzsonn V, Benz L, Olsen WA, Bass P. Effects of anionic surfactants on hamster small intestinal membrane structure and function: Relationship to surface activity. Gastroenterology **73**:501–511, 1977.
12. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem **193**:26–275, 1951.
13. Gilman AG. A protein binding assay for adenosine 3′,5′-monophosphate. Proc Natl Acad Sci USA **67**:305–312, 1970.
14. Brown BL, Albano JDM, Elkins RP, Sgherzi AM. A simple and sensitive saturation assay method for the measurement of adenosine 3′,5′-cyclic monophosphate. Biochem J **121**:561–562, 1971.
15. Steiner AL, Parker CW, Kipnis DM. Radioimmunoassay for cyclic nucleotides. I. Preparation of antibodies and iodinated cyclic nucleotides. J Biol Chem **247**:1106–1113, 1972.
16. Steiner AL, Pagliara AS, Chase LR, Kipnis DM. Radioimmunoassay for cyclic nucleotides. II. Adenosine 3′,5′-monophosphate in mammalian tissues and body fluids. J Biol Chem **247**:1114–1120, 1972.
17. Fordtran JS, Rector FC Jr, Ewton MF, Soter N, Kinney J. Permeability characteristics of the human small intestine. J Clin Invest **44**:1935–1944, 1965.
18. Soergel KH, Whalen GE, Harris JA. Passive movement of water and sodium across the human small intestinal mucosa. J Applied Phys **24**(1):40–48, 1968.
19. Malagelada JR, Holtermuller KH, McCall JT, Go VLW. Pancreatic, gallbladder, and intestinal responses to intraluminal magnesium salts in man. Amer J Dig Dis **23**:481–485, 1978.
20. Harvey RF, Dowsett L, Hartog M, Read AE. A radioimmunoassay for cholecystokinin-pancreozymin. Lancet **2**:826–828, 1973.
21. Moritz M, Finkelstein G, Meshkinpour H, Fingerut J, Lorber SH. Effect of secretin and cholescystokinin on the transport of electrolyte and water in human jejunum. Gastroenterology **64**:76–80, 1973.
22. Matuchansky C, Huet PM, Mary JY. Effects of cholecystokinin and metoclopramide on jejunal movements of water and electrolytes and on transit time of luminal fluid in man. Eur J Clin Invest **2**:169–175, 1972.
23. Malagelada JR, DiMagno EP, Summerskill WHJ, Go VLW. Regulation of pancreatic and gallbladder functions by intraluminal fatty acids and bile acids in man. J Clin Invest **58**:493–499, 1976.
24. Gadacz TR, Gaginella TS, Phillips SF. Inhibition of water absorption by ricinoleic acid: Evidence against hormonal mediation of the effect. Amer J Dig Dis **21**:859–862, 1976.
25. Kimberg DV. Cyclic nucleotides and their role in gastrointestinal secretion. Gastroenterology **67**:1023–1064, 1974.
26. Turnberg LA. Intestinal transport of salt and water. Clin Sci Mol Med **54**:337–348, 1978.
27. Hughes JM, Murad F, Chang B, Guerrant RL. Role of cyclic GMP in the action of heat-stable enterotoxin of *Escherichia coli.* Nature (London) **271**:755–756, 1978.
28. Field M, Graf LH Jr, Laird WJ, Smith PL. Heat-stable enterotoxin of *Escherichia coli,* in vitro effects on guanylate cyclase activity, cyclic GMP concentration, and ion transport in small intestine. Proc Natl Acad Sci USA **75**:2800–2804, 1978.


Received December 21, 1981. P.S.E.B.M. 1984, Vol. 176.
Accepted January 20, 1984.