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The Influence of Magnesium Sulphate on the Secretory Activity of the Digestive Glands

I. On the Gastric, Intestinal and Pancreatic Secretions

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THE INFLUENCE OF MAGNESIUM SULPHATE ON THE SECRETORY ACTIVITY OF THE DIGESTIVE GLANDS.

I. On the Gastric, Intestinal and Pancreatic Secretions.

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In our experiments with magnesium sulphate and the expulsion of bile into the duodenum we were unable to find references to the complete pharmacologic action of this salt on the gastrointestinal tract. The present treatise has to do with the action on the stomach, pancreatic and intestinal secretions, and in a second article we shall summarize our results with the influence of magnesium sulphate on the expulsion and secretion of bile.

1. **Stomach.** In three dogs ("Frant," "Snejok," "Riji"), having Pavlov stomach pouches,* we tried the effect of magnesium sulphate introduced through a gastric tube; and in a fourth dog ("Murzilka") which had both the Pavlov pouch and a gastric fistula we poured the solution directly in through the cannula. The first three dogs had been living in the laboratory for one or more years in good health after the operation, and had been used for other chronic experiments.

Twenty-five to 40 per cent aqueous solution was run in through the stomach tube in "Frant," "Snejok" and "Riji" and allowed to remain. In none of them did we obtain a definite acid secretion. In "Frant" in practically every case there was always within a few minutes nausea and vomiting of a bile-tinged or even a more concentrated biliary secretion mixed with the vomitus. The following is a typical protocol:

* For a complete description of the method of making the Pavlov miniature stomach or pouch, see Babkin (Die Äussere Sekretion der Verdauungsdrüsen, Berlin, 1928, p. 180).

TABLE I.—EFFECT OF INTRODUCTION OF MAGNESIUM SULPHATE, "SNEJOK," JUNE 17, 1925.

12:15—Experiment begun.
12:30—One drop from the little stomach (Pavlov pouch).
12:45—One drop.
12:46—50 cc. of 30 per cent magnesium sulphate solution introduced through the stomach tube.
1:00—0.0 cc. from the little stomach.
1:15—0.0 cc.
1:30—0.0 cc.
1:45—0.0 cc.

In control experiments with water introduced through the tube there was no vomiting and no acid secretion.

TABLE II.—CONTROL EXPERIMENT. "FRANT."

12:15—Brought on the stand.
12:30—0.4 cc. from the little stomach.
12:45—0.3 cc.
12:46—35 cc. of water introduced through the stomach tube.
1:00—0.0 cc.
1:15—0.1 cc.
1:30—0.0 cc.
1:45—0.3 cc.

The results of eleven experiments in "Frant," "Snejok" and "Riji" are given in Table III.

TABLE III.—EFFECT OF MAGNESIUM SULPHATE ON GASTRIC SECRETION FROM THE PAVLOV POUCH. AVERAGE OF ELEVEN EXPERIMENTS.

	Before magnesium sulphate, cc.	After magnesium sulphate, cc.
First fifteen minutes	0.15	0.16
Second fifteen minutes	0.13	0.14
Third fifteen minutes	0.10	0.21
Fourth fifteen minutes	0.12	0.10
Total, one hour	0.50	0.51

In "Murzilka" 25 to 80 cc. of a 25 to 35 per cent solution was put in through the gastric fistula, with the dog on its back, allowed to remain in for five minutes, and then drained out while the dog was placed in the supports; in some cases it was allowed to remain in. The collection was made from the little stomach.

TABLE IV.—"MURZILKA," JULY 8, 1927. LAST FEEDING YESTERDAY EVENING.

15:05—On stand; tube inserted; alkaline reaction; stomach washed with 150 cc. distilled water; returned clear; no nausea.
15:31—Alkaline reaction.
15:31–34—50 cc. of 30 per cent magnesium sulphate solution at room temperature introduced through the gastric fistula; 45 cc. was recovered; no retching, etc.
15:36—Alkaline reaction.

	From large stomach.	From stomach pouch.
15:46	12.0 cc.; strongly alkaline	0.2 cc.; alkaline.
16:01	6.0 cc.; alkaline	0.1 cc.; alkaline.
16:16	4.0 cc.; alkaline	0.6 cc.; neutral.
16:17	20	drops bile-colored fluid
16:18	2.0 cc.; saliva	
16:20	.....	Acid.
16:31	5.0 cc.; strongly alkaline (some bile)	0.3 cc.; acid.
16:46	0.5 cc.; alkaline	0.3 cc.; acid.
For one hour	29.5 cc.	1.5 cc.

The results of ten experiments in "Murzilka" are summarized in Table V. Collection was from the Pavlov pouch.

TABLE V.—INFLUENCE OF MAGNESIUM SULPHATE ON GASTRIC SECRETION.

	Average 6 experiments.	Average 4 experiments.
One hr. before $MgSO_4$	0.7 cc. Magnesium sulphate left in for five minutes	0.15 cc. Magnesium sulphate left in altogether.
One hr. after $MgSO_4$	1.7 cc.	0.44 cc.
Total average	0.49 cc.	1.18 cc.

2. **The Local Action of Magnesium Sulphate on the Gastric Mucous Membrane.** In two dogs, "Frant" and "Snejok," we washed the little stomach for several minutes with a 15 to 30 per cent solution of magnesium sulphate and determined the rate of flow and the reaction before and afterward. In every one of these experiments except the first the reaction either continued to be alkaline or changed from acid to alkaline.

In two other dogs ("Bertha" and "Murzilka"), we introduced the magnesium sulphate directly through the gastric fistula, into the main stomach, allowed it to remain five minutes, drained it off, and then observed the effect on both the large stomach and isolated pouch. The secretion was parallel in the two, that is, the change from acid to alkaline and *vice versa* occurred at about the same time. There was always an alkaline secretion from the stomach. Only once when we used a weak solution of the salt was there an

TABLE VI.—"SNEJOK," JANUARY 6, 1926. THE LOCAL ACTION OF MAGNESIUM SULPHATE (15 PER CENT SOLUTION) ON THE MUCOUS MEMBRANE OF THE STOMACH.

11:40—Dog brought on stand.
13:00—1.2 cc.; acid.
13:15—0.2 cc.; acid.
13:15–20 50 cc. of 15 per cent magnesium sulphate solution run through the Pavlov pouch.
13:20–22—Allowed to drain off.
13:22–28—0.5 cc., neutral.
13:35—0.2 cc, neutral.
13:50—0.3 cc.
14:05—0.0 cc.; mucous membrane is slightly alkaline.
14:20—0.2 cc.; slightly alkaline.

For eighty minutes before the experiments: 1.4 cc.; slightly acid.
For sixty minutes after the magnesium sulphate: 1 cc.; slightly alkaline.

acid reaction. A typical protocol, which also shows the close parallel between the main and isolated stomach, follows:

TABLE VII.—SIMILAR EFFECTS IN STOMACH AND PAVLOV POUCH.

1:30—On stand.
2:15—Tube inserted.
2:15—Alkaline.
2:15–30—0.2 cc.; alkaline.
2:45–53—Alkaline, Pavlov pouch; large stomach neutral; stomach washed with 400 cc. distilled water, 100 cc. at the time, so as not to distend.
2:53—Pavlov pouch alkaline; large stomach neutral.
2:58—Alkaline Pavlov pouch.
2:47–3:02—0.4 cc.; Pavlov pouch, alkaline.
3:17—5 cc.; Pavlov pouch, mucoid.
3:22—Alkaline, both Pavlov pouch and large stomach.
3:23–28—28 gm. of magnesium sulphate in 56 cc. water (33.33 per cent solution in gastric fistula at room temperature; dog on back; recovered 30 cc. clean colorless fluid; no signs of nausea.
3:30—Alkaline in both stomach pouch and large stomach.

	Pavlov pouch.	Large stomach.
3:30–45	0.4 cc.; alkaline	12 cc.; alkaline.
4:00	0.4 cc.; slightly acid	6 cc.; neutral.
4:15	0.3 cc.; slightly acid	2 cc.; very slightly acid.
4:30	0.4 cc.; slightly acid	0 cc.; slightly acid.
4:33–35	....	2 cc.; green-yellow fluid
	....	like mixed acid and bile.
4:30–45		3 cc.; acid.
4:45	0.5 cc.; acid.	

We often also obtained bile in the large stomach, accompanied by retching and vomiting. This will be referred to in a subsequent paper. The presence of the alkaline reaction in the isolated Pavlov pouch shows that it could not have been due to the regurgitation from the duodenum.

Our experiments show that magnesium sulphate acts as a weak irritant to the mucous membrane of the stomach. The effect on the gastric secretion was nearly the same whether the magnesium

sulphate was allowed to remain in the stomach or was drained out after five minutes.

3. **Action on the Intestinal Juice.** To determine the effect of magnesium sulphate on the intestinal glands we used three dogs, "Milka," "Achill" and "Zazula," having Thiry-Vela fistulas. In this operation the nerves are intact. "Milka" was operated on one year previously, "Zazula" nine years before and "Achill" two years before. In "Zazula" the loop of gut came from the duodenum and upper jejunum, while in the other two dogs it was from the jejenum. (For complete description of the operation see Babkin: "Die äussere Sekretion der Verdauungsdrüsen," Berlin, 1928.) The magnesium sulphate solution, 25 to 30 per cent was run through in a stream for five minutes, allowed to flow out, and then the fluid collected in an attached graduate, measured every five minutes.

Table VIII shows that the secretion after introduction of the magnesium sulphate is much greater than before. Control solution of physiologic saline run through in the same way as the magnesium sulphate was, without effect.

TABLE VIII.—EFFECT ON INTESTINAL SECRETION. "ZAZULA," APRIL 17, 1925.

11:55—On stand.
12:00—0.1 cc.
12:05—0.1 cc.
12:10—0.0 cc.; 0.2 cc.
12:15–40—0.0 cc.
12:40–45—20 cc. warm 30 per cent magnesium sulphate (38°) and allowed to drain five minutes.
12:55—1.0 cc.
1:00—0.5 cc.
1:05—1.6 cc.; 3.2 cc.
1:10—2.6 cc.
1:20—0.2 cc.; 2.8 cc.
1:25—0.0 cc.
1:30—0.0 cc.
1:35—0.0 cc.; 0.0 cc.
1:45—0.0 cc.
2:00—0.0 cc.; 0.0 cc.

TABLE IX.—SUMMARY OF NINE EXPERIMENTS SHOWING EFFECT OF MAGNESIUM SULPHATE ON INTESTINAL SECRETION.

	Before magnesium sulphate, cc.	After magnesium sulphate, cc.
First fifteen minutes	0.05	1.8
Second fifteen minutes	0.15	1.2
Third fifteen minutes	..	0.5
Fourth fifteen minutes	..	0.3
Totals:		
One-half hour	0.20	
One hour	..	3.9

4. **Action on the Pancreatic Secretion.** We tried the effect on the pancreatic secretion by injecting the magnesium sulphate solution

through a tube into the stomach in dogs with permanent pancreatic fistulæ. The results of four experiments are summarized in Table X.

TABLE X.—AVERAGE OF FOUR EXPERIMENTS IN TWO DOGS, SHOWING EFFECT ON PANCREATIC SECRETION.

	Before injection, cc.			After injection, cc.			
	First 15 min.	Second 15 min.		First 15 min.	Second 15 min.	Third 15 min.	Fourth 15 min.
First experiment	0.2	0.2	Magnesium	1.4	1.6		
Second experiment	0.5	0.6	sulphate	2.0	0.5	0.6	1.9
Third experiment	0.5	0.0	(30 per cent)	0.3	0.2	0.6	0.9
Fourth experiment	0.6	0.3	injected in-	0.3	0.7	3.0	0.8
Average	0.4	0.3	to stomach	1.0	0.8	1.4	1.2

These experiments are too few to admit of definite conclusions, nor is it possible to say, without further experimentation, how much of the action is due to the water and to the passage of the tube.

In our protocols the pancreatic juice was somewhat increased for the first hour after injection. It has been shown in Pavlov's laboratory that water* in the stomach is an independent exciter of the pancreatic juice, that is, it has an action in addition to that of the hydrochloric acid which it also calls forth.

Summary. A 30 per cent magnesium sulphate solution acts in the stomach as a mild irritant, producing a very small flow, which is usually alkaline. In a few experiments with the pancreatic secretion there was a slight increase in the pancreatic juice, which began immediately after giving the magnesium sulphate through the stomach tube. There is, however, a copious secretion of the intestinal glands all along the small gut, produced by the local contact of magnesium sulphate with isolated loops of gut. This occurred in the upper and lower duodenum as well as in the ileum and jejunum.

NOTE.—We desire to thank Prof. V. V. Savitch, of Leningrad, and Dr. Babkin, of Montreal, for suggestions regarding these experiments.

* The other independent exciters of the pancreatic flow are acid, fat and its products, and bile.

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In the first paper of this series we showed that magnesium sulphate caused a great flow of intestinal juice, but that it had very little effect on the stomach, and probably but little on the pancreatic secretions.

The results of our experiments in six dogs having various operations on the digestive tract, to be described in the present article, show that magnesium sulphate introduced whether into the stomach or directly into the duodenum has no specific action on the expulsion and secretion of bile.

We previously described the failure to obtain expulsion of bile into the duodenum on the introduction of magnesium sulphate directly into the duodenum through a cannula in a dog having a fistula of the gall bladder.[1]

The next dog, "Sharik," had a choledochus fistula after the method of Pavlov.[2] In this operation the end of the choledochus and surrounding mucous membrane of the duodenum containing the papilla of Vater is brought out on the skin and the duodenum closed. Thus all the secretion of bile has an external flow. We performed seven experiments altogether in "Sharik" with magnesium sulphate, introducing 25 to 40 cc. of a 30 per cent magnesium sulphate solution through the stomach tube. There was no flow of bile for the first hour in any of these experiments, but in two of them a small amount was expelled during the second hour. In the only case in which we saw a noteworthy expulsion of bile, retching and nausea occurred, a little bile was expelled simultaneously, and a considerable amount the second hour. Control experiments of meat produced a flow; and alkaline mineral water caused

an average expulsion of 6.2 cc. for the first hour, and 4 cc. for the second hour, but distilled water was without effect.

Two protocols follow:

TABLE I.—EFFECT OF INTRODUCTION OF MAGNESIUM SULPHATE INTO STOMACH ON EXPULSION OF BILE.

"SHARIK," JULY 24, 1925.

12:45—0.0 cc.
1:00—0.0 cc.
1:15—0.3 cc.; thin yellow.
1:30—0.0 cc.; 0.3 cc.
1:45—0.0 cc.
2:00—0.0 cc.
2:15—0.0 cc.; 0.0 cc.
2:22—25 cc.; 30 per cent magnesium sulphate at room temperature through stomach tube.
2:30—0.0 cc.
2:45—0.2 cc.; at 2:40 retching, and attempt to vomit; bile only after retching.
3:00—0.0 cc.
3:15—0.0 cc.; 0.2 cc.
3:25—Begins to drop.
3:30—0.2 cc.; yellow-brown.
3:45—1.2 cc.; yellow-brown.
4:00—1.0 cc.; yellow-brown.
4:15—1.4 cc.; yellow brown; 3.8 cc.
4:30—2.0 cc.; yellow-brown.
4:45—0.5 cc.; yellow-brown.
5:00—0.2 cc.; yellow-brown.

"SHARIK" AUGUST 8, 1925.

11:10—On stand and duct probed.
11:30—0.0 cc.
11:45—0.0 cc.
12:00—0.0 cc.
12:15—0.0 cc.; 0.0 cc.
12:20–22—43 cc.; 30 per cent magnesium sulphate about 43° C. through stomach tube.
12:30—0.0 cc.
12:45—0.0 cc.
1:00—0.0 cc.
1:15—0.0 cc.; 0.0 cc.
1:30—0.0 cc.
1:45—0.0 cc.
2:00—0.0 cc.
2:15—0.0 cc.; 0.0 cc.
2:16–19—200 gm. fine raw beef, well mixed, 200 gm. distilled water.
3:30—0.0 cc.
2:35—Bile begins.
2:45—1.0 cc.
3:00—1.8 cc.
3:15—2.4 cc.; 3.2 cc.

From this series of uniform experiments it is quite evident that the magnesium sulphate in the stomach caused no effect whatever on the expulsion of bile with the exception of the single instance in which retching and nausea occurred.

In the second dog, "Ajax," the magnesium sulphate was put in directly through a duodenal fistula, the papilla of Vater having been left in its normal position. The operation had been done a month before the experiments, and a cannula inserted into the duodenum.

We performed two experiments in this dog, running in magnesium sulphate for five minutes and then allowing it to drain out. In neither experiment did we get a definite spurt of bile, though there was such a spurt after milk was given. There was a marked flow of alkaline duodenal juice, but it contained very little bile.

TABLE II.—EFFECT OF INTRODUCTION OF MAGNESIUM SULPHATE INTO DUODENUM. "AJAX," OCTOBER, 7, 1925.

10:15—9 cc.; golden-yellow bile, coming in spurts, sometimes cloudy.
10:25—18 cc.; 27 cc.
10:30—6 cc.; light amber.
10:35—3 cc.; light amber.
10:40—5 cc.; 14 cc.
10:45—3 cc.; light straw.
10:50—0 cc.
10:55—1 cc.; yellow; 4 cc.
11:00—0 cc.
11:05—0 cc.
11:10—0 cc.; 0 cc.
11:10—25 cc.; 30 per cent magnesium sulphate run in for five minutes through fistula, allowed to run out; 13 cc. yellow bile-colored fluid obtained.
11:20—11 cc.; yellow (duodenal juice).
11:25—3 cc.; straw color.
11:30—11 cc. dirty straw; 25 cc.
11:35—4 cc.; straw.
11:40—6 cc.
11:45—3 cc.; 13 cc.
11:50—0 cc.
11:55—0 cc.
12:00—0 cc.; 0 cc.
12:05—25 cc. milk given just as magnesium sulphate (allowed to remain five minutes, and then run out 10 cc. returned).
12:10—
12:11—Bile appears; 5 cc. milk.
12:15—3 cc. acid.
12:19—3 spurts of pure bile.
12:20—1 cc.
12:25—4 cc.; 8 cc.

The third dog, "Spot," had a stomach fistula and also the choledochus fistula after Pavlov as in "Sharik." The dog was turned on its back and 25 to 40 cc. of magnesium sulphate at room temperature run into the stomach, and allowed to remain there. In two experiments, after a latent period of three minutes a definite flow of darker bile set in. In the other two experiments, there was no expulsion of bile whatever for an hour after the injection. This expulsion of bile may have been due to the coincidence with the periodic secretion or something in the procedure.

In two other dogs, "Murzilka" and "Frant," we introduced magnesium sulphate through the stomach tube. "Frant" vomited every time and in each instance the vomitus was bile colored. "Murzilka" had a gastric fistula, and we could observe the contents of the stomach. It seems significant that in five of the six experiments there was no regurgitation of bile and no retching or nausea, and that in the single case in which more than a trace of bile was present there was retching.

Effect on the Secretion of Bile. In one dog, "Tulpan," which had a gall bladder fistula with the choledochus tied so that all the secretion could be collected and measured, we introduced 50 to 70 cc. of 30 per cent magnesium sulphate solution through the stomach tube, and allowed it to remain. The quantities before and after introduction are shown in the following table.

Control experiments of distilled water and of alkaline mineral water had little or no effect on the amount of bile secreted. (Experiments of Drs. Gefter and Martinson.)

TABLE III.—CONTROL EXPERIMENTS (DISTILLED WATER AND ALKALINE MINERAL WATER.) AVERAGE OF SIX EXPERIMENTS.

	Bile excreted.
Two hours before injection	7.5 cc.
One hour before injection	4.2 "
Two hours after injection of magnesium sulphate in stomach	9.5 "
One hour after injection of magnesium sulphate in stomach	6.6 "

Although this seems to indicate a slight effect on the amount of bile secreted, the material we have is not enough to be conclusive.

We feel we can state with assurance, however, that in the dog, 30 to 40 per cent magnesium sulphate solution introduced either directly into the stomach or the duodenum has no effect on the expulsion from the gall bladder. In the few cases when bile appeared it could be explained by the nausea and retching. Frazer[7] found after injecting magnesium sulphate into the duodenum no increased secretion of bile from a choledochus fistula, though he employed a slightly different operative technique from ours.

Summary. My own clinical experience, as well as that of Lyons, Friedenwald and other prominent gastroenterologists, showed that there was very often a flow of bile from both the biliary passages and gall bladder after magnesium sulphate introduced through a stomach tube. Subsequent experimental work on dogs in which the magnesium sulphate was put directly into the duodenum rarely produced bile and never any increase of pressure in the gall bladder. In other dogs in which we gave the magnesium sulphate by mouth through a tube, bile was usually secreted; but some of these animals never reacted in this way. Finally in another dog in which we ran the magnesium sulphate directly into the stomach through a fistula we sometimes got bile regurgitated and sometimes did not.

Reviewing our results, we found that the dog in which we always obtained bile was one which always had nausea and vomiting after the magnesium sulphate, those which never gave bile never had nausea and vomiting after the procedure; and in the one in which we sometimes found bile and sometimes did not, whenever there was bile it was preceded by nausea and vomiting and when there was no nausea and vomiting there was no bile.

This reconciled our own clinical and laboratory results in man and

in dogs, and, furthermore, we think clears up much of the mystery of magnesium sulphate which has lasted for a decade. It is quite likely that magnesium sulphate may cause a contraction of the duodenum (Auster and Chron, Diamond, Kawashima), and a local relaxation of the sphincter of Oddi, and under these conditions if there is nausea or vomiting, which may quite readily be produced by the passage of the tube alone or by the injection of substances into the duodenum, or under other conditions bringing about expulsion from the gall bladder as shown by Winkelstein, there may follow expulsion of bile from the bladder into the duodenum. We must remember that a large number of other substances in the duodenum also produce a flow of bile, and that bile enters the duodenum periodically.

Recently an assistant of Pavlov, K. M. Bykov,[10] has shown that conditioned reflexes may play a part in the secretion of bile, and moreover that this secretion may be an enteroreceptory one (that is, from the internal nerves) instead of an exteroreceptory one (as for example from the eye, ear, skin).

If this is so—that even so complicated a process as the secretion of bile may be conditioned, then it is quite clear that if there were (as there usually is in most patients) nausea and vomiting from the introduction of the duodenal tube and the magnesium sulphate, once or several times, with the expulsion of bile, the flow might subsequently become conditioned to the method of the procedure even though the nausea failed to appear. The nausea and antiperistalsis could thus explain the expulsion of bile occurring the first times, and it seems quite likely in view of Bykov's experiments, that later, in those patients who are drained often, there might be a conditioned flow elaborated which is analogous to that of Pavlov's conditioned reflex.*

* Bile (unconditioned stimulus) was injected into the blood and there followed an increase of the bile secretion (unconditioned reaction). This procedure was repeated a good many times. Later on, merely putting the dog on the stand and making the necessary preparations for the injections (conditioned stimulus) proved sufficient to increase the biliary secretion (conditioned reaction).

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