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THE INFLUENCE OF MAGNESIUM SULPHATE ON THE EXPULSION OF BILE FROM THE GALL BLADDER*

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MAGNESIUM sulphate has been widely used during the past six years to cause expulsion of bile into the duodenum. Upon this alleged property of the salt rests its reputation in the drainage of the gall bladder by the Meltzer-Lyon method.[1, 2]

However the subsequent work of some clinicians who have applied this method in the treatment and diagnosis of gall bladder conditions and of several physiologists have not substantiated the original claims made for magnesium sulphate as a stimulator for the contraction of the gall gladder and relaxation of the sphincter of Oddi. (Max Einhorn,[3] Thos. R. Brown, Frazer,[4] J. W. McNee,[5] Bickel.[6]) The marked discrepancy in the views of prominent clinicians, coupled with the fact that one of us (W. H. G.) had had good clinical results (in diagnosis) from this method, led us to make several experiments in the hope of throwing additional light on the action of this salt when introduced into the duodenum.

In 1921 Bassler[14] could not see a contraction of the gall bladder nor obtain bile from the duodenum when magnesium sulphate was introduced through the duodenal tube in anesthetized patients, but the results of Matsuo[16] and of Silverman and Menville[15] are at variance with those of Bassler. Matsuo saw in the duodenum an appearance of dye which he injected into the gall bladder at the same time that magnesium sulphate was given, and Silverman and Menville using a fluoroscope and visualizing the gall bladder by the injection of phenoltetrabromphthalein into the blood, saw the gall bladder become smaller after the administration of $MgSO_4$. Friedenwald, Martindale, and Kearney[13] performed experiments which did not confirm the positive clinical reports, noted above.

In our experiments we tried to have the conditions as near to normal as possible, concerning both the physical condition of the dog and the nerve connections and the condition of the duodenum and of the papilla of Vater, as it is upon this part that the magnesium sulphate is supposed to act. For this reason we did not use the choledochus fistula operation of Prof. Pavlov[7] in which a section of the duodenum surrounding the papilla is excised and sutured to the skin; nor the double biliary fistula as performed by one of us (G.v.V.) previously.[8] We selected the gall bladder fistula of Schiff,[9] because the connections of the papilla of Vater are not disturbed, and the choledochus is pre-

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served intact in this operation. One of us has shown[10] that in a dog with such a fistula, the beginning of the expulsion of bile into the duodenum can be clearly recognized, that the expulsion of bile through the gall bladder is at the same time inhibited, and that within ten to fifteen minutes after the bile begins to flow into the duodenum, there appears in the gall bladder a pure colorless mucus, without a suggestion of bile. With the cessation of the flow of bile into the duodenum, i.e., at the end of the period of digestion, bile reappears in the gall bladder, and the mucus flowing from the gall bladder fistula becomes suddenly colored.

In addition to the gall bladder fistula of Schiff we performed in our dogs a lateral duodenal fistula, according to Pavlov.[7] Without disturbing the continuity of the duodenum, it was sutured to the surface of the abdomen, so that the opening in the duodenum was about 7 to 9 cm. below the papilla of Vater. This operation is to a certain degree a substitute for the choledochus fistula in the double fistula operation.[8] The arrangement of the duodenal fistula (close to the papilla of Vater) permits us to introduce the magnesium sulphate directly into the duodenum, as was done by Meltzer,[1] so that the possibility of the action on the biliary apparatus is insured. And though we cannot quantitatively determine the amount of bile in the duodenum, we can make certain at any moment whether it is flowing into the duodenum, for we can at any time obtain a specimen of the duodenal contents through this fistula.

The following experiments in dogs were not carried out until a month had elapsed after the operation, and we had assured ourselves that the condition of the animals and of the biliary secretions were normal. The experiments were performed in the fasting condition, fifteen to twenty-four hours after the last feeding, and according to the general conditions of experimentation in Pavlov's laboratories.[7]

Fifty c.c. of a 25 to 33 per cent solution of magnesium sulphate at a temperature of 35-40° C. was introduced into the duodenal fistula, and after ten to fifteen minutes, the duodenal fistula was opened and the solution allowed to run out.

We append here protocols from two of our dogs. Table I shows the influence of magnesium sulphate upon the volume of bile secreted (the fluid from each fistula being collected and measured every fifteen minutes). Table II shows the influence of magnesium sulphate on the pressure of bile in the biliary system.

The objection can be raised that conditions are not normal when there is a gall bladder fistula because the bile continuously flowing out of the fistula may prevent a filling of the gall bladder and ducts, and secondly in such a case the magnesium sulphate could not exert its influence to cause expulsion of the bile into the duodenum, because the gall bladder would contract to force the bile along the line of least resistance, i.e., through the wide fistula instead of along the smaller cystic duct. Although this objection was partly refuted through an earlier experiment by one of us,[8] we devised here a special arrangement of the apparatus to prevent the flow of bile from the gall bladder fistula and to maintain a constant and normal pressure in the biliary system.

A schematic representation of the operation and apparatus is shown in Fig. 1.

TABLE I

DOG 1, "JACK". APRIL 10, 1923

TIME	GALL BLADDER FISTULA		DUODENAL FISTULA
11:15			
11:30	2.8 c.c.	All specimens = pure bile.	Little or no flow into the duodenum.
12:45	2.2		
12:00	2.6	Amt. secreted for 1st hr. (12:00-	
11:45	0.9	1:00) = 4.6 c.c.	Reaction weakly acid.
12:30	0.5		
12:15	0.6		
12:50§		§Introduction of 20.0 c.c. 30% $MgSO_4$ through the duodenal fistula, and allowed to remain 10 min.	
1:05	1.8	All specimens pure bile as for-	Fistula opened at 12:40 P. M.: 5.0 c.c.
1:20	0.8	merly.	clear fluid, without bile obtained; reac-
1:35	1.2		tion weakly acid.
1:50	0.6	Amt. excreted for 2nd hr. (1:05-	
2:05	1.0	2:05) = 4.4 c.c.	
		During the whole experiment there was practically no flow into the duodenum.	

DOG 1, "JACK". APRIL 13, 1923

TIME	GALL BLADDER FISTULA		DUODENAL FISTULA
9:45			
10:00	0.4 c.c.	Pure mucus.	
10:07		Pure bile begins to flow and con-	
10:15	4.8	tinues till end of experiment.	
10:30	4.2		
10:45	4.6	Amt. secreted for 1st hour.	
11:00	2.8	(10:00-11:00) = 17.4 c.c.	
11:00§		§Introduction 50.0 c.c. 30% $MgSO_4$ into the duodenal fistula and allowed to remain 10 min.	
11:10			Duodenal fistula opened and a few drops
11:15	3.1	All specimens pure bile.	of clear fluid without bile obtained.
11:30	2.2		After 11:00 A. M. there was a flow of
11:45	1.71	Amt. excreted for the hr.	clear fluid without bile; reaction neutral.
12:00	1.1	(11:00-12:00) = 8.1 c.c.	
12:15	1.1		

DOG 1, "JACK". APRIL 14, 1923

TIME	GALL BLADDER FISTULA		DUODENAL FISTULA	
12:00				
12:15	1.6 c.c.	Secreted ¾ hr. (12:45-1:15) =	24.0 c.c.	Weakly colored bile.
12:30	2.0	3.8 c.c.	16.0	Reaction acid; no bile.
12:45	2.0		8.0	Idem.
1:00	0.8		4.5	"
1:15	1.0		6.00	Reaction acid; bile colored.
1:15§		§Introduction 50.0 c.c. 25% $MgSO_4$ in duodenal fistula, and allowed to remain 10 minutes.		
1:30	2.3	Secreted for ¾ hr. (1:15-2:00)	8.0 c.c.	Reaction acid; no bile.
1:45	1.2	= 4.5 through g. b. fist.	30.0	Idem. " "
2:00	1.0		95.0	" " "

DOG 1, "JACK". APRIL 20, 1923

TIME	GALL BLADDER FISTULA		DUODENAL FISTULA	
10:30				
10:40	1 drop mucus.			Fistula opened; slight amt. bile.
10:45	0.8 c.c.		3.0 c.c.	
11:00		Amt. excreted through the g. b.		Reaction neutral; strongly bile
11:15	2.0	fist. for the hr. (11:00-12:00)	3.2	colored.
11:30	2.2	= 6.6 pure bile.	11.0	Neutral no bile.
11:45	1.6		" " "	
11:45§		§Introduction 50.0 c.c. 25% $MgSO_4$ through duo. fistula and allowed to remain 15 min.		
12:00	1.4		18.5 c.c.	Clear bile free fluid; reaction
12:15	1.4		3.0	neutral.
12:30	1.0		1.0	Reaction alkaline; bile free, for
12:45	1.1		0.5	all specimens till end of exp.
1:00	1.1		0.5	
1:15	1.1		0.5	

TABLE I—CONT'D

DOG 2, "LORA". FEBRUARY 6, 1924

TIME	GALL BLADDER FISTULA		DUODENAL FISTULA	
5:30				
5:45	0.6 c.c.	All specimens pure bile. Amt.		
6:00	0.4	from g. b. for the hr. (5:30-		
6:15	0.2	6:30) = 1.5 c.c.		
6:30	0.3			
6:30§		§Introduction 50 c.c. 30% $MgSO_4$ through duo. fistula and allowed to run out after 5 min. At 6:35 fistula was opened for $MgSO_4$ to drain out. At 6:40		
6:40		some alkaline flow of mucus from the duodenal fistula.		
6:45	0.8		20.0 c.c.	Bile free fluid, mucoid,all specimens, to end of experiment.
7:00	0.4	All specimens pure bile. Amt.	0.5	
7:15	0.3	from the g. b. fist. for the hr.	0.5	
7:30	0.0	(6:30-7:30) = 1.5 c.c.	0.0	

TABLE II

EXPERIMENTS ON THE PRESSURE OF BILE IN THE BILIARY SYSTEM, MEASURED IN MM. OF BILE. SEE FIG. 1.

DOG 1, "JACK". APRIL 15, 1924

TIME	BILE PRESSURE IN BILIARY SYSTEM		DUODENAL FISTULA
11:45			
12:00	17. mm.	Rises gradually to 25. mm.	Several drops bile-free fluid.
12:15	25.		
12:15§		§Introduction 50.0 c.c. 30% $MgSO_4$ into the duodenum through the duo. fistula.	
12:30	24-38	Sinks to 24 mm., and then	
12:45	46.	rises gradually to 38 mm.;	Fistula opened; 10 c.c. of a cloudy alkaline fluid obtained; bile-free.
1:00	51.	then rises gradually to 46 mm. and becomes stationary at 51 mm.	At 1:00 P. M. several drops of a clear alkaline, bile-free fluid.

DOG 2, "LORA". FEBRUARY 19, 1924

TIME	BILE PRESSURE IN BILIARY SYSTEM		DUODENAL FISTULA	
11:50	50. mm.			
12:10	50-56	Rises from 50 to 56, and in	4.0 c.c.	Clear, alkaline, bile-free.
12:25	72-74	last min. to 72. Varies between 72 and 74.	Several drops,	" " "
12:25§		§Introduction 50 c.c. 30% $MgSO_4$ through duo. fist. and after 7 min. duodenal fist. opened.		
12:40	78-80	Varies 78-80.	13.5 c.c.	Cloudy, bile-free fluid.
12:55	80-82	" 80-82.	18.5	Clear, alk., " " "

DOG 2, "LORA". FEBRUARY 11, 1924

TIME	BILE PRESSURE IN BILIARY SYSTEM		DUODENAL FISTULA
5:00	22 mm.		
5:15	22-24		Several drops of mucus.
5:30	24-28		" " clear, bile-free fluid.
5:30§		§Introduction 70 c.c. 30% $MgSO_4$ through the duodenal fistula; fist. opened in 15 min.	
5:45	28-36		Reaction alkaline; bile-free.
6:00	36-46		" " " "
6:15	44.		" " " "

DOG 2, "LORA". FEBRUARY 13, 1924

TIME	BILE PRESSURE IN BILIARY SYSTEM		DUODENAL FISTULA	
5:30	80.00 mm.			
5:45	80-84		9.0 c.c.	Clear, bile-free fluid.
5:45§		§Introduction 40 c.c. 25% $MgSO_4$ through the duodenal fistula; fistula opened after 10 min.		
6:00	84-80		10.0 c.c.	Neutral, bile-free fluid.
6:15	82-84		1.0	Alkaline, bile-free.
6:30	80		1.0	" " "

The cannula of the gall bladder fistula was closed with a cork containing a glass rod of 4 mm. diameter, and a rubber tube was used to connect the cannula with an ordinary burette. The latter was filled with fresh bile collected from the same dog, and the burette was adjusted so that the height of the fluid therein stood slightly higher than the inner opening of the gall bladder fistula. (See Fig. 1.) Consequently the gall bladder and biliary ducts were kept filled with bile, and a normal pressure maintained—the same that would be in a normal animal without a fistula. Every new portion of the bile coming from the gall bladder fistula must now be forced out against the pressure of the column of bile in the burette, and consequently the pressure in the whole biliary system will be raised. This pressure can be controlled and measured by the height of the column of bile in the burette above the level of the inner end of the tube in the gall bladder fistula. We are thus able to prevent the abnormally low pressure which would otherwise result from the escape of bile

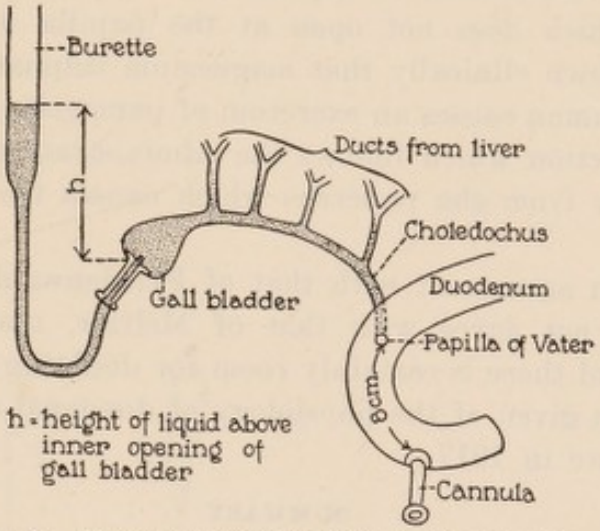

Fig. 1.—Schematic representation of operation.

from the gall bladder fistula; and by opening the duodenal fistula we can ascertain at any moment whether bile is entering the duodenum.

Table II represents the observations on the change in pressure resulting from the introduction of magnesium sulphate into the duodenum, and observations on the appearance of bile in the duodenum. This salt had no constant effect on the pressure of bile in the gall bladder and ducts, and in not a single case did we see an expulsion of bile into the duodenum as a result of the action of the magnesium sulphate.

When comparing the specimens of bile secreted before and after the introduction of the magnesium sulphate, we could not perceive in our dogs the effect on the color of bile, as noted by Einhorn in patients.[3] Our experiments here cannot be considered as giving conclusive evidence on the secretion of bile after $MgSO_4$, because secondary influences such as the acid secretion of the peptic glands and the expulsion of the stomach contents into the duodenum were not absolutely ruled out, but they agree with the results of Nissen and Jordan.[11, 12] The effect of food was, however, eliminated, as the dog was fasted for twenty-four hours preceding the experiment.

Just after performing each experiment, in order to convince ourselves that the secretory and motor functions of the biliary apparatus were working

normally, we tested them through the application of their normal stimulators, viz., through the introduction of HCl into the duodenum or through the feeding of milk. In the former case we noted a copious outflow of bile through the bladder fistula, as a sign of the increased secretion; and with milk, bile appeared promptly in the duodenum.

DISCUSSION

In the hands of many eminent clinicians (Friedenwald, Smithies, J. Meakins, Langdon Brown) duodenal drainage by means of magnesium sulphate has proved of value. The discrepancy between our experimental results and the clinical findings may be another one of those cases in which the clinical method is in the empiric stage. It is also possible that the physiology of the dog here differs from that of the human. There is an anatomic difference because the dog has two pancreatic ducts, one of which does not open at the papilla of Vater. We intend to repeat our experiments after ligating that pancreatic duct which does not open at the papilla of Vater. One of us (W. H. G.) has shown clinically that magnesium sulphate introduced into the duodenum of the human causes an excretion of pancreatic juice equal in enzyme activity to the secretion which follows the administration of beef extract; and it may be this flow from the pancreas which causes the relaxation of Oddi's sphincter.

Our work is in agreement with that of Friedenwald and Martindale[13] on dogs; but it does not agree with that of Meltzer, upon which the clinical method is based, and there is certainly room for doubting the ordinary explanation which has been given of the physiology of duodenal drainage, as suggested in Meltzer's footnote in 1917.

SUMMARY

In our experiments with dogs, using a special device for maintaining normal pressure in the bile ways, we found absolutely no influence of magnesium sulphate on the expulsion of bile into the duodenum.

We desire to thank Prof. Pavlov, in whose laboratory these experiments were performed, for his advice and general supervision of our work.

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