THE PHYSIOLOGICAL VARIATIONS IN RESISTANCE TO BILE FLOW TO THE INTESTINE.

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PLATE 5.

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The flow of bile, from its source within the liver to its issue into the duodenum, is greatly influenced by two structures situated along the path of flow. These, the musculature about the lower portion of the common duct and the gall bladder, not only effect the actual movement of bile but by their combined activities modify the character of the secretion as well. The common bile duct, after entering the wall of the duodenum, passes for a considerable distance through its muscular coat to enter the intestinal lumen at the ampulla of Vater. At this terminal portion is situated the sphincter of Oddi. This structure, aided perhaps by the musculature of the duodenum surrounding the lower portion of the common duct, exerts a pressure sufficient to maintain closure of the orifice of the duct during much of the time. Under these conditions the direction of the flow of bile is not continuously from the liver to the intestine but more often in the reverse direction, from the liver back into the gall bladder. Here, as has been shown in this laboratory, the bile is concentrated with remarkable rapidity. The gall bladder is thus enabled to admit and store the bile coming to it during the usual digestive interim. Nearly 30 years ago Bruno, working with "Pavlov biliary fistula" dogs, noted that bile emerged from the intact ampulla only at long intervals of 1½ to 2½ hours, and in small amounts during fasting periods. According to

1 Rous, P., and McMaster, P. D., J. Exp. Med., 1921, xxxiv, 47.
Babkin⁵ this observation was confirmed by Klodnizki⁶ and also by Boldyreff.⁷

The demonstration of the fact that bile need not enter the intestine save at long intervals of time has made it a matter of greater interest to study the conditions under which the escape of bile to the gut actually does take place. Though much work has already been done upon the theme⁸ there is little information to be had that is not based on indirect methods of observation; and there is but slight accord among workers upon the problem.

In the present paper the alterations occurring under pathological circumstances in the resistance to the flow of bile into the intestine will be described. The observations were made upon healthy, un-anesthetized animals. In a paper to follow, the influence of the gall bladder will be considered.

PREVIOUS LITERATURE.

Anatomically the sphincter of the common duct is a well defined structure. As far back as 1680, Glisson⁹ suggested its existence but nearly two centuries elapsed before other investigators took up its study. In 1878 Gage¹⁰ first described the presence of circular fibers surrounding the duct in the ampulla of Vater, but the sphincter is best known through the detailed work of Oddi.¹¹ In many animals and in man there is about the lower portion of the common duct a discrete ring of muscle, distinct from the surrounding duodenal musculature.¹²–¹⁴

The physiology of the musculature of the lower portion of the common duct has only recently received much attention.⁸,¹⁵ Oddi¹⁶ on the basis of his experi-

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⁵ Babkin, B. P., Die äussere Sekretion der Verdauungdrüsen, Berlin, 1914, 338 et seq.
⁹ Glisson, F., Anatomia hepatis, 1681, quoted by Oddi.¹¹
¹¹ Oddi, R., Arch. ital. biol., 1887, viii, 317.
¹⁶ Oddi, R., Sperimentale, 1894, xliv, 180, as abstracted in Schmidt's Jahrb., 1895, ccxlv, 120.
merits claimed for the sphincter nervous control independent of that of the neighboring intestinal muscle, further describing a center for it in the spinal cord opposite the first lumbar vertebra. He measured the sphincter tonus by observing the height of a column of water supported in a tube tied in the common duct. Doyon determined in anesthetized animals the amount of fluid passing through the ampulla from a specially constructed manometer connected with the common duct. He claimed for the sphincter a reaction on reflex stimulation only, with contraction upon irritation of the gastric mucosa with acetic acid and relaxation following electrical stimulation of the central end of the cut vagus or upon section of the medulla. He quoted the observation of Vulpian, that after "piqûre" of the medulla in rabbits, the duodenum is found, at autopsy, filled with dark brown bile. Reach studied the resistance offered to the passage of bile through the ampulla in a way similar to that of Doyon but used the completely isolated common duct immersed in warm Ringer solution. Bruno, Klodnizki, Boldyreff, and much later Rost employing unanesthetized dogs with a duodenal fistula, observed intermittent gushes of bile from the ampulla, under a variety of circumstances, and deemed them indicative of a relaxation of the sphincter. These findings will be discussed in detail further on, as too will the recent work of Cole, who found in anesthetized dogs a relationship between the resistance to the flow of bile through the lower common duct and the reaction of the gastric contents. Recently the importance of the action of the sphincter of Oddi as apart from that of the duodenal musculature surrounding the lower end of the common duct, has been called in question.

In the present work we have employed as a criterion of the activity of the musculature about the lower portion of the common duct the pressure necessary to force bile past it into the intestine. No attempt has been made to differentiate the activity of the duodenal musculature in this region from that of the sphincter. The circumstances of the observations have been especially favorable, involving as they have natural conditions in healthy, robust animals, with no disturbance of the biliary tract other than that incident to an intubation of the common duct. The pressure determinations, made long after operation, required no anesthetic since they produced not the slightest

17 Doyon, M., Arch. physiol. norm. et path., 1894, vi, series 5, 19.
18 Doyon, M., Arch. physiol. norm. et path., 1893, v, series 5, 683.
19 Reach, F., Zent. Physiol., 1912-13, xxvi, 1318.
discomfort. No such observations on the unanesthetized animal have been made in the past. The above mentioned observations by workers in Pavlov’s laboratory\textsuperscript{6,4,7} were indirect in nature and were frequently complicated by difficulties inherent in the procedure. Under the circumstances of the Pavlov biliary fistula\textsuperscript{4} the portion of the duodenal mucosa transplanted to the body surface and containing the sphincter undergoes a gradual atrophy and retraction. The biliary tract and especially the portion about the ampulla becomes infected and the flow of bile is frequently obstructed.

\textit{Technique.}

Normal, quiet, healthy dogs were employed in which the common bile duct was intubated, under ether, in two directions, toward the liver and toward the ampulla of Vater, the duct being cut between\textsuperscript{24} The gall bladder was excluded by section of the cystic duct between ligatures. A diagram of this scheme of intubation, “\textit{altercursive intubation},” has already been published\textsuperscript{24} By means of it the bile is brought to the surface and can either be collected there or turned back into the common duct at will to flow as usual through the ampulla of Vater into the duodenum.

In Fig. 1 is shown a dog with the “\textit{altercursive intubation}” installed, but with the protective wrappings removed from the joints of the tubing. The tube nearer the animal’s head leads to the cannula that receives bile from the liver, the other connects with the cannula directed toward the ampulla of Vater. The excellent healing about the tubes should be noted. By means of a clamp placed on the tubing one can direct the flow of bile into the bag for collection, or prevent it from entering with result that it returns to the common duct at a point not over \( \frac{1}{2} \) cm. from where it left it. As the figure shows, the rubber balloon is supported in a light wicker basket which is held in place against the animal’s side by adhesive strips. This in turn is covered by a muslin and canvas jacket which laces up the back and, while permitting freedom of motion to the animal, prevents it from dislodging the apparatus. Sterility of the tube system is maintained by collecting the bile under aseptic precautions.

During the manipulations incident to the experiments sterility of the system can be maintained only by the most scrupulous care. Manometers and tubes were ster-

\textsuperscript{24} McMaster, P. D., and Elman, R., \textit{J. Exp. Med.}, 1925, xli, 513.
ilized before use, and all joints protected with gauze sponges soaked in 5 per cent carbolic acid. Routine cultures of the bile and examinations of stained sediment from centrifuged specimens were made to discover the presence of organisms. Despite all precautions infection frequently occurred, not through the bile but as result of the repeated opening of the tube system to connect it with the manometer. Usually saprophytes such as did not change the character of the bile in important ways were the invading organisms. Nevertheless when this occurred experiments with the animal were at once abandoned as was done also whenever any obstruction developed in the cannulas, even a temporary one. In the present paper we consider only results that were obtained during the maintenance of sterile and unobstructive conditions within the biliary tracts of animals.

For the purpose of determining the resistance to the flow of bile into the intestine the tube leading to the lower common duct was temporarily disconnected at intervals and attached under aseptic precautions to a manometer filled with the animal’s own uninfected bile. While the tests were in progress the liver bile was allowed to flow either into the balloon or into a sterile flask. In a number of experiments (as in that of Text-fig. 8) the manometer was temporarily substituted for the collecting balloon, with result that the pressure existing within the tube-duct system was registered. The latter arrangement is shown in Fig. 2. Under these circumstances, too, the tube draining liver bile could be clamped temporarily, with result that only the resistance offered to the flow of bile into the intestine was measured.

After a few repetitions of the procedure, at most, the dogs learned to stand quietly beside the manometer, for hours even, and they evidently enjoyed the attention bestowed upon them. The level of the common duct above the table on which they stood was roughly estimated by external measurements and the zero point of the manometer set at this level. Many pressure readings were taken from each animal daily, over long periods of time, and in each individual the zero point of the manometer was placed at the same height above the table as in the first determinations. The actual level of the common duct was determined at autopsy. The error from the presumptive level was so slight as to be negligible.

The resistance offered to the passage of bile into the intestine was tested by noting the height to which it was necessary to raise the column of bile or salt solution in the manometer, attached to the tube leading to the lower common duct, in order to start a flow. The height of this column when flow ceased was also noted. In one series of experiments we joined the lower common duct with a special manometer, to be described below, which was arranged to show the rate of bile flow into the intestine at a relatively constant pressure.

At the outset of these studies observations were made at random. Soon however an influence of the ingestion of food on the resistance offered within the lower common duct became evident to us. Thereafter, in the experiments which will now be described, feedings were
given at stated times and the measurements made in relation to these times. The food consisted in every case of a liberal mixture of lean meat and bread soaked in milk, 450 gm. of the former to each kilo of the latter. The dogs were allowed to eat until satiated and the food was then removed. Special attention was paid to the influence of incidental body movements of the animals during the observations. In most cases the dog stood quietly for long periods with only occasional turning movements of the body, as it looked from one part of the room to the other. Since many duplicate observations were made at one time the influence of such body movements could be tested. It was found to be very slight.

The Normal Resistance to the Flow of Bile into the Intestine.

In the past numerous workers have measured how high a column of water had to be in a tube connected with the common duct in order to start a flow through the common duct. Widely divergent values ranging from 80 mm. to 600 mm. have been quoted. The workers mentioned made their measurements on the anesthetized dog, however, and they had also to reckon with the influence of trauma incident to a laparotomy. No mention has been made in many of the studies of any time relation to the giving of food.

We have tested the resistance offered to the flow of bile through the lower common duct in eighteen dogs appropriately intubated. A value for the “normal” pressure was found that was uniform within narrow limits though subject to alterations from feeding and digestion. In scores of experiments on sixteen animals it was a regular finding that the column of bile in the manometer connected with the lower common duct had to be raised to a level 100 to 120 mm. above it before flow started. This always ceased when the column had fallen to the 80 or 90 mm. level. The values were obtained between 4 and 12 hours after feedings.

The Increase in the Resistance to the Flow of Bile into the Intestine during Fasting.

Fasting for 24 to 72 hours results in a great increase in the resistance offered at the lower portion of the common duct to the flow of bile
into the intestine. This finding was regularly obtained on twenty
different occasions, in ten animals, that is to say in all of the tests
made under the conditions. Whereas the pressure exerted by a
column of bile 100 to 120 mm. in height usually sufficed to cause flow
through the ampulla of Vater when the test was carried out 4 to 12
hours after a feeding, it was often necessary to raise the column to a
height of 200 to 250 mm., to obtain this result in the fasting dog.

In relation to this phenomenon the findings of Bruno⁸ and Rost⁹
have a suggestive interest. They observed unanesthetized dogs with
Pavlov biliary fistulas and state that during fasting periods bile
emerged from the ampulla only in small amounts and at long intervals
of 1½ to 2½ hours.

Type experiments follow.

Dog 3, Text-Fig. 1.—At the time when the experiments were begun, 83 days
after intubation, the animal was healthy and active. The resistance offered to the
flow of bile through the lower common duct was tested 2 hours after a feeding by
bringing the manometer and reservoir filled with the animal's own sterile bile
into connection with the tube leading to the lower common duct.

In Text-fig. 1 and in the others to follow, the dotted lines indicate an artificial
raising or lowering of the level of bile in the manometer, the continuous lines in-
dicate changes in the pressure level consequent on physiological changes within
the animal influencing the resistance to flow. Wherever a sinking of the bile
column is depicted by a continuous line it is due to the flow of bile out of the
manometer, through the lower common duct, into the intestine. As the figure
shows, for Dog 3 the column of bile in the manometer was gradually raised and
frequently allowed to remain, unaltered by the observer, during 1 minute or
more. When it had been raised by him to 115 mm. spontaneous fallings of the
column occurred, to the level of about 100 mm. After the tests had continued
over half an hour, the column of bile in the manometer was abruptly raised to 200
mm. It fell almost as promptly to 100 and then more gradually to 90 mm. When
the column of bile was now raised to 110 mm. there was a fall to 100 mm. as in
previous tests of the sort.

Food was withheld for 72 hours, and after this the tests repeated. As the
second portion of Text-fig. 1 shows, the column of bile in the manometer was raised
gradually, with frequent pauses to give time for readjustment to take place on
the part of the animal. Only when a pressure of 270 mm. had been reached did
any flow into the intestine take place and this was checked when the pressure
had fallen to 250 mm. Raising the column again to 270 mm. caused a drop to
the 255 mm. level. Two attempts to cause lessening of the resistance to the
flow of bile into the intestine by increasing the pressure considerably failed of
their object. Even when the bile column had been raised to the height of 400 mm., it fell back only to the 250 mm. level.

Dog 4. Text-fig. 2.—36 days after intubation the animal was healthy and active, following a fast of 48 hours.

11.00 a.m. Flow did not start until the column of bile in the manometer con-

Text-Fig 1. Influence of fasting on the resistance offered to the flow of bile into the intestine. See text.

nected with the lower common duct was raised to a level 180 to 190 mm. above it. Flow ceased when this had fallen to 150 mm. Twice thereafter the bile column was raised to 400 mm. but each time bile flow ceased when the pressure had fallen to about the 150 mm. level.
12.00 noon. The dog was given food. 2 hours later a flow of bile into the intestine occurred repeatedly at the pressure exerted by an 80 mm. column of bile, and did not cease until the pressure had fallen almost to 50 mm. When the column of fluid in the manometer was raised to 200 mm. a fall followed and bile did not cease to pass into the intestine until the 50 mm. level had been reached.

Dog 5.—48 days after intubation the animal was healthy and active. 6 hours after feeding, 150 mm. of bile, in the manometer connected with the lower common duct, was sufficient to cause bile flow through the ampulla. This ceased when the level fell to 135 mm.

Text-Fig. 2. Effects of fasting and of feeding on the resistance offered to the flow of bile into the intestine.

The dog was then fasted and 2 days later the tests repeated. A 240 mm. column of bile was needed to start flow. This ceased at the 200 mm. level.

Immediate Decrease in the Resistance to the Passage of Bile into the Intestine at the Perception of Food.

Increased resistance to the passage of bile into the intestine during a fast was a constant finding in all the experiments made upon ten different animals. It now became a matter of interest to study the
direct influence of feedings. Accordingly food was proffered to a fasting dog while a manometer was connected with the tube leading to the lower common duct. The recorded pressure had shown a great resistance to the passage of bile into the intestine, as always during a fast. At the mere perception of the food, before any had been given the animal, the column of bile suddenly dropped. This experiment was tried again and again in ten different animals and in over 75 per cent of the trials the result was the same, that is to say there was a relaxation of the musculature about the lower end of the common duct, due, most obviously, to a "psychic reflex." In these instances the actual act of eating often brought about a further relaxation as evidenced by a still greater drop of the bile column (Text-figs. 3 to 5). In all instances, including those in which no drop occurred at the perception of food, the act of eating regularly caused a sudden decrease in the resistance to the passage of bile into the intestine as shown by a drop of the column of bile in the manometer. Soon after this a somewhat increased resistance made its appearance. This will be discussed below.

Usually but two or three experiments demonstrative of the psychic effect could be performed with one animal, because the mere act of placing it on a table for connection with the manometers brought about a conditioned reflex—the animal sniffed expectantly, became excited, and by the time the tubes could be connected to the manometer the change in resistance to bile flow which it was desired to study had already occurred,—a low column of bile now sufficed to cause flow through the ampulla.

What appears to be a phenomenon of similar nature was recorded years ago by Bruno in Pavlov's laboratory.

Bruno worked with a dog in which a Pavlov biliary fistula had been made,—the ampulla of Vater surrounded by a good portion of duodenum had been transplanted into the anterior abdominal wall and the defect in the duodenum closed. On six occasions the animal was shown food but not allowed to eat, and on two of these occasions bile was seen to issue from the ampulla in amounts of 1.7 and 1.9 cc. respectively, though ordinarily the secretion did not appear until 15 to 45 minutes after the taking of food. Bruno also records the observation of Pavlov that gastric juice collected from fasting dogs during periods of "fictitious feedings" frequently contained appreciable amounts of bile. These instances of apparent sphincter relaxation are classed by Bruno among "psychophysiologic" reflexes.
The phenomenon as we have observed it is represented graphically in Text-figs. 3 to 5. In Text-figs. 3 and 5 one can note as well the further lessening in resistance to the passage of bile into the duodenum when the animal began to eat.

**Dog 5, Text-Fig. 3.**—55 days after operation the dog was healthy and active. Following a fast of 72 hours the resistance to bile flow was such as to uphold a 155 mm. column of bile in the manometer attached to the tube leading to the lower common duct. The animal was then shown food and at the first perception of it the column dropped immediately to 90 mm. and in 1½ minutes to 70 mm. Eating was then allowed and at the first swallows the pressure fell at once still further, to 30 mm. The animal continued to eat. The column was raised within a period of 2 minutes to 60 mm. by allowing bile to flow into the manometer from the reservoir. No flow through the ampulla now occurred. The column was then raised to various levels as shown in the chart and allowed to remain 1 or 2 minutes at each. It did not fall until it reached the 160 mm. level. Following the initial decrease in the resistance offered to the flow of bile there had occurred almost immediately an increased resistance to it.

Another experiment on the same dog is represented in Text-fig. 4. It was performed 10 days later and after a fast of 48 hours. The result was similar but not as marked. The level of bile in the manometer connected to the lower common duct, and standing at 135 mm. above the latter, dropped to 60 mm. at the first perception of the nearness of food. No further change occurred with the actual taking of food but 2 minutes later while the animal was still eating, the column of bile in the manometer was raised to various levels as shown in the chart. Within 6 minutes it had been raised to 200 mm. Only then did flow of bile through the ampulla occur.

**Dog 9, Text-Fig. 5.**—35 days after operation the dog was healthy and active. Following a fast of 72 hours the resistance to the flow of bile into the intestine was tested as shown on the chart and found capable of supporting a 240 mm. column of bile. Food was then offered to the animal and immediately at the perception of it and before any had been eaten the bile column in the manometer dropped to 175 mm. and a minute later to 135 mm. Following the first swallows of food it fell further to 80 mm. After a minute of eating the column was raised by allowing bile to flow into the manometer from the sterile reservoir and after several such tests which disclosed a gradually increasing pressure the resistance was found to be high enough to hold back a column of bile 400 mm. in height.

The phenomenon was also demonstrated by measuring the amount of fluid passing through the ampulla of Vater at a constant pressure, using for such determinations a type of "flow" manometer. Any decrease in the resistance offered to the passage of fluid into the intestine
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Text-Fig. 3.

Text-Figs. 3 to 5. Influence of the sight of food and feeding upon the resistance offered to the flow of bile into the intestine.
resulted in a sudden increase in the rate at which the fluid flowed through the apparatus into the ducts.

The manometer used for this purpose is represented schematically in Text-fig. 6. A reservoir (R) was connected with a tube to an ordinary separatory funnel (S) which could be attached in turn to the tube leading to the lower common duct. The apparatus was sterilized by boiling or autoclaving. With all joints air-tight, the reservoir alone was open to the air but protected from contamination with a sterile cotton plug (P). By adding the heights of the two columns of fluid A to B plus C to D the pressure exerted by them could be estimated; and this could be varied at will by raising or lowering the apparatus. The rate of bile flow through the ampulla was measured roughly by counting the drops issuing from the nozzle B in quarter-minute intervals. Since 3 to 6 cc. of bile entered the intestine during the observations the surface level in the large reservoir was not appreciably changed, for a flow of 10 cc. reduced this but 1 or 2 mm.

*Dog 19, Text-Fig. 7.*—The operation for intubation of the common duct under ether had been performed 10 days before and the dog was healthy and active. After a fast of 48 hours the “flow” manometer was connected to the tube leading to the lower common duct and the pressure exerted by the apparatus was so ad-
justed as to equal that of a column of bile 160 mm. high. There was a slight flow of about 50 drops (1.6 cc.) to the intestine before food was given, as the chart shows. But at the perception and taking of food there was a sudden and pronounced increase in this. Within 2 minutes three times as much fluid had entered the intestine as in the 2 minute period preceding the taking of food. Flow then ceased entirely. 1½ minutes later there was a second period of flow lasting 4 minutes. In all 105 drops, or about 3.5 cc., of bile flowed into the intestine in the 7 minutes following the taking of food.

**Text-Fig. 7. Influence of food ingestion on the flow of bile into the intestine.**

*The Secondary Increase and Decrease in the Resistance to the Flow of Bile into the Intestine after Feeding.*

Following the transient decrease in the resistance to the passage of bile through the lower common duct after taking food, as described in these experiments, we observed a prompt increase in it as has just been noted. This was found by later experiments to endure for a variable time, becoming gradually less and less. Within half an hour or more the "normal" resistance was approached, namely that capable of supporting a column of bile 100 to 120 mm. in height. The increased resistance shortly after feeding has been illustrated in the experiments described above (Text-figs. 3, 4, 5, and 7). Babkin has reviewed the experiments with a Pavlov biliary fistula and has
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described a "latent period" between the giving of food and the first appearance of bile at the ampulla. The interval varied between 15 and 45 minutes depending upon the type of food given.

In our experiments the period of increased resistance in the lower common duct soon after feeding was of variable duration from 10 to 35 minutes. The degree of increase was often very great. In one case a 400 mm. column of bile was supported a few minutes after eating (Text-fig. 5). Eighteen feeding experiments in all were performed on ten dogs and the phenomenon was observed in every one. A type protocol will be given.

This experiment (see also Text-fig. 8) is chosen for description because it was carried out upon an animal fasted and then fed, several times previously, while the manometers were connected to the tube leading to the lower common duct. Through the experience of the repeated tests the animal had developed a conditioned reflex which resulted in the passage of bile into the intestine at a low pressure, but in spite of this a secondary increase in the resistance offered to passage regularly occurred after food was taken, and it became necessary to raise the column of bile in the manometer to a level of 275 mm. before fluid flowed into the intestine. Soon after this, however, relaxation of the musculature about the lower common duct began, as shown by the passage of bile through the ampulla at lower pressures.

Dog 9, Text-Fig. 8.—45 days after intubation the animal was healthy and active. It had been fed many times while manometer measurements upon it were under way. No food had been allowed for 48 hours previous to the present test. The animal became restless and sniffed about expectantly when placed on the table in order that the manometer might be connected to the tube leading to the lower common duct. It was not surprising, therefore, to find when this had been done, that a column of bile only 100 mm. in height was sufficient to cause a flow of bile through the ampulla, as the chart shows. The animal was shown food and permitted to eat. Within 2 minutes a 125 mm. column of bile was supported and in 10 minutes one of 240 mm. although a much lower column had caused flow into the intestine a few minutes before. Only after 20 minutes did the resistance decrease so that bile passed into the intestine at a lower pressure head, 175 mm. In half an hour the resistance had lessened to that originally noted, one supporting a column of about 100 mm. of bile; but even then it fluctuated. At one moment flow of bile into the intestine occurred at a pressure of 120 mm., and a little later only at one of 160 mm. Tests were made at short
intervals, the results of each being represented on the chart. The broken lines indicate artificial raisings of the pressure, the solid lines movements of the column of bile in the manometer in response to changes in the resistance.

Text-Fig. 8. The secondary increased resistance offered to the flow of bile into the intestine, following ingestion of food, and its gradual lessening, as shown by variations in the height of a column of bile in the manometer.

The Effect of the Ingestion of Weak Acid and Alkali upon the Resistance Offered to the Passage of Bile into the Intestine.

The reaction of the gastric contents may conceivably influence the resistance to the flow of bile into the intestine. For there is an immediate lessening in the resistance upon the taking of food, and a gradual increase in the half-hour or hour following, during which the reaction of the gastric contents is presumably becoming more acid. Since food may at this time be passing through the pylorus, a possible mechanical effect of peristalsis may in addition be invoked to explain the findings.
Fasting dogs were fed weakly acidified and alkalized solutions and the resistance offered to the passage of bile through the ampulla was estimated at such times. Very recently while these experiments were under way Cole\textsuperscript{31} has reported observations of the sort on the anesthetized dog. He introduced acid or alkali into the stomach and observed an immediate decrease or increase respectively in the resistance to bile flow into the intestine as measured by the height of a column of fluid supported in a manometer tied in the common duct. We have noted the same relationship, though owing to the impossibility of controlling precisely the reaction of the gastric contents in the unanesthetized animal, our findings were not as constant as Cole's.

Seven experiments were performed in four animals appropriately intubated. Various amounts of $\nicefrac{1}{10}$ HCl or 5 per cent NaHCO$_3$ were given to the fasting animals by stomach tube. A type experiment follows.

\textit{Dog 9, Text-Fig. 9.}—18 days after an "altercursive intubation," the animal was healthy and active. No food had been given for the 48 hours previous to the experiment. An empty manometer was substituted for the balloon and, with the secretion of bile by the liver, a column of it 220 mm. high collected as a result of the resistance to passage of the secretion into the intestine. The findings after this level had been attained are charted in Text-fig. 9. They were recorded by the cooperation of two workers, one constantly observing and calling out the level of the bile column in the manometer, the other, who held a stop-watch, plotting as ordinates on graph paper the reported level with minutes as the abscissae. The text-figure is the graphic representation of the findings obtained in this way, not a kymographic tracing, which it superficially resembles. The slight vertical fluctuations in the level of the bile column which will there be noted were due to respiratory movements. As the chart shows, a column of bile about 250 mm. in height could be maintained in the manometer. Slight decreases in the resistance occurred but the column did not fall below the 200 mm. level.

It has been estimated\textsuperscript{29} that the acidity of gastric juice is equivalent to or slightly stronger than that of $\nicefrac{1}{10}$ hydrochloric acid. Accordingly the animal was now given 100 cc. of $\nicefrac{1}{10}$ HCl by a stomach tube already \textit{in situ}. The tube had been passed 10 minutes previously without affecting the level of bile in the manometer. Practically at once, upon giving the acid, a drop of the bile column in the manometer to 90 mm. occurred. 10 minutes later when the pressure ex-

\textsuperscript{29}Menten, cited by Mathews, A. P., Physiological chemistry, New York, 4th edition, 1925, 357.
pressive of the resistance had risen but only to 130 to 140 mm. another drop took place and again, 20 minutes later, when the manometer showed that the pressure in the biliary tract had risen to the equivalent of the weight of a column of bile 180 to 190 mm. in height, it once more, without obvious cause, fell rapidly to 100 mm.

Now 7.0 gm. of sodium bicarbonate in 100 cc. water was given. 15 minutes later the bile that was being secreted had raised the pressure in the biliary tract to 230 mm., and 10 minutes later to 260 mm., when there once more occurred a flow into the intestine with a fall in pressure.

Control feedings of water elicited no changes in the resistance offered to the flow of bile into the intestine.

Experiments like this one, while not conclusive in themselves, point to the occurrence of changes in the resistance to the flow of bile through the common duct referable to alterations in the reaction of the gastric contents.

Text-Fig. 9. Influence of the ingestion of acid and alkali upon the resistance offered to the flow of bile into the intestine.
DISCUSSION.

The work here reported is the first of this nature, so far as we are aware, that has been done upon animals under practically normal conditions. Since the approach to the normal is of prime importance, procedures rendering the musculature of the lower portion of the common duct visible have been avoided. Under the circumstances of the experiments described it has been possible to measure the resistance offered to bile flow through the ampulla at any time desired. We have used this measurement as a criterion expressive of the conditions under which bile makes its escape into the intestines. No attempt has been made to differentiate experimentally the activities of the duodenal musculature about the lower common duct as apart from that of the sphincter of Oddi. Recently Carlson and Burger have stressed the possible importance of the duodenal musculature in the retention or escape of bile. It undoubtedly plays a rôle especially during active peristalsis. More will be said of this below.

If the control of bile flow through the ampulla is due to the sphincter it might be objected that the operative interference incident to intubation of the common duct would probably destroy or at best interfere with nerve filaments passing to and from the muscle of Oddi. Since our findings were positive ones, the sphincter retaining its power of relaxation and contraction, such disturbances cannot have been very serious. Either the nerves affected play an unessential part in the function of the sphincter, or they had reestablished their normal connections.

Whatever be the explanation of our findings, they show definitely that the escape of bile into the duodenum is under a definite control and is markedly influenced by varying the physiological conditions.

In these experiments there was a remarkable constancy of the findings. In the normal unanesthetized animal recently fed the resistance to the passage of bile through the ampulla supports a column of bile or physiologic saline solution 100 to 120 mm. in height, a finding

Since this was written, J. C. Potter and F. C. Mann have published in the *Am. J. Med. Sc.*, 1926, cixi, 202, studies on the "Pressure changes in the biliary tract" in unanesthetized dogs, also under practically normal conditions. We regret that the appearance of this most interesting paper occurred too late to permit of discussion of their findings herein.
which agrees well with many of the observations of others made under ether. In the fasting animal this resistance is always without exception much increased. However, at sight and smell of food it usually decreases and invariably does so at once upon eating, and, as our experiments show, permits an increased flow of fluid through the ampulla, at constant pressure. This marked but transient relaxation is followed almost as soon as food reaches the stomach by an increased resistance to the flow of bile which endures for about half an hour. Experiments with acid and alkali feeding show that the sequence of events just described with the exception of that due to the psychic stimulus may be explainable by changes in the gastric acidity after the taking and digestion of food. That this may not be the only factor engaged, and probably is not, is well recognized by us.

Whether the intermittent ejection of acid chyme through the pylorus stimulates relaxation of the musculature about the lower common duct cannot be determined from our observations. In favor of such a view is the finding that the resistance offered to bile flow through the ampulla during gastric digestion is a fluctuating one (see Text-fig. 8), but almost all our further evidence argues against it. For example, the lessening in the resistance to the passage of bile into the intestine which occurs when food is shown the animal takes place so promptly and rapidly that it must certainly be the result of a reflex. The same may be said of the rapid relaxation following administrations of acid to the fasting animal (Text-fig. 9). In the fluctuation of the resistance to the flow of bile through the ampulla during gastric digestion the duodenal musculature may well play a part.

A consideration of the rôle of the gall bladder in the passage of bile into the intestine is essential to any discussion of the physiology of bile flow. This will be taken up in a succeeding paper.

SUMMARY.

Under specially controlled conditions in the healthy unanesthetized dog we have measured the resistance offered to the flow of bile through the lower common duct.

The average resistance 4 to 12 hours after a feeding was found to correspond to the pressure of a column of bile 100 to 120 mm. in height.
After a 24 to 72 hour fast the resistance was such as to support a much higher column of bile, one of 300 mm. at times. The exhibition of food to the fasting animal usually precipitated a reflex lessening in the resistance to the flow of bile to the intestine, the actual taking of food always brought it about. This was transient and was soon followed by a period of increased resistance lasting 10 to 30 minutes after food had entered the stomach. There succeeded a drop in resistance which was gradual and fluctuating.

We have observed an increase in the resistance to the flow of bile into the intestine after alkali has entered the stomach, and a decrease after acid has been administered.

We attribute the sudden changes chiefly to the activity of the sphincter of Oddi.

EXPLANATION OF PLATE 5.

Fig. 1. Animal with an “altercursive intubation.” For description see text.
Fig. 2. Manometer connected with the collecting tube of an “altercursive intubation.” For description see text.
(Elman and McMaster: Resistance to bile flow to intestine.)