ON THE EXPULSION OF BILE BY THE GALL BLADDER; AND A RECIPROCAL RELATIONSHIP WITH THE SPHINCTER ACTIVITY.

BY PHILIP D. McMASTER, M.D., AND ROBERT ELMAN, M.D.

(*From the Laboratories of The Rockefeller Institute for Medical Research.*)

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In the present paper we shall offer proof that the gall bladder discharges bile on physiological occasion, through the agency of forceful contractions. The phenomenon has been encountered in healthy, unanesthetized animals with the biliary passages permanently intubated in such a way[1-3] that the pressure exerted by the vesica fellea and the resistance to the flow of bile into the gut could be studied simultaneously and under controlled conditions. The existence of a relationship between the activity of the gall bladder and that of the musculature about the lower common duct, as expressed in alterations of the resistance just mentioned, has been demonstrated by the method.

The most diverse views of gall bladder activity and function have been proposed in the past, and they all still find adherents. Some workers hold the gall bladder to be an active, contractile viscus,[4-8] capable of expelling its contents. In contrast to such an opinion Sweet,[9]—who reasons from the anatomic structure of the human viscus and cystic duct,—believes that nothing entering the gall bladder through the duct ever leaves it by the same route but is sooner or later resorbed. The midground between these positions is held by many ob-

[1] Elman, R., and McMaster, P. D., *J. Exp. Med.*, 1926, xliv, 151.

[2] McMaster, P. D., and Elman, R., *J. Exp. Med.*, 1925, xli, 513.

[3] Rous, P., and McMaster, P. D., *J. Exp. Med.*, 1923, xxxvii, 11.

[4] Doyon, M., *Arch. physiol. norm. et path.*, 1893, v, series 5, 678, 710.

[5] Bainbridge, F. A., and Dale, H. H., *J. Physiol.*, 1905, xxxiii, 138.

[6] Okada, S., *J. Physiol.*, 1915–16, l, 42.

[7] Judd, E. S., and Mann, F. C., *Surg., Gynec. and Obst.*, 1917, xxiv, 437.

[8] Mann, F. C., and Giordano, H. S., *Arch. Surg.*, 1923, vi, 1.

[9] Sweet, J., *Internat. Clin.*, 1924, i, 187.

servers. Winkelstein,[10] most recent among them, believes that the organ is purely passive, filling and emptying as result of extraneous alterations of the pressure brought to bear upon it, more especially in the course of respiration. That the gall bladder fills with bile is disputed by nobody.

Renewed interest in the problem of the contractility of the gall bladder has sprung from an application to it of the law of contrary innervation proposed by Meltzer.[11] He advanced an attractive hypothesis according to which, at each discharge of acid chyme from the stomach, the sphincter of Oddi relaxed and the gall bladder synchronously contracting, ejected a gush of bile into the duodenum. He noted in another connection that local applications of magnesium sulfate solutions to the duodenal mucosa cause relaxation of the muscles of the intestinal wall. The clinical application of this hypothesis and fact by Lyon[12] has resulted in many attempts at "non-surgical drainage of the gall bladder" with the accumulation of a great mass of conflicting evidence as to whether this object is ever accomplished. Since the literature has been reviewed by others[13-15] we need not enter into it here.

In a companion paper to the present one[1] it has been shown that an immediate decrease in the resistance offered to the passage of bile into the intestine takes place when an animal begins to eat, and usually indeed upon the mere perception of food. Conditions at such times are especially favorable to the escape of bile into the intestine. Does this occur in quantity, and what are the forces promoting it? Our first experiments have been directed to these points.

Technique.

A full description of the technique used in our studies has been given in the accompanying paper.[1] We have utilized healthy dogs in which some time previously there was installed, under ether anesthesia, the apparatus of an "altercursive intubation"[2] whereby bile flowing from the liver can either be collected under sterile conditions or turned back at will into the common duct to flow as usual through the ampulla of Vater into the duodenum. In order to study the influence of the gall bladder, the connections of the organ were left

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[10] Winkelstein, A., *J. Am. Med. Assn.*, 1923, lxxx, 1748.

[11] Meltzer, S. S., *Am. J. Med. Sc.*, 1917, cliii, 469.

[12] Lyon, B. B. V., *J. Am. Med. Assn.*, 1919, lxxiii, 980.

[13] Mann, F. C., *Physiol. Rev.*, 1924, iv, 251.

[14] Friedenwald, J., Martindale, J. W., and Kearney, F. X., *J. Med. Research*, 1922, ii, 349.

[15] Matsuo, I., *J. Am. Med. Assn.*, 1924, lxxxiii, 1289.

intact in a number of animals, with result that the cannula inserted into the upper part of the common duct formed the means of exit for both liver and gall bladder bile; while in others the cystic duct was sectioned and ligatured at the time of the intubation. In some cases the gall bladder influence was studied more directly by intubation of the cystic duct or of the duct which results from the union of this latter with the small tributary from the left central lobe of the liver. As an "altercursive intubation" of the common duct had also been carried out in these cases, they were the subject of what one may term a "triple intubation," the details of which will be described more fully below.

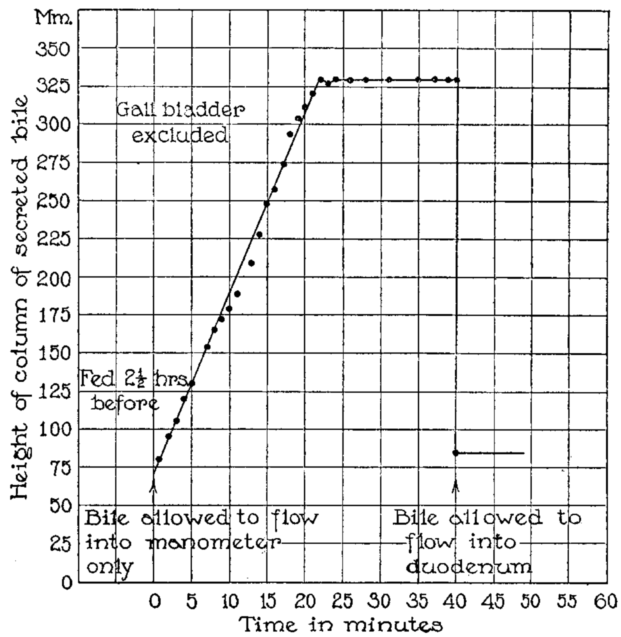
As in our many previous intubations of various sorts aseptic precautions were taken in the handling of the tubes. Only instances in which the bile and biliary tracts remained sterile will be considered in this paper. Cultures of the bile were taken at frequent intervals during the course of the observations and stained sediments from it, as obtained by centrifugation, were examined for bacteria. At autopsy the sterility of the bile was again ascertained by culture. Cultures from the liver tissue were also made on agar and in bouillon. Despite the most careful precautions the bile of many of our animals became infected owing to the constant handling of the tubes. All such instances were discarded as, too, were any suggestive of obstruction in the cannula-tube systems.

The animals were given a diet of bread wet with milk, and lean meat, 450 gm. of the latter to each kilo of the bread and milk. They were fed daily in the morning, and allowed to eat until satiated. The time when the animal was last fed proved to be an important factor in the results and careful record was made of it.

To determine the pressure exerted upon the contents of the gall bladder and bile ducts, and to measure resistance to the flow of bile into the intestine, the rubber tubes leading from and to various regions of the biliary tract were repeatedly brought into connection with sterile manometers previously filled with the animal's own sterile bile as collected some time previously. The changes in the level of the columns of bile in the manometers were recorded by the cooperation of two or four observers, according to the number of manometers to be observed. The watchers at each of these instruments read off all the alterations in levels of the bile columns in the manometers as they occurred, while the other workers, who held stop-watches, plotted, on graph paper, the pressures as ordinates against time in minutes as abscissæ. Text-figs. 1, 2, 5, and 6 represent these graphs as obtained.

Secretion Pressure of the Bile.

Before the action of the gall bladder can be intelligently discussed it is necessary to consider the cause of the pressure existing within the biliary tract. Of the forces producing it, that of bile secretion by the liver is chief. This has been well studied, notably by Herring and Simpson,[16] who found in dogs under chloroform anesthesia with the gall bladder excluded, that the bile filled a manometer, to an average maximum of 300 mm. when obstruction was produced. The animals were fed 6 hours before the experiment. The time required for the secretion to reach the high level was variable, from 1 or 2 to often as much as 4 hours. Mitchel and Stifel[17] found in



TEXT-FIG. 1. The maximum secretion pressure of bile and its rate of formation in the presence of a pressure obstacle. The dots record the actual observations on an animal. It will be seen that the rate of secretion was unaffected by the increasing pressure obstacle.

the bile ducts of cats anesthetized after total biliary obstruction of 2 to 6 days duration a pressure equivalent to 250 to 300 mm. of water.

It seemed advisable to determine the pressure developing on

[16] Herring, P. T., and Simpson, S., *Proc. Roy. Soc. London, Series B*, 1907, lxxix, 517.

[17] Mitchel, W. T., and Stifel, R. E., *Bull. Johns Hopkins Hosp.*, 1916, xxvii, 78.

obstruction in our unanesthetized animals. Accordingly, many days or weeks after intubation, the liver bile of dogs with gall bladder excluded by severance of the cystic duct was allowed to flow directly into a vertical manometer tube from which there was no escape except by way of the opening at the top. The fluid rose to a height slightly greater than that noted by Herring and Simpson in anesthetized animals, that is to say to about 320 mm. on the average, the figures for the individual animals, two of which were tested a second time, being as follows: 302,* 305, 308,* 314, 318, 321, 324, 326, 326,† 330, 333,† 335.[18] The time required to reach the maximum point was much shorter than in the experience of these observers, being only 15 to 30 minutes. No relation was evident between the size of the animal and the pressure obtained.

In Text-fig. 1 is charted an instance typical of all. The animal yielding it had undergone an "altercursive intubation" 2 months before and was healthy and active. $2\frac{1}{2}$ hours before the experiment was begun food was given. The tube draining the liver bile, which up to that time had been delivering the fluid to the intestine by way of the rubber detour, was then brought into connection with a vertical glass manometer of 3 mm. bore. As the liver secreted bile the column rose rapidly to a level 330 mm. above that of the duct-cannula junction. It will be noted that despite the progressive pressure obstacle the rate of secretion remained constant, the bile column rising regularly, so that the readings of its height plotted against the time formed a straight line. The finding was obtained in all such experiments, twelve in number in ten different animals. The formation of bile, then, was as rapid against high pressures as low, until a maximum point was reached at which secretion suddenly ceased in the face of the high pressure.

When bile was collected at zero pressure for the brief periods necessitated by the experiments the same uniformity was noted in the rate of secretion from minute to minute. More will be said of this below.

[18] * and † indicate that the figures were obtained from the same animals upon different occasions.

The Effect of Food on the Flow of Bile in Animals with Gall Bladder Excluded.

Although changes in the pressure exerted against bile secretion do not affect its rate of formation, the giving of food does. This latter fact has long been a truism of physiology.[19,20] Yet as a preamble to further observations, it has been necessary to study the phenomenon carefully in our dogs.

In eight animals with ligated and sectioned cystic duct, the tube draining liver bile was connected to a sterile graduate and the amounts of bile secreted during 5 minute periods were recorded. While the bile was being collected the animals were allowed to eat the bread, milk, and meat mixture for 2½ to 3 minutes. No change in the rate of secretion was noted during the first 5 to 15 minutes. Then a gradual progressive increase appeared, as depicted in the lower portions of Text-figs. 5 and 6. The stimulus was short lived, the amount of bile secreted returning to "normal" in about 45 minutes. The bile was not markedly changed in its gross appearance at any time—it was still limpid, and a rather light brown in color—but it usually was found on analysis to contain less pigment per unit of volume than before the feeding, in conformity with previous knowledge.[21,22] When, however, the experiment was repeated in animals with the gall bladder connections undisturbed, the bile obtained after feeding was very different from that voided previously. Before this latter finding can be discussed in detail we must digress to consider certain pressure relations existing within the biliary tract.

The Filling of the Gall Bladder and Retention of Its Contents.

In an earlier paper from this laboratory[23] it was shown that the pressure exerted by a column of bile 60 to 70 mm. high connected with the common duct is sufficient to cause a flow of bile into the gall bladder of the anesthetized dog. In the unanesthetized animal the pressure within the viscus is generally about equal to that of a column

[19] Bruno, G. G., Dissertation, St. Petersburg, 1898; and Klodnizki, Dissertation, St. Petersburg, 1902; cited by Babkin, B. P., Die äussere Sekretion der Verdauungsdrüsen, Berlin, 1914, 344.

[20] Bruno, G. G., *Arch. sc. biol.*, 1899, vii, 87.

[21] McMaster, P. D., Broun, G. O., and Rous, P., *J. Exp. Med.*, 1923, xxxvii, 395.

[22] Dastre, A., *Arch. physiol. norm. et path.*, 1890, ii, series 5, 800.

[23] Rous, P., and McMaster, P. D., *J. Exp. Med.*, 1921, xxxiv, 47.

of bile 100 mm. in height, as our experiments to be detailed below will show. The secretion pressure being much more than this, it is obvious that no force other than that resulting from the liver activity is needed to fill the gall bladder, provided bile does not escape into the intestine. However, in our companion paper[1] several factors have been recognized which may conceivably be responsible for such an escape of bile through the alterations they excite in the resistance offered to bile flow by the musculature about the lower portion of the common duct. This resistance in the normal animal, fed 4 to 12 hours previously, is sufficient to support a column of bile 100 to 120 mm. in height. In the fasting animal, however, it will support one 250 to 300 mm. high. Immediately after taking food and again later, during the process of digestion, the resistance is greatly lowered, and a bile column 50 to 80 mm. in height suffices to cause a flow of bile through the ampulla. From this it is evident that save at these latter times the bile, as secreted, backs up perforce into the gall bladder, this being the way of least resistance. Whether there is an aspirating effect on the organ due to the respiratory movements, as suggested by Winkelstein,[10] it is not necessary to consider, for the foregoing facts alone will suffice to explain the filling of the organ. Once within the gall bladder the bile undergoes rapid concentration.[23] This concentrating activity may well be more important for the retention of the gall bladder contents than the valve-like reduplications of the mucous lining of the cystic duct (Heister's valves). What part these may play remains to be determined as does that of the circular ring of muscle sometimes situated in the cystic duct.[24]

The Influence of the Gall Bladder on the Pressure of Bile in the Common Duct.

From the circumstance that the gall bladder receives and concentrates large amounts of bile, as well as because of the delay which its presence causes in the development of jaundice after obstruction of the common duct,[25] it might be inferred that the organ acts to

[24] Westphal, K., *Klin. Woch.*, 1924, iii, 1105.
[25] Afanassiew, M., *Z. klin. Med.*, 1883, vi, 281.

prevent the development of a high pressure within the duct system. And such is the case.

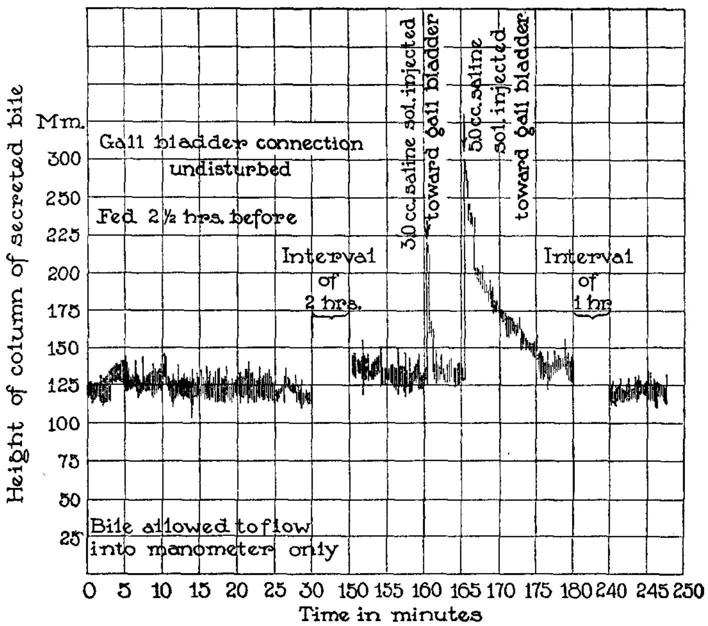
In six animals an "altercursive intubation" was done without interference with the gall bladder connections. In such instances the bile simply made the detour of the tubes on its way to the duodenum, and encountered at the lower end of the common duct the normal resistance to its passage into the gut. This, from our figures given in the previous paper, would be sufficient, except after the taking of food, to keep the gall bladder full.

In nine experiments upon these animals with undisturbed gall bladders, we connected to a manometer the tube leading from the upper portion of the common duct, taking due care that no bile escaped from the latter during the process. The animals had been fed the usual meal of bread, milk, and lean meat several hours previously. During the succeeding several hours the column of bile never rose to more than 100 or 150 mm. above the level of the duct, that is to say it never more than approximately equalled the resistance which would normally have been exerted against the escape of bile into the intestine. In none of our experiments did the pressure within the common duct ever approach the maximum secretion pressure of the liver.

In Text-fig. 2 is plotted the result of such an experiment. In sharp contrast to this are the findings already described above (Text-fig. 1) when the gall bladder had been cut off from connection with the duct-manometer system.

Dog 12, 9½ kilos, Text-fig. 2. An "altercursive intubation" had been carried out 9 days previously, with the gall bladder connections left intact. The animal had been fed each morning and at the time of the observation was in the best of health. 2½ hours after feeding, the experiment was begun, the tube leading from the upper portion of the common duct being then connected with a manometer of about 3 mm. bore, one that is to say which required only 1 cc. of bile for a rise of 141 mm. in the column. As the chart shows, the pressure that developed and was maintained in the common duct during the next 4 hours equalled that of a column of bile about 125 mm. in height. There were frequently repeated, rapid but slight, incidental fluctuations due to the respiratory movements. Usually the column then rose or fell about 10 to 15 mm., occasionally on a deep breath 20 to 30 mm. The amplitude of the larger of these fluctuations and of certain more considerable yet still slight excursions of the bile column in the manometer is shown in the text-figure which is typical of all such experiments. Only the readings of two brief periods each of half an hour and another of 10 minutes are recorded in the chart. As already stated the manometer remained connected and completely obstructing the common duct for over 4 hours.

From the failure of the bile column to rise far it was obvious that the gall bladder must be storing the bile almost as fast as it was formed. To test its ability in this connection, 3 cc. of 0.9 per cent sodium chloride solution was run



TEXT-FIG. 2. The pressure developing during the first few hours of total biliary obstruction in an animal with the gall bladder connections left undisturbed. Contrast with Text-fig. 1. The manometer was connected with the common duct for over 4 hours.

abruptly into the common duct through the tube connected with the manometer. The momentary increase in pressure caused by this disappeared almost at once. 5 minutes later 5 cc. more of the solution, injected into the common duct and toward the gall bladder, caused an increase in pressure sufficient to raise the bile column to 300 mm. in the manometer, that is to say, to almost the maximum pressure of total obstruction whether the gall bladder be in or out. There followed a rapid return of pressure to the previous level. Although the manometer remained in connection with the common duct for another hour there was still no evidence of an increase in pressure within the biliary tract above 125 mm., the level "normal" for the animal; and the experiment was discontinued.

Unlike the "straight line curve" of increasing pressure upon obstruction, obtained in animals with the gall bladder excluded, as noted in Text-fig. 1, no rise in the curve occurred during the first 4 hours when the gall bladder was present.

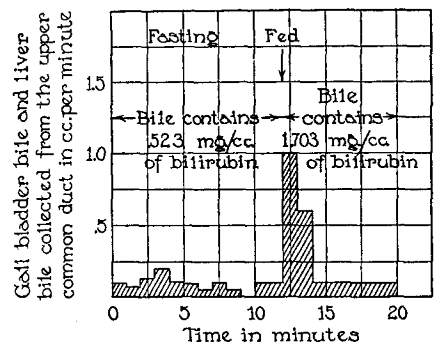
The Effect of Food on the Bile Yield of Animals with Gall Bladder Undisturbed.

In our dogs possessing intact gall bladders a decided difference was to be noted in the gross appearance of the bile collected before and after feeding, as already has been said. It may be recalled that the "altercursive intubation" in these animals permitted the bile simply to make a detour on the way to the gut. The normal resistance to the passage of bile into the intestine would be sufficient to divert the secretion to the gall bladder soon after a feeding.

The bile secreted by these animals when they had been fasting for 24 to 48 hours was allowed to drain freely into sterile graduates and then, after half an hour, food was given while the bile collection was continued. The secretion of these animals while fasting showed the characteristics of liver bile under such circumstances, that is to say it was more concentrated than in full fed animals; but immediately after the first swallows of food an abundant gush of far darker and more viscid bile suddenly flowed into the graduate, the darkness in color being due, as quantitation showed, to a high concentration of bilirubin. This experiment was performed twice with each of the six dogs with undisturbed gall bladder connections, and in all instances the same result was obtained. The phenomenon suggests, of course, a discharge of gall bladder contents. The finding (Text-fig. 3) should be compared with the delayed, and slow and gradual increase in the flow of bile observed after a feeding in animals with the gall bladder excluded from the collecting system (lower portions of Text-figs. 5 and 6). In instances of the latter sort in which liver bile alone is collected the food stimulus to secretion, far from causing the bile to become thicker and darker has effect to render it more abundant, more watery, and light in color,—a fact long known.

Specimen Protocols.

Dog 9, Text-fig. 3, weight 8½ kilos. 53 days prior to this experiment an "altercursive intubation" was carried out under ether. The gall bladder connection with the common duct was left undisturbed. During the long preliminary period the animal remained in excellent health, and bile was allowed to flow into the intestines as usual, by way of the altercursive detour. The dog was now fasted for 72 hours, after which the tube,—which drained not only the liver but the gall bladder,—was disconnected, and the amount of bile collected from it in each minute was recorded for half an hour. Food was then given

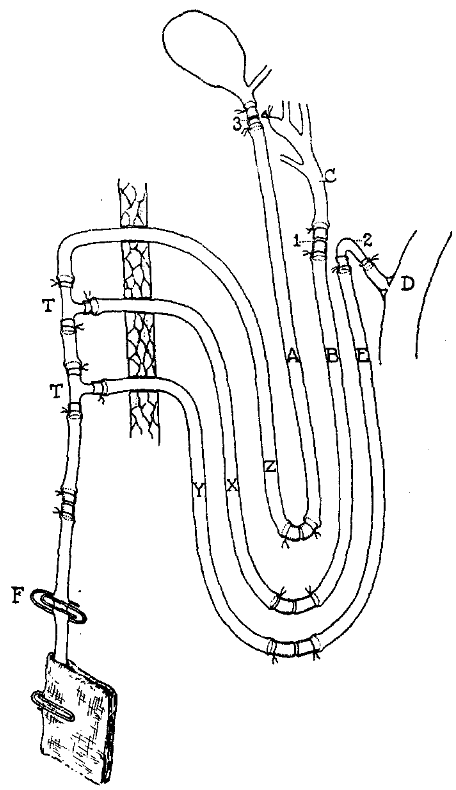


TEXT-FIG. 3. Food as a stimulus to the discharge of bile from the gall bladder. Bile was collected from the upper common duct draining both liver and gall bladder. The gall bladder connections had been left undisturbed. When food was given a large amount of viscid and highly pigmented bile was voided practically at once. Compare the finding with the gradually increasing output of bile from animals with the organ segregated (lower portions of Text-figs. 5 and 6). The differences in the amount and nature of the bile collected point to a discharge of bile from the gall bladder.

while the collection of bile was continued. As the chart indicates, only 1.1 cc. of bile had appeared during the 15 minutes before this. It was light in color, limpid, and contained 0.523 mg. of bilirubin per cc. Pigment determinations on it were carried out by a method described elsewhere.[21] Within 2 minutes after food was first taken a gush of dark viscid bile appeared (1.6 cc.) which contained upon analysis 1.703 mg. of pigment per cc.

Dog 11, weight 9¼ kilos. 18 days before this experiment an "altercursive intubation" had been done under ether. The gall bladder connection had been left undisturbed. Thereafter bile was allowed to flow to the intestines as usual. For the 72 hours previous to the experiment the animal was fasted, after which the bile from the tube draining liver and gall bladder was collected into a sterile graduate and the amounts recorded every 5 minutes.

In the first 10 minutes but 1.2 cc. of relatively light-colored limpid bile was obtained, though one not nearly so light as liver bile is in an animal which had not fasted. It contained 0.77 mg. of bilirubin per cc. The dog was then fed and in the next 10 minutes 10.2 cc. of a dark, viscid bile having a bilirubin content of 1.61 mg. per cc. flowed into the graduate.



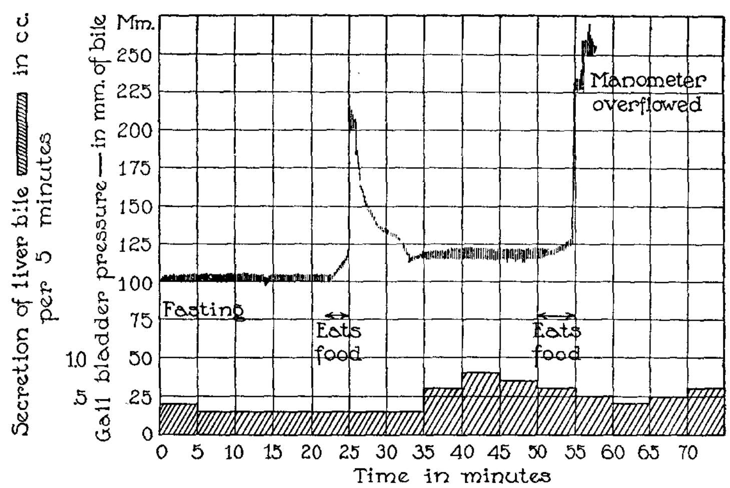
TEXT-FIG. 4. Plan of the "triple intubation." Besides the tubes *XB* and *YE* leading from and to the common duct which constitute the so called "altercursive intubation" of previous papers, there is a third tube *ZA* communicating with the gall bladder. When the tube was clamped at *F* bile flow to the intestine went on as usual for weeks or months. There was merely a detour of the fluid to the outside.

Proof that the Gall Bladder Expels Bile by Forceful Contraction.

The phenomena as described suggested a forceful discharge of bile from the gall bladder. In order to study them to advantage we resorted to an accessory intubation, whereby a tube was connected directly with the organ in addition to the usual "altercursive intubation." This "triple intubation" already referred to is represented schematically in Text-fig. 4.

The third cannula, *3*, connected to the rubber tubes *A* and *Z* was placed either directly in the cystic duct or (as shown in the figure) just far enough below it to allow the tiny duct draining part of the left central lobe of the liver to enter above the point of intubation and thus supply bile directly to the gall bladder. The findings were similar by both methods of intubation.

The ends of the three tubes introduced into the abdomen were passed through



TEXT-FIG. 5. Pressure changes within the gall bladder after the taking of food. The upper curve shows the sudden increases in gall bladder pressure, immediately after eating. The lower columns show the amount of bile secreted by the liver in 5 minute periods.

separate orifices in the lateral body wall and joined outside by means of glass *T*-tubes and short rubber connections. All of these joints were protected with wrappings of phenolized gauze. When a clamp was set upon the drainage tube *F*, bile secreted by the liver into tubes *BX*, upon arriving outside the body, was free to flow in two directions—on into tubes *YE* and thence into the duodenum, or backward into tubes *ZA*, and thence to the gall bladder. This latter course would be taken when the physiological resistance to the passage of bile into the intestine was high. By disconnecting the tubes leading to the gall bladder and to the lower common duct and bringing them into connection with manometers it was possible to measure simultaneously the pressure conditions within the gall bladder, the resistance to the passage of bile into the intestine, and the amount of liver bile secreted.

With five dogs triply intubated as described we have repeatedly observed upon the taking of food abrupt pressure increases in the column of bile in a manometer connected with the gall bladder,—clear evidence that the organ contracts. The data of one such instance are recorded in Text-fig. 5.

Dog 15, weight 11 kilos, Text-fig. 5. 10 days previous to the experiment a "triple intubation" had been done, with insertion of the third cannula directly in the cystic duct. The animal remained healthy and active. After a fast for 48 hours just prior to the experiment a manometer was connected to the tube leading to the gall bladder, while the tube collecting liver bile was allowed to drain into a sterile graduate. In the text-figure the amount of liver bile secreted in 5 minute periods is plotted in cross-hatched columns. During the first 20 minutes less than 0.5 cc. was obtained in each period and the column of bile in the manometer connected with the gall bladder remained constantly at the 100 mm. level, showing slight fluctuations referable to the respiratory movements.

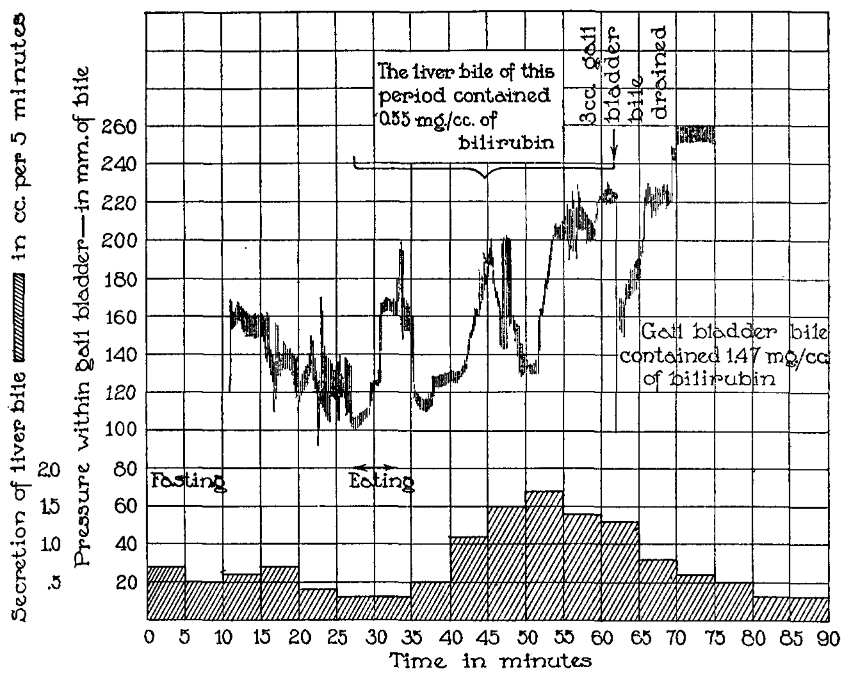
Food was then offered to the animal and it was allowed to eat for 2½ minutes, consuming in this time about 150 gm. Almost at once the bile column in the manometer, registering pressure changes within the gall bladder, rose to over 200 mm. and it returned again slowly toward its previous level in the course of the next 8 minutes reaching 115 mm. and there remaining. In the meantime food was removed. The column of bile in the manometer remained level until, 17 minutes later, food was again offered. Soon after eating the bile rose above the 250 mm. level, overflowed the manometer, and the experiment was discontinued. Through all this the animal stood quietly making no movements of its body. There is to be noted in the chart a gradual increase in the amount of liver bile secreted after the taking of food. Its flow was constant and continuous. No gush of fluid occurred from the cannula yielding liver bile, such as would suggest a generalized increase in the intraabdominal pressure, and of course no bile could reach the gall bladder from the liver because the tube leading to the viscus had been attached to the manometer. 4 days later while the animal was in excellent condition, it was killed with chloroform. At autopsy all the bile ducts were found normal in appearance and the cannulas patent.

The following instance shows the same phenomenon and its rhythmic recurrence in the absence of any further ingestion of food.

Dog 16, weight 9 kilos, Text-fig. 6. Under ether anesthesia a "triple intubation" was performed, and the three tubes inserted precisely as represented in

Text-fig. 4. It will be seen that a small duct from the left central lobe of the liver opened into the cystic duct above the point of intubation. Recovery from the operation was prompt and the animal continued active and healthy.

9 days after operation, and following a fast of 48 hours, the tube connecting with the gall bladder was joined to a manometer. The tube collecting liver bile was allowed to drain freely into a sterile graduate and the amount of bile received was recorded at 5 minute intervals for half an hour. A little food was then given, the animal eating about 150 gm. of the bread, milk, and meat mixture in 5 minutes.



TEXT-FIG. 6. Pressure changes within the gall bladder after the taking of food. The upper curve shows four rhythmic increases and decreases in pressure each of 5 minutes duration or more. The cross-hatched columns record the quantities of liver bile voided. Feeding stimulated secretion.

During the 30 minutes prior to the feeding the gall bladder pressure fluctuated as shown in the chart. Shortly after the first ingestion of food the column of bile rose to 200 mm. and gradually sank again to 120 mm. 5 minutes later it began to rise, again attaining the 200 mm. level and again sinking, this time to 130 mm. 25 minutes after the taking of food it showed another increase, this time to 220 mm., which pressure was maintained for 5 minutes. The tube was now opened for a few seconds during which 3 cc. of bile flowed from it. The pressure fell to 100 mm. but soon rose again to 220 mm. and 5 minutes later to 260 mm. The dog was very quiet during the entire period of the observations.

The 3 cc. of bile collected was dark and viscid and contained 1.47 mg. of bilirubin per cc., this despite the fact that there was an admixture with liver bile derived from the left central lobe of the liver; the 7.3 cc. of liver bile from the remainder of the liver obtained during the 35 minute interval between the taking of food and the collection of bile from the gall bladder was light and limpid and contained but 0.55 mg. of the pigment per cc.

The cross-hatched columns in the text-figure show that there was a slightly increased output of bile by the liver after the feeding.

It is noteworthy that in these two experiments, and in all similar ones as well, there was no sudden gush of bile from the liver, the increase in bile secretion after feeding being very gradual. The abrupt rises in the column of bile in the manometer connected with the gall bladder can therefore have been due only to pressure changes within the viscus. Are they the result of true gall bladder contractions or of extraneous pressure factors?

The observed phenomena cannot be the effect of a generalized increase in abdominal pressure consequent upon an increase in the gastric contents; for it is well known[26] that this pressure remains constant during the taking of food unless enormous quantities are eaten. Kelling[27] has shown that in the case of the dog more than 300 gm. of food can be taken without increasing the intraabdominal pressure, owing to a compensating relaxation of the muscles of the abdominal wall. In some of our experiments (as that shown in Text-fig. 5) the column of bile in the tube connected with the gall bladder rose abruptly when the animal had taken not more than 150 gm. of food, into a stomach previously empty. In several experiments, like that charted in Text-fig. 6, the rhythmic recurrence of abrupt increases in pressure within the gall bladder, in the absence of any further ingestion of food, rules out the possibility that a generalized increase in intraabdominal pressure was the direct cause of the phenomenon. Furthermore in several other instances, none of which have been charted, increases in pressure within the gall bladder did not occur until 10 to 15 minutes after food had been

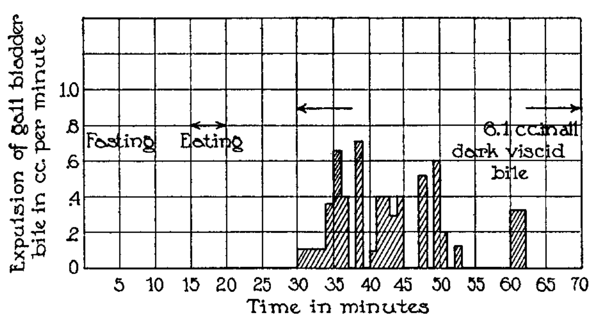
[26] Cannon, W. B., The mechanical factors of digestion, London, 1911.

[27] Kelling, G., *Z. Biol.*, 1903, xliv, 161.

eaten. In an experiment to be described below (Text-fig. 7), the tube leading to the gall bladder was allowed to drain freely into a sterile graduate. Even under these conditions no bile drained from the organ for 10 minutes after food had been eaten. Obviously in this instance and in those cited above increases in the gastric contents had caused no increase in pressure within the gall bladder.

The pressure changes within the viscus endured so long, for example nearly 10 minutes in the case shown in Text-fig. 5, 5 or 10 minutes in that of Text-fig. 6, and occurred at such lengthy intervals, that they cannot be ascribed to the transmission of rhythmic peristaltic pressure changes from the other viscera.

Obviously then, these findings can have come about through



TEXT-FIG. 7. Expulsion of bile from the gall bladder during gastric digestion. The intermittency of the flow is evidence of separate increases in pressure within the organ such as have been charted in Text-fig. 6.

nothing but prolonged forceful contractions of the gall bladder, following the stimulus of taking food, and occurring repeatedly during early digestion. They had the character of rhythmic smooth muscle contractions.

In an accessory experiment in which the same animal was employed, as in the experiment described in the previous protocol, the amount of bile emerging from the intubated gall bladder was studied, not the pressure exerted upon it.

Dog 16, Text-fig. 7. 16 days after a "triple intubation" and following a 24 hour fast the tube leading to the gall bladder was opened, so that it might drain freely into a sterile graduate. For a period of half an hour no bile appeared. 200 gm. of food was then offered to the animal and eaten in 5 minutes. The usual expulsion of bile at the first taking of food did not occur; and only 15 minutes later did bile flow from the open end of the tube. The amount collected during each minute thereafter was recorded, and is shown in the text-figure. It appeared in sudden gushes, each enduring but a few seconds and followed by a slow ooze from the open end of the tube. These ejections persisted intermittently for 35 minutes and then ceased. As the chart shows, no bile was obtained during certain periods. Of these there were four of 1 minute each, one of 2 minutes, and one of 7 minutes. 6.1 cc. of bile in all were expelled in this way.

At autopsy, performed a week later, after the animal had been killed with chloroform while in excellent health, the bile ducts were all found normal in appearance, and no obstruction was noted. There was a small duct secreting bile into the hepatic duct above the point of intubation. It was found to drain about 40 gm. of liver and, from what is known of the rate of bile secretion in the dog, can have provided but very little of the 6.1 cc. of bile. This latter had the general character of "gall bladder" bile, being dark and viscid and with a pigment content of 1.94 mg. of bilirubin per cc.

The intermittent voidings of bile recorded in the chart suggest that individual contractions of the gall bladder took place at intervals throughout a period of half an hour during gastric digestion. As just mentioned a duct from a small proportion of the liver secreted its bile into the hepatic duct above the point of intubation. But the voidings can hardly be ascribed to the influence of the food stimulus to increase the formation of liver bile, a part of which was voided through the tiny duct. For, as shown in Text-fig. 6, the increase in bile formation which occurred after the taking of food by this same animal was slow and gradual, as in all our feeding experiments. Moreover the bile was voided intermittently from the tube leading to the gall bladder, not continuously, and it had the general characteristics of "gall bladder" bile, being dark and viscid.

Reciprocal Activities of the Gall Bladder and the Musculature about the Lower Portion of the Common Duct.

The assumption that the gall bladder contracts and the sphincter of the common duct relaxes at the same time has been much disputed in the past.

Doyon[28] was the first to believe that he had shown such an occurrence. He experimented with the anesthetized dog. Rost[29] more recently, through ob-

[28] Doyon, M., *Arch. physiol. norm. et path.*, 1894, vi, series 5, 19.
[29] Rost, F., *Mitt. Grenzgeb. Med. u. Chir.*, 1913, xxvi, 711.

servations on the voidings of bile in unanesthetized dogs with the Pavlov biliary fistula,[30] came to the same belief. Meltzer[31] accepted such an occurrence as constituting a special instance of the law of reciprocal innervation.

We have shown in an accompanying paper that at the first perception of the nearness of food and also upon its ingestion the physiological resistance to the passage of bile into the gut relaxes. In the present contribution we have presented evidence that the same stimulus causes a discharge of bile from the gall bladder, presumably by its contraction. In experiments now to be reported we have attempted to determine whether there is a relationship in time between the two phenomena. There is one. They occur synchronously. A type experiment follows.

Dog 19, male, weight 12 kilos, Text-fig. 8. 2 weeks prior to the experiment a "triple intubation," under ether anesthesia, with insertion of the third cannula directly in the cystic duct, was followed by prompt and complete recovery. The dog remained healthy and active, with the bile draining as normally save for the detour.

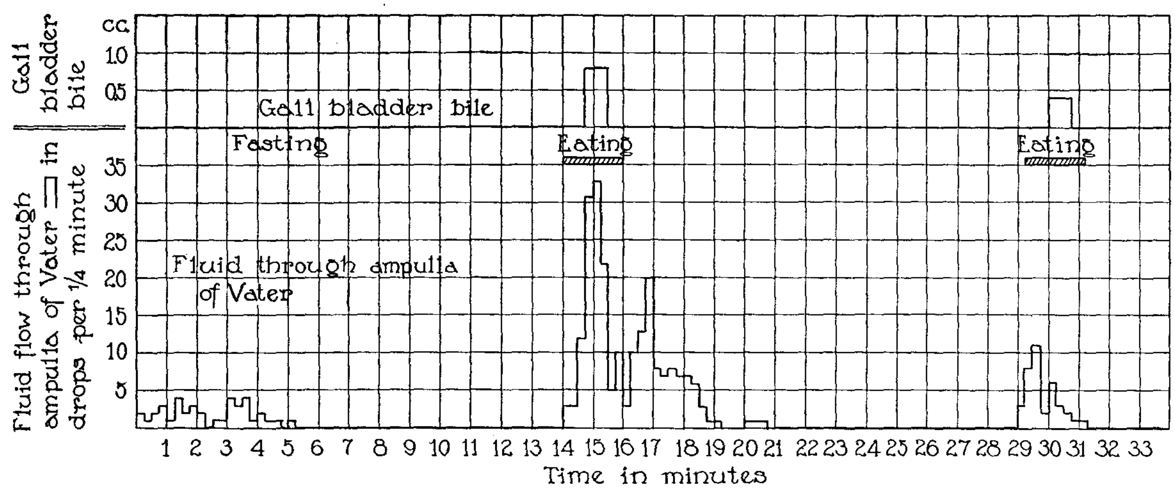
After a fast of 30 hours the tube connecting with the lower common duct was joined to the "flow" manometer, described in the accompanying paper,[1] for measuring the flow of fluid through the lower common duct at a constant pressure. The bile columns in this manometer were adjusted to exert a pressure equal to that of a 170 mm. column of bile. The flow of fluid was estimated by counting the drops emerging from the nozzle in periods of 15 seconds. The tube connected with the gall bladder was allowed to drain into a sterile, vertical tube of such length that no bile could be collected from it into a sterile graduate at its end until the pressure of a 200 mm. column of bile had been overcome. For the sake of simplicity the amount of liver bile drained by the third tube and collected during the period of the experiment is not recorded in the chart.

During an initial 15 minute period of observation no bile was forced out of the gall bladder and but little passed from the flow manometer into the duodenum.

Food was then given for 2 minutes. Almost at once, 5 to 10 seconds after the first swallow, the bile column began to rise in the vertical tube connected with the gall bladder. In 45 seconds, as shown in the chart, dark viscid "gall bladder" bile was forced into the collecting graduate at the end of this vertical tube, against the 200 mm. of pressure, and it continued to flow for 45 seconds more, delivering 0.6 cc. in all. Then the bile column in the tube fell to the 180 mm. level, so that bile no longer entered the graduate at its end, a finding not shown in the chart. During the next 2 minutes the column fell slowly to the

[30] Pavlov, S. P., *Ergebn. Physiol.*, 1902, i, 1. Abt., 246.

[31] Meltzer, S. S., *Am. J. Med. Sc.*, 1917, clxiii, 469.



TEXT-FIG. 8. Upon feeding there occurs simultaneously an expulsion of bile by the gall bladder and a lessening in the resistance to the passage of bile to the duodenum.

The upper curve shows when bile is expelled from the gall bladder against the resistance offered by a column of bile 200 mm. high, and also the amounts expelled. The lower curve records the periods of decrease in the resistance to the passage of bile into the intestine as evidenced by a flow of fluid to the gut.

original level of about 100 mm. Simultaneously with the intake of food, as shown in the chart, the flow to the duodenum occurred indicating a decrease in the resistance thereto and the flow kept up for some time thereafter, its rate indicating a progressive lessening in the resistance, one most pronounced at the precise period when bile was being ejected from the gall bladder. The flow ceased in 5 minutes but 10 minutes later recurred again upon a second brief feeding, as did also the expulsion of bile from the gall bladder. This time the greatest rapidity of flow was not quite synchronous with the expulsion from the gall bladder.

At autopsy 9 days later the bile ducts were found normal in appearance, the cannulas and tubes were open and intact.

In this experiment the pressure within the gall bladder increased sufficiently to force bile out of the organ against the weight of a column of bile 200 mm. in height. No similar expulsion occurred until food was again offered. These pressure increases were synchronous with a decrease in the resistance to the passage of bile to the gut. That only small amounts of bile were obtained from the gall bladder can be accounted for by the fact that it was necessary for the organ to do more work forcing bile out against this artificially high resistance than would be needed to expel the fluid through the normal channels under the condition of lessened resistance prevailing at the time.

In our five dogs with "triple intubation" this experiment was repeatedly carried out, with in each case the same result. Always upon taking food, frequently at the mere perception of it,[1] there was a sudden synchronous decrease in the resistance to the passage of bile into the intestine and an increase in the pressure within the gall bladder as shown by the expulsion of bile. The pressure increase on the part of the gall bladder did not at once reach its maximum, a point shown in Text-figs. 5 and 6, but endured at times several minutes and served to expel several cc. of bile from the viscus, when the resistance thereto was slight (Text-fig. 7).

DISCUSSION.

The observations recorded in this and the accompanying paper would appear to possess a special worth because they were made under controlled circumstances in the healthy, unanesthetized dog.

We have been able to prove that upon the taking of food some portion of the gall bladder contents is expelled forcibly by contraction of the viscus. But more than this, we have demonstrated the existence of the long supposed and equally as long disputed reciprocal relationship between gall bladder activity and that of the musculature about the lower end of the common duct, as expressed in resistance to bile flow. At the same time that the gall bladder contracts the resistance to the flow of bile into the gut markedly lessens, thus making for a more effective discharge of the gall bladder contents.

The discharge of bile into the duodenum may be thought of as chiefly dependent upon the interaction of three factors, the tonus of the muscles about the lower common duct, the activity of the gall bladder, and the pressure of bile secretion. To make clear the interaction of these in effecting the flow of bile to the intestine let us consider their activities in connection with the taking and digestion of food. The demonstration of the slight differences in pressure causing bile to flow, first toward the intestine, then toward the gall bladder, reveals a truly exquisite mechanism.

In a paper published with this one we have described certain physiological variations in the resistance offered to the passage of bile into the intestine. The "normal" resistance, 4 to 12 hours after a feeding, is sufficient to hold back a column of bile 100 to 120 mm. in height. The resistance increased, during fasting periods often supporting a column of bile 200 to 250 mm. high. Promptly at the mere perception of food and again upon its ingestion a decrease in this resistance was noted, bile flowing through the ampulla of Vater at 50 mm. pressure or even less. The reaction was so immediate that one must suppose it to have been reflex in nature. This decrease in resistance was but transient for the latter soon increased after food had entered the stomach and often became high enough during a brief period to support a 250 mm. column of bile. After a period varying from 10 to 30 minutes the resistance decreased and it fluctuated from high to low as gastric digestion proceeded.

The two other factors which affect the escape of bile into the duodenum—the pressure of bile secretion and the gall bladder activity—have been described in this present paper. We have shown in fasting animals with gall bladder cut off from the duct system that bile is secreted by the liver at a constant rate into a manometer tube until the column of bile has risen in the face of the progressive obstruction to 300 mm., when secretion abruptly ceases. If, however, the gall bladder is still connected with the ducts the pressure of bile developing within the biliary tract as measured by a manometer connected with the common duct remains for some hours below that of a column of bile 175 mm. in height and is usually equivalent to that of a bile column of 100 to 150 mm. When food is eaten there soon occurs within the gall bladder an increase in pressure such as would result from a contraction of smooth muscle, and with it an actual partial emptying of the organ, an activity synchronous with a relaxation of the resistance to the passage of bile to the gut. The phenomenon recurs at intervals during the process of gastric digestion.

It is of importance to note that the pressure developed within the gall bladder in these experiments was amply sufficient to force bile through the ampulla of Vater against the resistance of the muscles in this region, save when the latter were in that temporary state of high tonus, enduring 10 to 30 minutes, which closely follows their immediate relaxation upon the taking of food. It is probable that during this brief period but little bile entered the intestine. Even under these conditions, however, the pressure exerted by the gall bladder contractions about equalled the resistance offered. Later much bile may have entered the intestine, for these contractions, as we have shown, occurred repeatedly during gastric digestion.

From these observations it is possible to correlate the biliary factors which are responsible for the discharge of bile into the duodenum with the taking and digestion of food.

During fasting periods bile is prevented from entering the intestine by the high resistance of the muscles about the lower common duct. The force of secretion is thus directed toward the filling of the gall bladder, which, by its concentrating activity, is able to admit and store large amounts of bile. As result the liver may secrete bile continuously without its appearance at the ampulla of Vater, and the development of a high pressure within the ducts is prevented.

The escape of bile into the intestine occurs promptly at the first ingestion of food, practically ceases then for a short period, and later continues at intervals during the process of gastric digestion. Whether the actual ejection of bile is synchronous with and perhaps dependent upon the gushes of acid chyme through the pylorus cannot be said from our observations. That some relationship does exist is suggested by the fact that the resistance to bile passage into the intestine fluctuates during gastric digestion as further by the intermittent character of the expulsion of bile from the gall bladder.

The contractions of the gall bladder we studied were slow and endured often for several minutes, sometimes coming on quickly, sometimes slowly and wearing off gradually. They were such as to slightly more than double the pressure within the organ. It is of importance to note too that only a little bile was ejected at any one time. This fact may readily account for the failure of previous workers to observe contractions of the gall bladder when they have been sought by methods rendering the organ visible. Of course in such procedures the effects of the operations and the anesthetics employed have militated against success. To explain a supposititious discharge of gall bladder contents in the absence of visible contractions of the organ many authors have invoked the inspiratory increase in pressure on the viscus. Recently, on the basis of new work, Winkelstein[10] and Winkelstein and Aschner[32, 33] have concluded that respiration is the "motor of the gall bladder." During our observations we sometimes noted considerable fluctuations in the pressure within the biliary tract traceable obviously to the respiratory movements. While the dog was breathing or panting quietly the pressure changes were not more than a few mm., scarcely enough to affect the entrance of bile into the gall bladder or its exit therefrom. Usually, the column of bile in the manometer connected with the gall bladder rose and fell about 10 to 15 mm. with each breath. Occasionally, however, on deep inspirations, the pressure often increased 20 to 30 mm. The retching movements preparatory to vomiting raised it to 600 mm., and the straining incident to defecation was once seen to cause a rise in the column of 50 mm. It is to be remembered however that these pressure alterations affected not only the gall gladder but the gut which might

[32] Winkelstein, A., and Aschner, P. W., *Am. J. Med. Sc.*, 1924, clxviii, 812.

[33] Winkelstein, A., and Aschner, P. W., *Am. J. Med. Sc.*, 1926, clxxi, 104.

receive bile from it and that under these circumstances no flow could occur. As Doyon has pointed out,[28] it does not seem that respiratory changes in pressure can be held responsible for the normal discharge of the gall bladder contents. The average respiratory increase in pressure would seem to be insufficient to cause a flow of bile through the ampulla of Vater unless the musculature about the lower common duct is much relaxed as it is just after eating. At such times the mere pressure of bile within the ducts is sufficient for the task, as we have shown in the preceding paper.[1]

The facts reported here have an important clinical significance. That the normal resistance to the passage of bile through the ampulla is connected in some way with gall bladder function is sufficiently shown by the absence of this resistance in species lacking the viscus[34] and also by the dilatation of the ducts[29] and the breaking down of the resistance which occurs in individuals from which the organ has been removed surgically.[7] Cholecystectomy destroys the mechanism governing the intermittent expulsion of bile that we have described. The fact is of significance for it bears upon the origin of the digestive disturbances occurring in patients after removal of the gall bladder.

A further point deserves mention. The stimulus of food brings about a physiological bile drainage, by relaxation of the muscles about the lower common duct with contraction of the gall bladder. The value of frequent administrations of food to patients when it is desired to promote such drainage is evident. It is conceivable that such feedings will be more efficacious if the food is sufficiently acid to bring about the extreme relaxation of the musculature about the lower common duct noted under experimental conditions when acid is fed.[1,35]

SUMMARY.

After feeding a dog, forceful contractions of the gall bladder occur that are sufficient in strength to expel part of the contents of the viscus against a considerable pressure resistance.

The pressure within the gall bladder of a healthy, unanesthetized

[34] Mann, F. C., *J. Lab. and Clin. Med.*, 1919–20, v, 107.

[35] Cole, W. H., *Am. J. Physiol.*, 1925, lxxii, 39.

dog fasted 24 to 48 hours is usually about equal to a column of bile 100 mm. high. After a few swallows of food there is a rapid increase in the pressure to more than 200 mm. with a gradual fall in it again, and repeated similar rises and falls occur thereafter. The gall bladder contractions responsible for these alterations are accompanied by a lessening in the resistance to the passage of bile to the intestine, a resistance which is maintained by the muscles at the lower end of the common duct. There would appear to be a reciprocal response on the part of the two structures to the one stimulus.

The maximum pressure developing within the temporarily obstructed biliary tract in an animal with the gall bladder excluded about equals that of a column of bile slightly more than 300 mm. in height. The taking of food acts as a stimulus on the rate of bile secretion, but does not alter the maximum secretion pressure. When the gall bladder is connected with the duct system, obstruction does not lead until after some hours to the development of a pressure of more than 100 to 150 mm. within the biliary tract,—that is to say the pressure does not rise above the normal. Its failure to rise further is referable to the activity of the gall bladder to store and concentrate the bile as secreted.

The physiological and clinical significance of these findings is discussed.