

THE FUNCTION OF THE GALLBLADDER IN BILIARY FLOW

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Bile, a product of liver action, has a dual nature: (1) a secretion, a digestive fluid, produced in largest quantities and required most abundantly during the periods of digestive activity; (2) an excretion formed from the disintegration of hemoglobin in the destruction of red blood corpuscles, a continuous process in the body economy. The physiologically periodic outflow into the small intestine of a fluid continuously produced is maintained supposedly by a reflex mechanism between the alimentary canal and the gallbladder, the latter a diverticulum, so to speak, of the extrahepatic passages in which the bile is supposedly stored between the intervals of gastric activity.

In the gallbladder certain changes occur in the composition of this storage bile. There is a loss of water by concentration, a change in color and an increase in the specific gravity owing to the addition of certain mucins and nucleo-albumins. Whether these changes are essential to the body welfare or concerned in the expulsion of bile from the gallbladder, it is difficult to say. As a reservoir for bile, the gallbladder cannot be considered mechanically adapted not only because of its relatively small capacity as compared to the large amount of bile secreted but also because of its lack of inherent propulsive power. Certain features of a physiologic character, however, indicate that the gallbladder and passages exert an important function as regulators of biliary flow, and it is with this feature that this paper is primarily concerned.

ANATOMIC CONSIDERATIONS

According to Hendrickson¹ and Helly,² the gallbladder has a moderate amount of smooth muscle fibers, not arranged with any uniformity in definite muscle layers and coats but rather as a smooth muscle complex with fibers running in three directions, transversely, longitudinally, and obliquely; the greatest number of them run transversely, that

1. Hendrickson, W. F.: A Study of the Musculature of the Entire Extrahepatic Biliary System Including That of the Duodenal Part of the Common Bile Duct and Sphincter, *Bull. Johns Hopkins Hosp.* **9**:221-232, 1898.

2. Helly: Die Schliessmuskulatur an den Mündungen der Gallen und der Pankreasgänge, *Arch. f. mikr. Anat.* **54**:614, 1899.

is, perpendicularly to the long axis of the gallbladder. There is a small amount of connective tissue between these muscle fibers, and, as a rule, the walls are fairly well covered with this muscle complex. As a contractile mechanism, however, it forms quite a contrast to the more definite muscular viscera, such as the urinary bladder, stomach, intestine and uterus.

The wall of the cystic duct has also a plexiform arrangement of smooth muscle fibers, extending in the three above mentioned directions, the transverse fibers predominating, with only small amounts of longitudinal and oblique fibers. That portion nearest the neck of the gallbladder has a considerable amount of muscle tissue; but this gradually diminishes as the common duct is approached, so that at the junction of the cystic and common ducts it is of very small amount or entirely absent. Inside the cystic duct, there is a peculiar configuration of the walls described by Heister³ in 1732, and since named after him "Heister's valve," a "spiral valve" arrangement whose function has been, supposedly, to permit the passage of bile for storage purposes into the gallbladder and to allow its release to meet the demands of digestion. Hartmann⁴ made a careful macroscopic examination of this valve under water, and Faure⁵ studied it grossly by making metal models. These men noted the "bassinets" shape of the cystic duct and the angle it made with the neck of the gallbladder. They concluded that it did not have a spiral canal but that the lumen was free, with minor constrictions of the walls, producing a series of valvelike projections not of constant configuration. These leaflets or valves were most numerous in the upper portion of the duct. The upper two were the largest and extended about three-fourths the distance around the lumen of the cystic duct, so that it would be impossible to catheterize the duct without breaking the leaflets; there might be resistance to the passage of solid matter but hardly, in normal conditions, to liquids. Terrier and Dally⁶ supported this description, especially regarding the presence of the upper two large leaflets, but found a larger number of smaller valves in the lower part of the duct. In the specimens they examined, the number of leaflets ranged from four to twenty. Hendrickson¹ has carefully studied the microscopic anatomy of the cystic duct valves. According to him, the transverse muscle fibers of the wall

3. Heister: *Compendium anatomicum totam rem anatomicam brevissime complectens*, Ed. 4, Nuremberg 1:89; 2:65, 1732.

4. Hartmann: *Quelques points de l'anatomie et de la chirurgie des voies biliaires*, Bull. Soc. anat. de Par. 66:480, 1891.

5. Faure, J. L.: *Quelques points de l'anatomie du canal cystique*, Bull. Soc. anat. de Par. 66:511, 1891.

6. Terrier and Dally: *Du cathétérisme des voies biliaires*, Rev. de chir. 12:136, 1892.

of the cystic duct also run around the valves or leaflets in a circular direction. It is as if the wall of the duct was invaginated at the level of the valve and the circular muscle fibers carried out into the fold thus produced. Most of the longitudinal muscle fibers continue down the wall of the duct without entering the valve but some of these bend at right angles and enter the valve at the proper level. The oblique fibers did not enter the valve and formed no part of the musculature of that structure. It is thus seen that the transverse muscle fibers are the predominant ones in the valves of Heister. These valves near the common duct are very small indeed and have only a few muscle fibers, if any.

The hepatic and common ducts are almost alike in microscopic anatomy. There is a very small amount of muscle tissue, with a large amount of connective tissue between them. These muscle strands are mainly of the transverse variety.

The duodenal portion of the common duct has, during recent years, received considerable attention as the important feature of the mechanism of biliary control. The presence of some sort of sphincter about the orifice of the common duct was suggested by Glisson,⁷ as early as 1681. Ruggero Oddi,⁸ however, in 1887 was the first to describe a sphincter arrangement, which to this day is known as the sphincter of Oddi. After careful study of maceration specimens and microscopic sections of the duodenal end of the common duct, he described a definite and independent ring of muscle tissue about the mouth of the duct, entirely separate from the muscle of the intestinal wall through which it plunged, some of the delicate muscle fibers of which were reflected upon the sphincter's external surface. This sphincter, according to Oddi, could be put into spasm by irritation, mechanical or chemical, from the duodenal side. It was able to withstand an interductal pressure of 675 mm. of water; sphincteric action caused an intermittent flow of bile into the duodenum and seemed to maintain a definite pressure in the hepatic duct system. Oddi also observed the dilatation of the extra-hepatic ducts in dogs following the removal of the gallbladder. Oddi made no attempt to demonstrate this sphincter muscle in man. Hendrickson,¹ in 1898, and Helly,² in 1899, confirmed the microscopic anatomy, in man, of the sphincter of Oddi as a special and separate entity from the intestinal musculature through which the common duct enters at the ampulla of Vater. Archibald,⁹ in 1912 and 1913, verified the

7. Glisson, quoted by Hendrickson, W. F.: Footnote 1.

8. Oddi, Ruggero: Di una speciale disposizione a sfintere allo sbocco del coledoco, *Ann. d. Univ. libera di Perugia. Fac. di med. e chir.* **2**:249, 1886.

9. Archibald: A New Factor in the Causation of Pancreatitis, *Tr. Inter. Cong. Med., Surg. Sect. Part II*, pp. 7-21, 1913; The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter, *Surg., Gynec. & Obst.* **28**:529 (June) 1919.

action of the sphincter in maintaining an interductal pressure and showed that incision of the sphincter causes a reduction of the high interductal pressure from 650 mm. to 70 mm. of water, which low level persists for many weeks, if not permanently. He observed the production of acute pancreatitis by introduction of bile and other substances into the pancreas under pressures higher than the normal interductal pressures and suggested incision of the sphincter of Oddi as one of the steps in the surgical treatment of that condition. Judd and Mann,¹⁰ in 1917, by extirpation of the gallbladder in dogs, demonstrated the great dilatation of the extrahepatic ducts after cholecystectomy. Following the operation, the sphincter is evidently contracted, attempting to maintain the normal interductal pressure. The ducts as a consequence dilate, and the sphincter, under the continued pressure, becomes paralyzed, with ultimate reduction of the interductal pressure.

NERVOUS CONTROL

Heidenhain,¹¹ 1861, was the first to make accurate investigation of the nervous control of biliary flow. By stimulating the spinal cord in the cervical region, he obtained an increased flow of bile followed shortly afterward by decreased biliary output. Contraction of the gallbladder, with expression of its bile content, accounted for the increased flow; the increased pressure in the biliary passages, produced by the contraction, acted directly on the secretory cells and caused a decreased secretion.

Doyon,¹² 1893, by using the balloon and recorder method, showed graphically that the gallbladder underwent spontaneous contractions of a rhythmic character. By stimulation of the peripheral ends of the splanchnic nerves, he obtained a slow contraction of the gallbladder and the biliary passages while an inhibiting effect resulted from stimulation of the central end. Inhibition of gallbladder tone followed stimulation of the central end of the vagus nerve. He believed that the motor fibers reached the gallbladder by way of the splanchnic nerves and that the vagus nerve carried only afferent fibers from the gallbladder.

Courtada and Guyon,¹³ 1904, evidently accepted Doyon's conclusions regarding the motor mechanism of the splanchnic nerves and limited their efforts mainly to stimulating the peripheral end of the vagus nerve, from which they obtained definite motor responses. They

10. Judd and Mann: The Effect of the Removal of the Gallbladder: An Experimental Study, *Surg., Gynec. & Obst.* **24**:437 (April) 1917.

11. Heidenhain: Studien des physiologischen Instituts zu Breslau, Leipzig, Breitkopf and Härtel **2**:82, 1863.

12. Doyon, M.: Contribution à l'étude de la contractilité des voies biliaires, application de la méthode graphique à cette étude, *Arch. de physiol. norm. et path.* **5**:678-710, 1893.

13. Courtada and Guyon: Action motrice du pneumogastrique sur le vesicule biliaire, *Compt. rend. Soc. de biol.* **56**:313, 874, 1904.

asserted that they had traced these motor fibers into the gastric branches of the vagus nerve along the lesser curvature of the stomach and indicated that the motor control of intestine, stomach and gallbladder is contained in one and the same nerve, the vagus. Freeze,¹⁴ 1905, also obtained rapid rhythmic spontaneous contractions of the gallbladder. By stimulation of the splanchnics, he obtained a variety of results leading to the conclusion that these nerves contained both motor and inhibitory fibers from the gallbladder but that the motor fibers predominated. Bainbridge and Dale,¹⁵ 1905, also used the balloon and recorder method, with modifications, and endeavored to remove a number of extraneous factors which undoubtedly influenced Doyon's and Freeze's conclusions regarding the motor effect of the splanchnic nerves. They seem to have proved in no uncertain manner that: 1. There are spontaneous rhythmic contractions of the gallbladder. 2. Stimulation of the splanchnics always results in relaxation of the gallbladder. 3. The vagus contains the motor innervation of the gallbladder.

CHEMICAL HORMONE REFLEX CONTROL

Claude Bernard,¹⁶ 1856, was the first to observe the stimulating effect of acids upon the duodenal orifice of the common duct, a sudden gush of bile into the intestines resulting from such an application. Heidenhain,¹¹ 1861, attributed the sudden gush of bile occurring at a certain interval after a meal to the stimulating action of the acid and chyme upon the biliary papilla, causing a reflex stimulation of the gallbladder. Rutherford,¹⁷ 1880, observed that the introduction of nitrohydrochloric acid into the duodenum stimulated liver secretion. Wertheimer¹⁸ also observed, in 1890, increased biliary outflow in case acid is introduced into either the duodenum or upper jejunum. Baylis and Starling,¹⁹ 1902, using purified specimens of secretin (removal of depressor substance) intravenously, obtained an increased secretion of bile quite similar to the pancreatic outflow. Fleig,²⁰ 1904, noted that

14. Freeze, J. A.: The Force of Contraction of the Gallbladder and the Course of Its Motor and Inhibitory Nerve Fibres, *Bull. Johns Hopkins Hosp.* **16**:235, 1905.

15. Bainbridge and Dale: The Contractile Mechanism of the Gallbladder and Its Extrinsic Nervous Control, *J. Physiol.* **33**:138, 1905-1906.

16. Bernard, Claude: *Leçons de physiol. exper.*, 1856, p. 429.

17. Rutherford, Vignol and Doods: An Abstract of an Experimental Research on the Physiological Actions of Drugs on the Secretion of Bile, *Tr Roy. Soc. Edin.* **29**:133, 1880.

18. Wertheimer: De l'action et du chloral sur la sécrétion biliaire, *Compt rend Soc. de biol.* **55**:286, 1903.

19. Baylis and Starling: The Mechanism of Pancreatic Secretion, *J. Physiol.* **38**:21, 1902.

20. Fleig: Du mode d'action des excitants chimiques des glandes digestives, *Arch. internat. de physiol.*, 1904, p. 286.

the intravenous injection of blood from an isolated loop of duodenum-jejunum into which 0.5 per cent. hydrochloric acid had been introduced caused a similar increase in bile flow. On the other hand, Bainbridge and Dale,¹⁵ 1905, found no reflex effect on gallbladder contractions when 0.4 per cent. hydrochloric acid was injected into the duodenum or applied directly to the papilla or even when the papilla was electrically stimulated.

Prevost and Binet,²¹ 1888, found great acceleration of biliary secretion on introduction of peptone into the stomach. Doyon,²² 1897, on the other hand, concluded that peptone introduced into the stomach had an inhibiting effect upon the secretion of bile but caused an expulsion of bile from the gallbladder through vigorous contractions. Ascher and Barbera,²³ 1904, injected peptone intravenously into dogs with permanent biliary fistula and observed increased flow of bile. Fleig²⁰ noted also the increase in biliary flow on introduction of peptone into the intestine; and since the increase was more pronounced after ligation of the cystic duct, he concluded that it was essentially secretory in character, produced by reflex stimulation of the liver cells. A moderate stimulating effect of meat extract upon the biliary flow in animals with Pawlow stomachs was noted by Bruno; but quite opposite findings are reported by Klodnizka.²⁴ Fleig²⁰ found no acceleration of bile flow on injection into the rectum or into the blood stream of meat extracts or meat extract solutions of gastric or duodenal mucosa or on intravenous injection of blood from duodenal loops that contained in their lumen the above named solutions. More recently, Rost,²⁵ 1913, working with animals with duodenal and biliary fistulas, asserts that he has found an immediate discharge of bile as a result of the contractions of the gallbladder and a relaxation of the sphincter of Oddi when peptone was injected into the open duodenal fistula.

Nasse and Ritter²⁶ showed that a meat diet called forth a larger biliary outflow than a carbohydrate diet and that fat, in small quanti-

21. Prevost, J. E., and Binet, P.: *Recherches expérimentales relatives à l'action des médicaments sur la sécrétion biliaire et à leur élimination par cette sécrétion*, *Rev. méd. de la Suisse Rom.* **8**:249, 313, 368, 1888.

22. Doyon, M., and Dufourt, E.: *Contribution à l'étude de la sécrétion biliaire*, *Arch. de physiol. norm. et path.* **8**:587, 1897.

23. Ascher and Barbera, quoted by Fleig: *Arch. internat. de physiol.*, 1904, p. 286.

24. Bruno and Klodnizka, quoted from Babkin: *Die äussere Sekretion der Verdauungsdrüsen*.

25. Rost, F.: *Die funktionelle Bedeutung der Gallenblase. Experimentelle und anatomische Untersuchungen nach Cholecystektomie*, *Mitt. a. d. Grenzgeb. d. med. u. Chir.* **26**:710, 1913.

26. Nasse and Ritter, quoted from Stadelmann: *Der Icterus*, 1897.

ties, had a stimulating effect upon the bile flow, which was lacking with larger quantities. Bidder and Schmidt²⁷ found that continued meat diet increased the secretion of bile, while a continued fat diet diminished the secretion to a level found in starvation. The latter conclusion was confirmed by Prevost and Binet²¹ in 1888. Rosenberg,²⁸ 1890, believed that fat possessed a greater stimulating effect upon bile secretion than either a protein or carbohydrate diet; his observations indicated an interval or periodic secretion of bile at the usual time of feeding, the food itself not being a necessary factor. Albertoni and Barbera,²⁹ 1895, concluded that the greatest secretion occurred on a protein diet, less on a fat diet and very little or insignificant secretion on a carbohydrate diet. On a mixed diet, the ultimate biliary effect depended upon the predominant constituent; the duration of secretion was, however, longest on a fat diet, shorter on a meat diet and very short on a carbohydrate diet. On a mixed diet the duration of secretion also depended upon the amount of fat and protein present. They also observed that while the amount of bile secreted during starvation diminishes to a marked degree, there is never a complete cessation of secretion even up to the time of the death of the animal.

Schiff,³⁰ 1870, and later Rosenberg,²⁸ 1890, noted that introduction of bile into the alimentary canal was followed by an augmented flow of bile of increased concentration in contrast to the usual diluted bile produced by the action of ordinary cholagogues. This led him to infer that the bile was absorbed and re-excreted as a whole, thus forming a continuous circulation of bile, as it were, between the intestine and the liver. Socoloff,³¹ 1875, was led to believe otherwise, holding that the liver was incapable of resecretory the bile that had once been secreted and absorbed into the blood stream. He believed the augmented secretion was due to the mechanical passage of these absorbed substances from the blood which was overcharged with them. Rosenberg, however, points out that while this would account for the increased secretion, it would hardly account for the increased concentration which is found experimentally.

Okada,³² 1914, in a well managed, extensive series of feeding experiments on dogs, with permanent biliary fistulas and ligation of the com-

27. Bidder and Schmidt, quoted from Hermanns Handb. d. Physiol. **5**:256.

28. Rosenberg: Ueber die cholagogische Wirkung des Olivenöls im Vergleich zu der Wirkung einiger andern Cholagogen Mittel, Arch. f. Physiol. **46**:334, 1890.

29. Barbera: L'eliminazione della bile nel digiuno e dopo differenti generi di alimentazione, Arch. ital. de biol. **23**:165, 1895.

30. Schiff: Bericht über einige Versuchsreihen, Arch. f. d. ges. Physiol. **11**:589-624, 1870.

31. Socoloff: Ein Beitrag zur Kenntnis der Lebersekretion, Arch. f. d. ges. Physiol. **11**:166, 1875.

32. Okada: On the Secretion of Bile, J. Physiol. **49**:457-482, 1914-1915.

mon duct, by feeding by stomach, the more normal way, and by excluding many extraneous factors and extending his observations over longer periods after feedings, confirmed or refuted many of these former diversified conclusions. From his experimental findings he drew these conclusions: 1. There is little difference between the secretory effect of a diet of bread, butter and meat during six or seven hours if these substances are introduced in quantities of similar caloric values. 2. Starvation decreases the secretion of bile and also the stimulating effect of feeding upon the liver. 3. Fat, acid, peptone, meat extract, bile and bile salts, all produce increased secretion of bile. Bile and bile salts produce an augmentation of concentrated bile, the others of a more dilute bile. 4. Cane sugar, water and sodium carbonate have little or no effect upon the secretion of bile. 5. Intravenous injections of secretin and peptone cause increased secretion of a dilute bile. 6. Biliary flow in response to acid stimulation exhibits a course quite similar to that displayed by the pancreatic secretion.

LAW OF CONTRARY INNERVATION

In 1917 Meltzer³³ applied the law of contrary innervation to explain the interrelated and coordinated action of relaxation of the sphincter of Oddi and the simultaneous contraction of the gallbladder in the mechanism of biliary control. He had previously noted "that the local application of a 25 per cent. solution of magnesium sulphate to the duodenal mucosa had caused a completely local relaxation of the intestinal wall." No such action was noted when the salt was introduced through the stomach. He made the practical suggestion that in some pathologic conditions this coordinated nervous mechanism might be disturbed, as by some spasticity or rigidity of the sphincter. In such cases, the instillation of concentrated magnesium sulphate, through a duodenal tube, might cause a relaxation of the nonfunctioning sphincter, with relief of the distressing symptoms caused by cessation of biliary flow into the duodenum.

Lyon,³⁴ in a large series of cases and in several articles, claims to have confirmed Meltzer's theory in a practical manner. The instillation of concentrated magnesium sulphate into the duodenum by a duodenal tube, in human subjects, was followed by the evacuation of bile in large quantities; and he has been able to segregate and examine the bile coming from (1) the common duct, (2) the gallbladder, and (3) the liver. He believes that the method is of much moment in the nonsurgical drainage of the gallbladder and biliary passages. He con-

33. Meltzer: The Disturbance of the Law of Contrary Innervation as a Pathological Factor in Diseases of the Bile Ducts and the Gallbladder, *Am. J. M. Sc.* **153**:469-477 (April) 1917.

34. Lyon, B. B. V.: Diagnosis and Treatment of Diseases of the Gallbladder and Biliary Tract, *J. A. M. A.* **73**:980 (Sept. 27) 1919.

siders concentrated magnesium sulphate a "chemical messenger," hormone, which has the ability not only to cause relaxation of the sphincter of the common bile duct but also to cause simultaneously the contraction of the gallbladder and the expulsion of its contents.

No definite laboratory demonstration of the law of contrary innervation in the gallbladder mechanism has ever been shown and it is with this feature that the experimental data herewith given have been concerned.

EXPERIMENTAL DATA

Examination of the duodenum of a dog during the fasting stage reveals a slightly elevated papilla discharging no bile. Inserting a fine dropping glass cannula into the lumen of the common duct through the papilla, one can obtain a sudden gush of a few drops of bile, bile from the common duct and biliary passages, maintained there, no doubt, by the competent sphincter of Oddi. There then follows a drop of bile at long intervals, this bile being the continuous secretion of the liver. During digestion, there is a continuous flow of yellow thin bile into the duodenum. The papilla then is easily stimulated to contraction by rubbing with gauze, flicking with the finger or by chemical irritation. The duct appears suddenly to contract, becomes slightly erect, and the flow of bile ceases for from fifteen to thirty seconds. Relaxation follows and the continuous flow of bile is reestablished. In the fasting stage relaxation of the closed sphincter was readily obtained by mechanical and chemical irritation, being followed by a small momentary expulsion of bile. It is extremely difficult to say whether the papilla alone was stimulated; the reaction always seemed to include the duodenum surrounding the base of the papilla, and if the stimulus was great enough, to involve the whole segment of the duodenum and even to cause a progressive peristalsis.

SPHINCTER PRESSURE

With the ampulla exposed through an opening in the duodenum, with a right-angled cannula inserted into the common duct, with the open end toward the ampulla and connected with a pressure bottle filled with water deeply colored with methylene blue as an indicator, the sphincter pressure was determined in a series of dogs. By carefully elevating the pressure bottle, a level is reached at which there is a continuous flow of colored fluid through the papilla. When the pressure bottle is lowered slowly, there is a spurt of bile through the orifice, decreasing in quantity, with every respiratory effort, the respiratory impulse being transmitted through the diaphragm to the intestine as a wave. This continues until a still lower level is reached where no fluid is expelled through the orifice. The lower level represents, undoubtedly, the absolute pressure maintained or supported by the

sphincter of Oddi. The former level seems to represent this sphincter pressure plus the resistance of the valvelike effect produced by the oblique course of the terminal end of the common duct through the duodenal wall. Local application, by a cotton swab or by dropper, was then made to the papilla and neighboring duodenum of (1) 25 per cent. magnesium sulphate, (2) 5 per cent. peptone solution, (3) 0.4 per cent. hydrochloric acid, (4) 0.4 per cent. sodium hydroxid. Measurements of the sphincter pressure both before and after application in each case were made. The reaction appears to be mainly a local one, affecting both the papilla and the duodenum. It is of short duration and normal

TABLE 1.—DETERMINATION OF THE PRESSURES AT THE SPHINCTER OF ODDI IN A SERIES OF DOGS

| | Pressures in Mm. of Water | | | | | | | |
|--|---------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| | Animal 1 | Animal 2 | Animal 3 | Animal 4 | Animal 5 | Animal 6 | Animal 7 | Animal 8 |
| Normal: | | | | | | | | |
| Total pressure..... | 140 | 270 | 364 | 190 | 170 | 340 | 420 | 244 |
| Sphincter pressure..... | 90 | 160 | 100 | 110 | 94 | 140 | 210 | 114 |
| Difference..... | 60 | 110 | 264 | 80 | 76 | 200 | 210 | 130 |
| Magnesium Sulphate: | | | | | | | | |
| Sphincter pressure—before.... | 100 | 156 | 104 | 110 | 100 | 150 | 210 | 108 |
| Sphincter pressure—after..... | 40 | 62 | 48 | 60 | 42 | 60 | 120 | 38 |
| Difference..... | 60 | 94 | 56 | 50 | 58 | 90 | 90 | 70 |
| Peptone, 5 per cent. solution: | | | | | | | | |
| Sphincter pressure—before.... | 92 | 160 | 102 | 106 | 104 | 146 | 184 | 120 |
| Sphincter pressure—after..... | 72 | 112 | 70 | 82 | 86 | 96 | 142 | 84 |
| Difference..... | 20 | 48 | 32 | 24 | 18 | 50 | 42 | 36 |
| Acid, 0.4 per cent. hydrochloric: | | | | | | | | |
| Sphincter pressure—before.... | 92 | 148 | 110 | 116 | 98 | 152 | 200 | 132 |
| Sphincter pressure—after..... | 114-52 | 30 | 142-70 | 70 | 62 | 268-78 | 80 | 410-72 |
| Difference..... | 40 | 118 | 40 | 46 | 36 | 74 | 120 | 60 |
| Alkali, 0.4 per cent. sodium hydroxid: | | | | | | | | |
| Sphincter pressure—before.... | 98 | 144 | 112 | 122 | 104 | 148 | 190 | 126 |
| Sphincter pressure—after..... | 112 | 150 | 320-82 | 128 | 180-82 | 122 | 320-180 | 673-460 |
| Difference..... | 24 | 6 | 30* | 6 | 22* | 26 | 10† | 334† |

* Return to normal pressure in five minutes.

† Prolonged increase in interductal pressure; no return to normal in twenty minutes.

conditions are readily established. The results in eight typical cases, in dogs ranging from 35 to 45 pounds (15.9 to 20.4 kg.) in weight, are given in Table 1.

EFFECT OF MAGNESIUM SULPHATE ON SPHINCTER PRESSURE

1. The absolute sphincter pressures here determined are somewhat lower than those usually given. Oddi⁸ and Archibald⁹ found unusually high values, from 650 to 675 mm. of water. Herring and Simpson³⁵ report pressures of from 200 to 300 mm. Mann³⁶ finds most of them

35. Herring and Simpson: The Pressure of Bile Secretion and the Mechanism of Bile Absorption in Obstruction of the Bile Duct, *Proc. Roy. Soc., London* **79**:517-532, 1907.

36. Mann, I. C.: The Function of the Gallbladder: An Experimental Study, *New Orleans M. & S. J.* **71**:80 (Aug.) 1918.

ranging between 100 and 150 mm. McWhorter³⁷ reports the majority between 100 and 200 mm., with some as low as 50 mm. and others as high as 580 mm. of water. Smoothness of anesthesia, peristalsis, transmitted respiratory pressure, pressure from contiguous organs, all have their effect in modifying the results obtained; one gains the impression, however, that if all the extraneous factors could be removed, the absolute pressure maintained by the papillary sphincter of Oddi would be much lower than usually supposed, probably less than 150 mm. of water.

2. Magnesium sulphate does produce a relaxation of the papillary sphincter with reduction of the interductal pressure. As Meltzer has said, it produces a "completely local relaxation"; it involves the sphincter and the surrounding duodenum, and with an increase in the amount of the magnesium salt, there is segmental relaxation, leading to advancing peristalsis. The latter is especially well marked when magnesium sulphate in larger amounts (from 5 to 10 c.c.) is injected through the wall into the lumen of the bowel. A regular advancing peristalsis of the duodenal tube follows.

3. Local application of magnesium sulphate is followed by a momentary relaxation of the sphincter followed by a spurt of bile from the papillary orifice and a lowered intraductal pressure. Normal pressure is readily established, usually in less than two minutes and most commonly in less than one minute. When larger amounts of the magnesium salt are left in the unopened bowel, the relaxation may be of longer duration and complicated by the characteristic active peristalsis. It is quite impossible from the determinations made to conclude whether there was produced a local complete relaxation. McWhorter does not find the sphincter completely relaxed. Making the determinations as quickly as possible, the lowest intraductal pressure found in the animals under observation was 30 mm. of water. McWhorter has also reported changes in the intraductal pressure, from the application of magnesium sulphate to the duodenal mucosa, of from 50 to 100 mm. of water.

4. Much less relaxation was obtained by application of a 5 per cent. peptone solution. Acids, 0.4 per cent., tend to be followed by a contraction, with increased intraductal pressure but with a subsequent decrease in pressure greater than that caused by peptone. As a rule, alkali, 0.4 per cent. sodium hydroxid, was followed by a contraction and a long enduring increase in the intraductal pressure, the return to normal being delayed in some instances to twenty minutes. There seems to be a definite shrinking of the mucosa with the stronger acids and alkalis, and this no doubt alters the findings. Acids and alkalis, stronger

37. McWhorter, G. L.: The Surgical Significance of the Common Bile Duct Sphincter, *Surg., Gynec. & Obst.* **32**:124-129 (Sept. 17) 1921.

than 0.4 per cent. would not be encountered in the duodenum normally, and such results would have no special relation to the normal human mechanism.

Attempts were made to show graphically the change in the intraductal pressure in the common duct and in the gallbladder, if any, from the application of magnesium sulphate to the duodenal mucosa and the biliary papilla. The pressure is quite low and it was difficult to get a graphic record of the pressure change. A cannula was inserted into the common duct of an unusually large dog. To the free end was attached a very thin rubber balloon filled with water and in equilibrium with the intraductal pressure. This was introduced into a glass tube or bulb filled with oil and connected to a delicate piston, a lever recording manometer to record on a revolving smoked drum. Any change in the intraductal pressure was accompanied by a movement of the lever. Two different methods were used to determine the gallbladder pressure. In one there was cannula, balloon, water and oil manometer system, like that used for the common duct. In the other method, a balloon of very thin rubber was inserted into the gallbladder, filling it completely. The balloon was filled with thin oil and connected with a recording manometer and smoked drum. In no case was there any evidence of a change in the gallbladder pressure, either in the nature of a relaxation or of a contraction of the gallbladder itself, as a result of the application of the magnesium sulphate to the duodenal mucosa. A definite fall in the intraductal pressure in the common duct was demonstrated. Figure 1 shows a definite lowering of pressure in the common duct and no appreciable change in the gallbladder pressure on the application of 25 per cent. magnesium sulphate to the mucosa of the duodenum.

GALLBLADDER PRESSURE AND MAGNESIUM SULPHATE

The absence of any definite gallbladder effect due to the application of concentrated magnesium sulphate to the duodenal mucosa and the biliary papilla was further substantiated by the following procedures.

1. A fine water manometer attached to the gallbladder showed neither rise nor fall in pressure on such application of magnesium sulphate to the duodenum, though it was accompanied by a relaxation of the sphincter of Oddi and by a spurt of yellow bile through the papillary orifice.

2. With a fine right angled dropping cannula inserted into and attached to the fundus of the gallbladder, the gallbladder normally empties itself according to the following rate and curve plotted for that particular cannula and gallbladder: first five minutes, 59 drops; second five minutes, 55 drops; third five minutes, 48 drops; fourth five minutes, 38 drops; fifth five minutes, 28 drops, and sixth five minutes, 10 drops.

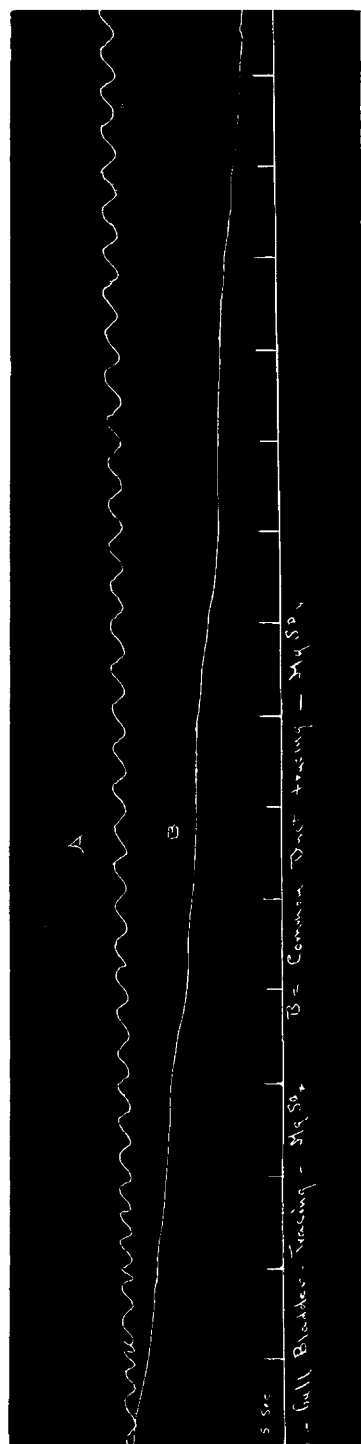


Fig. 1.—Simultaneous tracings of pressure changes in the gallbladder and common duct following duodenal instillation of concentrated magnesium sulphate. Tracing *A* indicates no appreciable change in gallbladder pressure; Tracing *B* shows decrease in intraductal common duct pressure.

When concentrated magnesium sulphate was applied, there was no change in the rate or curve. If a relaxation followed such an application, one would expect the altered curve to take the general form indicated by the dotted lines *C* in Figure 2. If a contraction had followed such application, the curve would take the general form illustrated by the Curve *B*.

FLOW OF GALLBLADDER BILE AND OF LIVER BILE

The common duct was catheterized with a fine dropping cannula and the normal biliary flow ascertained in drops for five minute intervals. Five c.c. of bile was carefully removed by an aspiration needle from the gallbladder and replaced by 5 c.c. of strong methylene blue bile solution in order to have an indicator of gallbladder bile, should it be expelled through the cannula. Drops from the cannula were recorded electrically on the revolving smoked drum. Five cubic centimeter amounts of 25 per cent. magnesium sulphate, of 5 per cent. peptone, of 5 per cent. meat extract, of 0.4 per cent. hydrochloric acid, and of 0.4 per cent. sodium hydroxid were injected into the duodenum by needle through the bowel wall and the biliary flow was registered on the drum. Return to normal flow occurred usually one half hour before another substance was injected. Ether anesthesia was maintained as evenly as possible. This procedure was carried out in eight animals. Three representative findings are given in Table 2. Figure 3 gives the curves of these effects for Animal 1.

The data show an increased biliary flow on injection of acid, meat extract, peptone and magnesium sulphate, with increasing amounts in the order named. There was only moderate increase in the flow following the magnesium sulphate and practically none with the alkali. The earliest augmentation was noted with the acid and the most delayed with the peptone. The bile secreted was that characterized as "liver bile," a thin yellowish fluid of low specific gravity. These results conform quite well with Okada's findings in animals with biliary fistula and in feeding by stomach. There were variations noted in the bile flow with changes in the respiratory rate, depth of anesthesia, with peristalsis and at times suggestive of cumulative effects of the substances injected. In no case, however, was gallbladder bile expelled or was there any evidence to indicate contraction of the gallbladder. Crohn, Reiss, and Radin,³⁸ in a recent article, report that they also failed to see any evidence of gallbladder bile being discharged even during active digestion; and they found no substance capable of causing expulsion of the bile from the gallbladder when applied to the

38. Crohn, B. B.; Reiss, J., and Radin, M. J.: Experiences with Lyons Test (Magnesium Sulphate Lavage of the Duodenum), *J. A. M. A.* **76**:1567-1571 (June 4) 1921.

duodenal mucosa. They were led to believe that the gallbladder was decidedly an inactive organ that took little action in the physiologic production, storage or expulsion of the bile. In the experimental work herein recorded, the only instance in which gallbladder bile was obtained from the common duct cannula, except on forcible mechanical expression from the gallbladder, occurred on introduction of 200 c.c. of 0.4 per cent. hydrochloric acid into the duodenum. Confirmatory

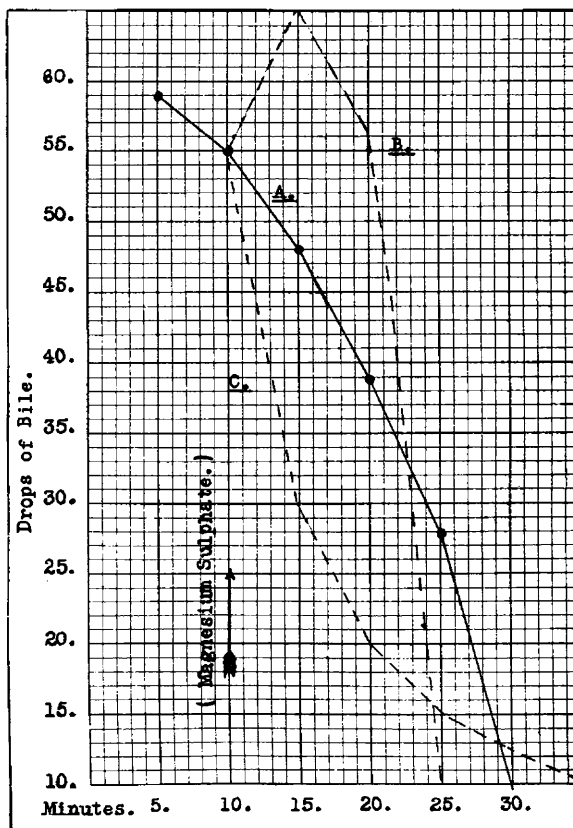


Fig. 2.—Effect of application of concentrated magnesium sulphate on rate of biliary flow: *A*, rate of flow; *B*, curve illustrating rate following contraction, and *C*, curve illustrating rate following relaxation.

of the work of Okada, there occurred in every case a long enduring, pronounced increase of flow of thin, dilute yellowish bile. In three of eight instances, however, the flow throughout was stained with methylene blue, indicative of gallbladder bile under the conditions of the experiment. In no other instance was gallbladder bile seen in the flow nor was there any visible manifestation of any contraction of the gallbladder. Figure 4 shows the long enduring biliary flow follow-

ing the introduction of 200 c.c. of 0.4 per cent. hydrochloric acid into the duodenum and the similarity of its flow to the pancreatic secretion under the same stimulus.

The experimental data herein presented fail to indicate that magnesium sulphate caused any contraction of the gallbladder or produced any expulsion of its bile content. Recently, Dunn and Connell,³⁹ in a human subject, with duodenal fistula and from whom the gall-

TABLE 2.—ESTIMATION OF TIME OF SECRETION OF BILE IN THE DOG

| | Time, Minutes | Amount in Drops from Fine Cannula | | | Remarks |
|--|------------------|--------------------------------------|-------|-------|---------------------|
| | | Dog 1 | Dog 2 | Dog 3 | |
| Magnesium sulphate: | | | | | |
| Before injection..... | 5 | 28 | 32 | 23 | Thin yellow bile |
| | 10 | 26 | 35 | 21 | No gallbladder bile |
| After injection..... | 5 | 28 | 29 | 20 | |
| | 10 | 36 | 33 | 28 | |
| | 15 | 32 | 40 | 27 | |
| | 20 | 25 | 32 | 22 | |
| | 25 | 25 | {53} | 19 | |
| | 30 | 22 | { } | 14 | |
| Peptone solution, 5 per cent.: | | | | | |
| Before injection..... | 5 | 22 | 39 | 22 | Thin yellow bile |
| | 10 | 20 | 35 | 19 | No gallbladder bile |
| After injection..... | 5 | 22 | 32 | 18 | |
| | 10 | 24 | 38 | 17 | |
| | 15 | 34 | 53 | 28 | |
| | 20 | 38 | 58 | 27 | |
| | 25 | 26 | 32 | 22 | |
| | 30 | 24 | 28 | 27 | |
| Meat extract, 5 per cent. solution: | | | | | |
| Before injection..... | 5 | 25 | 32 | 18 | Thin yellow bile |
| | 10 | 19 | 30 | 14 | No gallbladder bile |
| After injection..... | 5 | 39 | 44 | 10 | |
| | 10 | 38 | 57 | 11 | |
| | 15 | 33 | 54 | 12 | |
| | 20 | 22 | 42 | 6 | |
| | 25 | 19 | 35 | 6 | |
| | 30 | 19 | 26 | 12 | |
| Acid, hydrochloric, 0.4 per cent.: | | | | | |
| Before injection..... | 5 | 22 | 26 | 17 | Thin yellow bile |
| | 10 | 26 | 24 | 22 | No gallbladder bile |
| After injection..... | 5 | 42 | 38 | 56 | |
| | 10 | 48 | 58 | 66 | |
| | 15 | 36 | 44 | 61 | |
| | 20 | 34 | 28 | 42 | |
| | 25 | 28 | 31 | 30 | |
| | 30 | 19 | 26 | 28 | |
| Alkali, sodium hydroxid, 0.4 per cent. | | | | | |
| Before injection..... | 5 | 18 | 24 | 23 | Thin yellow bile |
| | 10 | 22 | 20 | 17 | No gallbladder bile |
| After injection..... | 5 | 12 | 17 | 22 | |
| | 10 | 14 | 26 | 19 | |
| | 15 | 20 | 29 | 12 | |
| | 20 | 28 | 34 | 16 | |
| | 25 | 18 | 22 | 19 | |
| | 30 | 21 | 12 | 20 | |

bladder and common duct had been removed, were able to get the increased biliary flow and the sequence of "A, B, C Bile" from the injection of magnesium sulphate either into the stomach or into the duodenum. This sequence, according to Lyon's theory, depended upon

39. Dunn, A. D., and Connell, K.: Report of a Case of Hepatoduodenostomy, With Some Observations on the Lyon-Meltzer Method of Biliary Drainage, J. A. M. A. **77**:1093-1096 (Oct. 1) 1921.

the integrity of the gallbladder and the common duct and the expulsion of their contained bile under the effect of this concentrated magnesium sulphate solution.

FUNCTION OF THE GALLBLADDER

It seems quite evident that the major part of the biliary secretion, the digestive fluid at least, is produced by hormone stimulation to meet the demands of digestion and in a manner identical with that con-

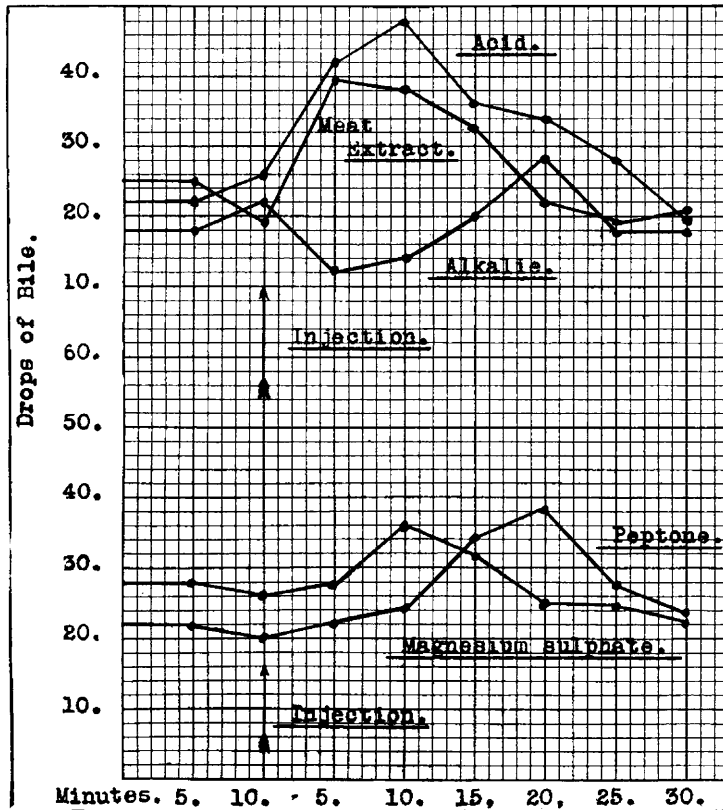


Fig. 3.—Effects of injection of acid, meat extract, alkalis, peptone and magnesium sulphate on rate of biliary flow.

trolling the pancreatic secretion. The period of most abundant bile production seems to coincide with the passage of the acid chyme into the intestine, and the liver continues to produce it as long as the digestive functions demand it. The smaller portion of the biliary flow, the continuous secretion, finds its way into the gallbladder and is there stored up until active digestive processes allow its evacuation. As a reservoir, the gallbladder has been said to be poorly adapted mechanically for such a function, both because of its small relative capacity to the large amount secreted during the twenty-four hours and also because

of its lack of inherent, efficient propulsive powers. Mayo⁴⁰ has indicated that its storage capacity is only from one fortieth to one fiftieth of the twenty-four-hour secretion, and Mann³⁶ states that it can afford storage for about the amount secreted in one-half hour of active liver function.

Under normal conditions, one does not meet with a distended gallbladder, distended as that organ may become under certain pathologic or mechanical conditions. In common duct obstruction we may see a tense well-filled gallbladder; but one does not encounter the huge

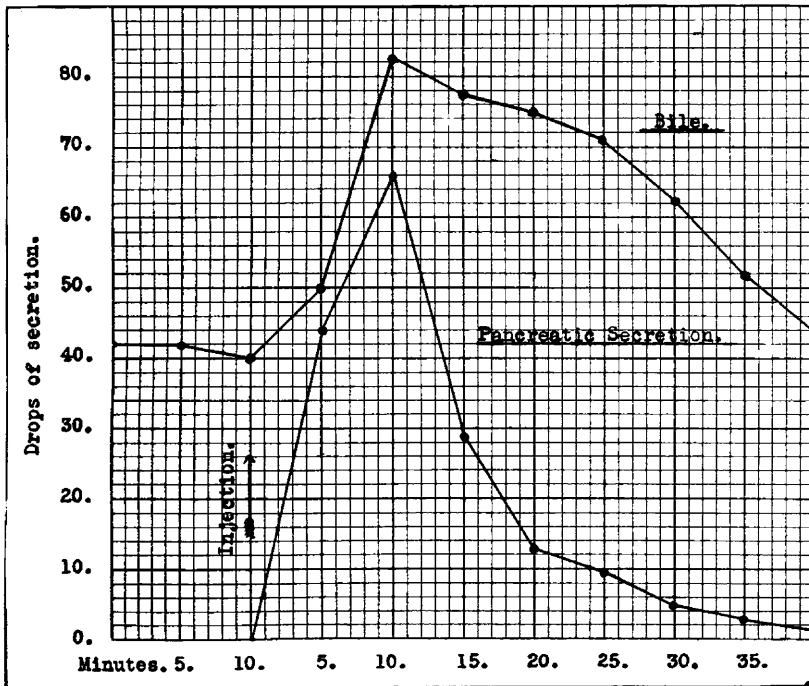


Fig. 4.—Comparison of biliary flow and pancreatic secretion following the introduction of 200 c.c. of 0.4 per cent. hydrochloric acid into the duodenum.

distended bladder. This is usually explained by saying that the storage of bile ceases when the biliary pressure is equal to the secretory pressure of the liver, usually given as 350 mm. of water. The liver at this pressure does not cease to secrete bile; but this, probably, is the pressure at which the bile secreted escapes from the obstructed bile ducts into the blood stream at the margins of the liver lobules. The large distended gallbladders are encountered in cystic duct obstruction in which the gallbladder is distended, not with the bile from the liver, but with its own secretion, produced as a result of a pathologic condition of the gall-

40. Mayo, W. J.: "Innocent" Gallstones a Myth, J. A. M. A. **56**:1021 (April 8) 1911.

bladder wall. On the other hand, increase in pressure in the fundus of the gallbladder tends to prevent entry or exit of bile to, or from, the gallbladder beyond a certain pressure by kinking the S-shaped portion of the neck of the gallbladder and cystic duct. Inability to express bile from the gallbladder by manual pressure may or may not be indicative of a pathologic condition of the bladder. One can fill the gallbladder with fluid to a very high pressure, almost to the point of rupture, and get no flow from the cystic duct; straightening out the neck and the cystic duct by a little pressure on the S-shaped portion will immediately produce an abundant flow of bile. One can readily see how this S-shaped portion, neck or ampulla of the gallbladder, prevents the gallbladder from becoming overdistended and also how an inflammatory condition of the gallbladder and biliary passages might so modify the configuration of the neck, ampulla, cystic duct and leaflets as to make it a nonfunctioning gallbladder.

In a recent article, Rous and McMaster⁴¹ have given us an insight into another function of the gallbladder and biliary passages. Using bile pigment in the bile as the criterion, they found a concentration of bile to ten times the normal in gallbladders which had been emptied and allowed to fill *in vitro*. In distended bladders, the concentration was about nine times the normal in the twenty-four hours. Mere passage of bile through the gallbladder concentrated the bile from two to four times. This was done by the abstraction of water. The gallbladder was thus made a rather capacious organ not so much from its size as from its singular power of reducing the bulk of the fluid reaching it. By this concentrating power it was enabled to maintain the liver output between the periods of gastric activity. According to these men, the gallbladder and the ducts have opposite influences upon the bile. Stasis of bile, connected with or in conjunction with, the gallbladder, always results in a thick, black syrupy bile due to this concentrating effect of the gallbladder. On the other hand, stasis of bile unassociated with the gallbladder results in a thin "white bile" due to the diluting effect of a specific duct secretion. The ducts evidently have the power of secreting a characteristic fluid of their own even under pressures great enough to cause distention of their tough and inelastic walls, a secretion that is devoid of cholates even when the rest of the organism is heavily jaundiced.

As far as has been ascertained clinically, the removal of the gallbladder has resulted in no special detrimental effects. In the Mayo Clinic, cholecystectomized patients showing no untoward symptoms have been followed for more than fifteen years. Mann has kept cholecystectomized dogs for three and one-half years, and they appear to be normal

41. Rous, P., and McMaster, P. D.: Concentrating Activity of the Gallbladder, *J. Exper. Med.* **34**:47 (July) 1921; Physiological Causes for the Varied Character of Stasis Bile, *J. Exper. Med.* **34**:75 (July) 1921.

as far as nutrition and outward appearances are concerned. Judd and Mann have shown the great dilatation of the extrahepatic passages and the reduction of intraductal pressure with relaxation of the sphincter of Oddi following removal of the gallbladder. Eisendrath and Dunlavy⁴² and Haberer and Clairmont⁴³ have reported cases in which the incompletely removed cystic ducts have dilated to form structures similar to the gallbladder and which supposedly function like one. Rost²⁵ has shown that animals subjected to cholecystectomy formed two groups: (1) those with continent sphincters and with dilated bile ducts, the action of which was similar to that of a gallbladder; (2) those having incontinent sphincters and with little or no dilatation of the ducts. In these there was a constant dribbling of bile into the duodenum. During fasting periods, in certain of these animals, the biliary flow was so profuse as to be voided in the stools. Rost has also found a decrease in the secretion of bile and pancreatic juice in cholecystectomized animals after a test meal or after the injection of large amounts of acid chyme into the duodenum.

The gallbladder seems mechanically placed as a distensible pouch or bag interposed in a system of biliary tubes for the purpose of minimizing extremes of pressure within that system, as when bile comes too rapidly from the liver or when its passage into the duodenum is prevented by the sphincter of Oddi. It is doubtful whether, under normal conditions, the intraductal or gallbladder pressure ever exceeds 350 mm. of water, the pressure required for obstructive symptoms. Forced movements of the abdominal muscles, of diaphragm and contiguous organs produced by excessive respiratory movements, struggling, vomiting, violent peristalsis, all undoubtedly produce fluctuations in pressure that are equalized by the gallbladder. The production of mucus and the concentrating power of the gallbladder itself in contrast to the biliary passages are indicative of some distinctive and purposeful differentiation of that organ for present function or possibly of a function that is more actively important in the embryologic history of that structure. The fact that on removal of the gallbladder no special detrimental effects develop clinically may also be indicative of the wonderful adaptability of the human mechanism to such an altered condition as well as confirmatory of any lack of present function. One wonders whether the gallbladder is in the same category, with respect to function, as the vermiform appendix.

42. Eisendrath, D. M., and Dunlavy, H. C.: The Fate of the Cystic Duct After Cholecystectomy, *Surg., Gynec. & Obst.* **26**:110 (Jan.) 1918.

43. Haberer and Clairmont: Experimentelle Untersuchungen über das Verhalten des Cysticusstumpfes nach Cholecystectomie, *Arch. f. klin. Chir.* **73**:679, 1904.

SUMMARY

1. Bile as a secretory product of the liver is produced probably through hormone stimulation associated with the production of acid chyme in the stomach. The height of biliary flow is coincident with the passage of the acid chyme into the duodenum.

2. There is a marked similarity between the curve of bile production and that of pancreatic secretion.

3. The smaller continuous secretion of the liver is stored in the gallbladder, which acts as a reservoir, until evacuated by the demands of digestion. The storage capacity of the gallbladder is augmented by its remarkable concentrating power.

4. The S-shaped configuration of the neck and ampulla of the gallbladder prevents overdistention of the gallbladder. When overdistended it prevents the exit of bile. By altering the peculiar configuration of this portion of the gallbladder and cystic duct, inflammatory conditions may readily produce a nonfunctioning gallbladder.

5. The sphincter of Oddi, a definite muscle entity at the duodenal end of the common duct, sustains an absolute pressure of about 150 mm. of water. The gallbladder undoubtedly equalizes the great fluctuations in this pressure due to movements of the abdominal muscles and contiguous organs. Cholecystectomy tends to produce a lowered intraductal pressure and a relaxed tone of the sphincter of Oddi. The sphincter is probably under reflex nervous control associated with the passage of acid chyme into the duodenum and with intrinsic movements of the duodenum itself.

6. Magnesium sulphate does produce a complete, local relaxation of the duodenal wall and the papillary sphincter, with reduction of the intraductal pressure. Relaxation is transient and is usually accompanied by a flow of bile from the orifice.

7. There was no evidence that concentrated magnesium sulphate produced any contraction of the gallbladder or any specific change in the gallbladder pressure. The augmented biliary flow from its application is probably due to the evacuation of the bile from the bile ducts as a result of sphincter relaxation and also to the stimulating effect of the salt upon the liver secretion.

8. Flow of bile from the gallbladder has been produced in certain cases by injection of large amounts of 0.4 per cent. hydrochloric acid into the duodenum. This probably is the mechanism of its discharge at the beginning of digestion.

9. The production of mucus and the concentrating power of the gallbladder are suggestive of some purposeful differentiation of that structure, although its removal has been, in human beings, without any definite, clinically demonstrable deleterious effects.