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Gallbladder function

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GALL BLADDER FUNCTION

BY

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GENERAL DISCUSSION

There are many problems relating to the functional activities of the gall bladder which are still obscure in spite of the great amount of experimental work that has been done in this field. However an epoch in the advance of knowlege of the physiology and functional pathology of the biliary tract has been witnessed during the past decade.

In writing this paper I have collected material from experimental investigations and clinical observations, which I will attempt to present in such a manner that my conclusions will appear logical.

Before beginning a somewhat detailed account of gall bladder physiology, it would not be amiss to include a brief sketch of the liver function, that related activities may be better understood. The products of digestion, as they are absorbed from the alimentary canal, pass by means of the portal vein to the liver to be broken down or built up into other substances according to the needs of the body. The glucose, may be stored, depending upon body needs, to be freed into the circulation when needed. Metabolism of proteins and fats is another important function. The individual liver cells, the all important unit, receive their oxygen from the hepatic artery. All cells are apparently uniform thruout the entire liver substance. Between these cells of the lobules are found the origins of the bile capillaries, which carry off the bile secreted within the cells. Thus we see liver physiology from two points of view: (1) that which has to do with the formation of the bile and (2) that which deals with the metabolic changes produced in the substances brought to the liver cells by the portal vein, such as the formation of urea, and the formation and storage of glycogen. In a study of the gall bladder the former is obviously of the greater import.

From the physiological standpoint the bile, representing as it does the channel by which the products of the disintegrated hemoglobin are eliminated from the organism, must be considered partly as an excretory function, as it carries off waste products, but as the bile salts or bile acids appear to be specifically synthesized in the liver[27] and as the bile plays an important role in the absorption of fats, the bile must be considered as a true secretion as well as an excretion. Bile is secreted continuously. For humans of average weight the quantity of bile excreted during twenty-four hours has been estimated to vary from five hundred to fifteen hundred cubic centimeters. The color of human bile varies from a yellow or golden color to a dark olive with a greenish tint. Specific gravity varies from 1.010 to 1.050.

The bile salts consist of the sodium salts of glycocholic and taurocholic acid. The relative amounts vary in different animals, as will be taken up later. Bile acids are formed directly in the liver cells and are not formed in any other part of the body. These bile acids or their decomposition products are absorbed in part by the intestines and are again secreted by the liver, this is of considerable physiological significance as the bile acids constitute a very efficient stimulus to the bile secreting activity of the liver cells. The bile salts assist greatly in the splitting and absorption of fats, and keep the cholesterin in solution.

Cholesterol is not formed in the liver, but is elaborated by the cells from the blood which collects it from various parts of the body, being exogenous--derived from the food or endogenous--derived from the envelope of the red corpuscles and the nerve tissue. Cholesterol is very soluble in bile because of the solvent action of the bile acids, being normally present in about 1.6 parts per 1000.

The bile pigments are BILIRUBIN and BILIVERIDIN, which is an oxidation product of the former. When bilirubin is reduced urobilin is formed, this occurs in the intestine, part of the urobilin being excreted in the feces and part being absorbed into the blood and excreted in the urin. The bile pigments are produced from blood pigments which are derived from the destruction of erythrocytes either in the liver or in some other viscus, as the spleen. The bilirubin is formed from the hematin of the hemoglobin by the action of the liver cells, or by the combined action of the liver and endothelial (Kupffer) cells.

Bile also contains lecithin, fats and nucleoalbumin.

These functions of the liver, are in the normal individual closely related to the extra-hepatic biliary system as it is means of excretion of these products, or perhaps we should say the channel by which these products enter the rest of the body.

ANATOMY

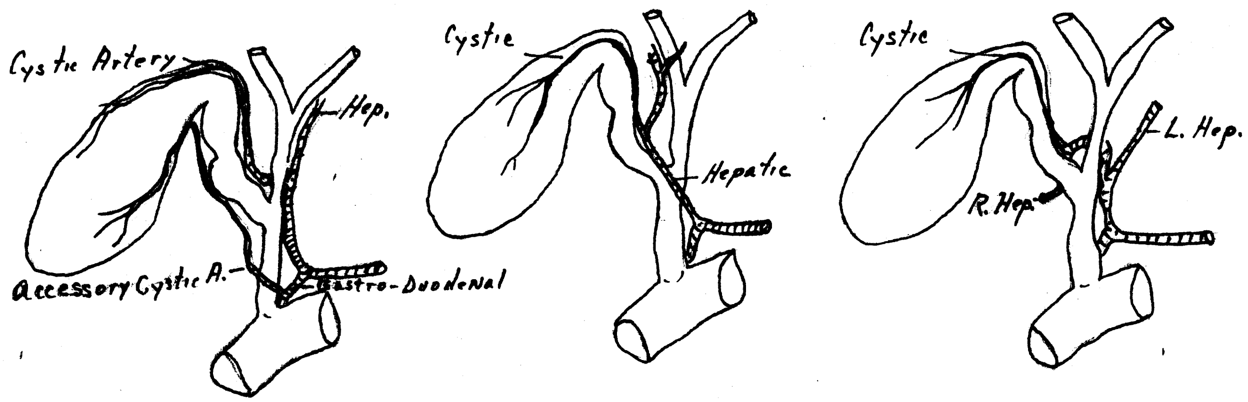
In order to appreciate the discussion of the possible functions of the gall bladder, a few phases of its anatomy should be considered. Although the size, position, relations and other characteristics usually given in connection with the anatomy of an organ are of some importance, in reference to the physiology of the gall bladder, the histological anatomy, the character of its blood, nerve and lymphatic supply, are of greater importance. It should be recognized at the outset that these structures vary greatly in the different species and that the data of their comparative anatomy are at present far from being complete. An important anatomic fact with some physiological significance is the relatively small capacity of the gall bladder as compared with the size of the liver, and its volume of secretion. The position of the gall bladder varies greatly in different species, but it is usually in direct relation with the liver and often is partially or completely embedded in it. The ducts draining the gall bladder and liver also vary greatly, but they all have a variable relationship to the pylorus and pancreatic ducts.

The wall of the gall bladder is composed of four coats [98] (1) mucous, (2) fibro-muscular, (3) sub-serous, and (4) serous, in the part covered by the peritoneum. The mucous layer is composed of simple columnar epithelium which rests on an incomplete muscularis mucosa. The mucosa is thrown into a series of folds which form irregular pockets the size of which decreases progressively from the fundus to the neck of the gall bladder. Mucous material is secreted by the cells of the mucose, but no goblet cells have been reported. In the crypts formed by the folds of mucosa there are solitary lymph follicles.

The fibro-muscular coat is composed of smooth muscle fibers and interlacing bands of connective tissue. While certain observers have described a definite arrangement of the muscle fibers in layers, such an arrangement is difficult to find.[73] The bundles of muscle and elastic connective tissue are very irregularly distributed, the greatest number tending toward a transverse direction.[57]

The subserous layer is composed of dense interwoven elastic tissue bands, and the serous layer is composed of the typical peritoneal endothelial cells.

In all the species in which the blood supply to the gallbladder has been determined, the blood comes from a definite main artery, and also from blood vessels from the liver. The course of the cystic artery is exceedingly variable in man.[38]



Variations of the Cystic Artery.

The large blood vessels run in the subserous layer, the thickest plexus of capillaries is in the connective tissue layer of the fibro-muscular coat, just under the mucosa. The capillaries in this region are very numerous and especially thick in the folds of mucosa.

The lymphatics draining the gall bladder are a relatively large system. The larger channels pass down the cystic duct, under the serous coat and drain into the adjacent lymph glands, communicating freely with the lymphatics of the liver. There are two sets of lymphatics in the gall bladder, a relatively poor one in the subserous layer, and a very rich one in the connective tissue just under the mucosa.

There are two types of nerves in the gall bladder, sympathetic ganglia with connective fibers and medullated fibers accompanying the large arteries.

The gall bladder in man lies on the under surface of the liver, usually attached to it over a flat area, but sometimes free and mobile or embedded into the liver substance. It can hold about 50cc. of liquid, and is relatively thin walled. The smooth muscle in the wall is found mainly at the two ends. There is a good deal in the fundus, much less in the body. The fibers are arranged longitudinally and obliquely. There is much elastic tissue in the body, less in the more muscular fundus and infundibulum. The muscle in the infundibulum tends to a more circular arrangement, which persists into the neck and valvular parts of the cystic duct. There is morphological evidence[82] that the neck region may act by peristalsis or as a sphincter, but this is at present uncertain.

The cystic duct leads out of the gall bladder at an angle, an arrangement which led to probable misconception as to the cause of obstruction, especially at that time when functional disturbances were explained as "kinks". From the neck to half way down the cystic duct the interior of the passage is thrown into folds, Heister's Valves, which form a sort of irregular corkscrew like passage. These folds contain some circular muscle fibers. The lower portion of the cystic duct, together with the hepatic and common bile ducts down to the ampulla are similar in structure, in that they are simply fibro-elastic tubes, with very little muscle.[8 57]

In the ampulla smooth muscle re-appears, in fact, Newman[82] states that here the muscle coat is thicker than anywhere else in the extrahepatic biliary system. The fibers in the upper intramural part are mostly oblique and longitudinal [57] with a circular ring of muscle at the tip of the papilla. The muscular end of the common bile duct, then consists of two structures: The long, oblique fibered ampulla, and the small terminal ring in the tip of the papilla. This structure in most papers is referred to as the "Sphincter of Oddi". Newman [82] compares the described gall bladder and common duct to the urinary bladder, the wall of the ampulla to the ejaculatory muscle coat around the urethra.[83].

Thus the anatomy suggests that the extrahepatic biliary system has a motor function, but the thinness of the gall bladder wall prevents any certain conclusions, indeed this fact is most often used as an argument against motor function.

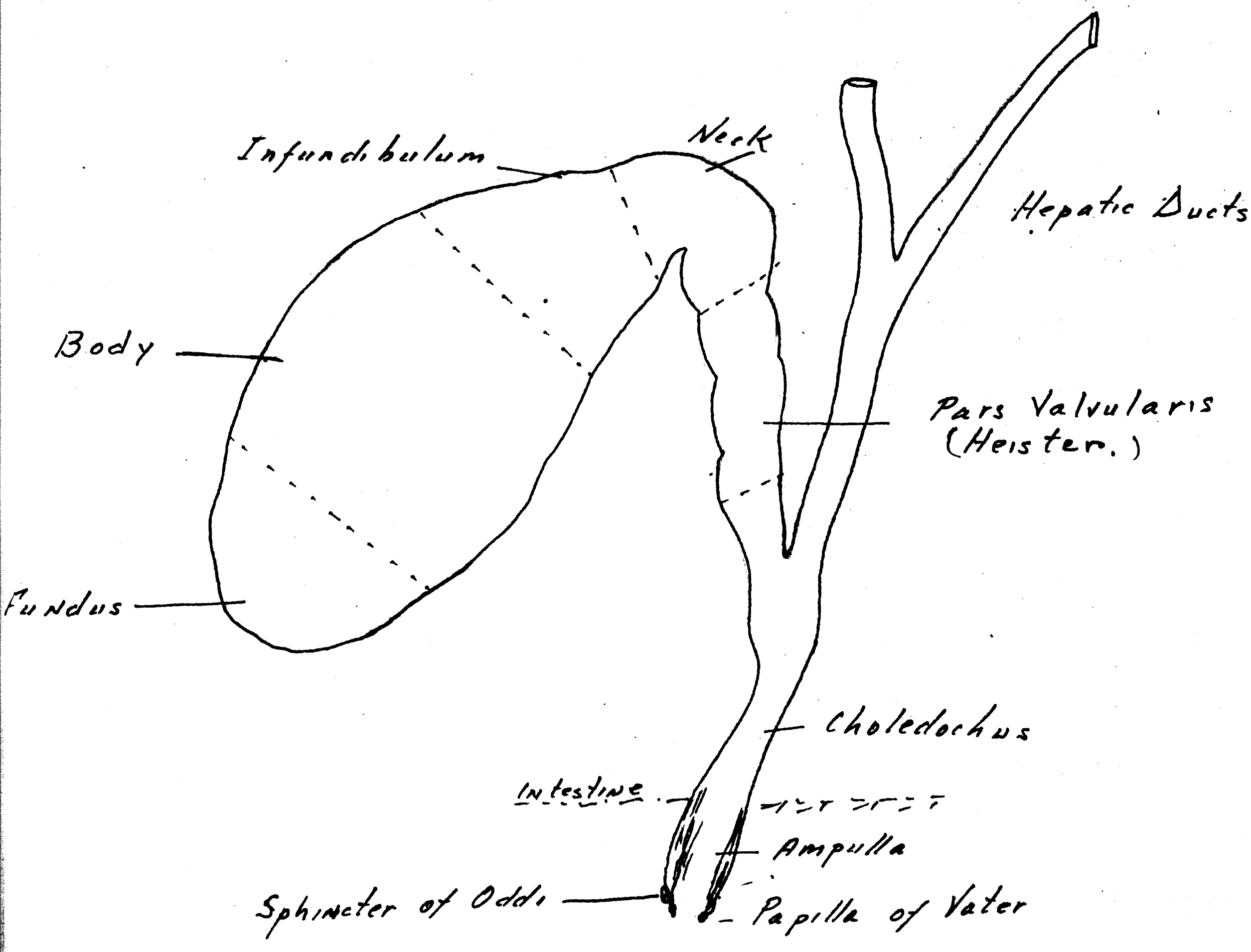


Diagram of Extra-Hepatic Biliary System

Certain anatomic structures of the gall bladder and biliary ducts have been described, and while their functional significance had not been determined they have been very intimately associated with the discussion of the function of the gall bladder.

The "Valves of Heister" : Heister described certain folds in the cystic duct of man which he believed functioned as valves. These have been studied by subsequent observers,[6 56 57] who have noted muscle fibers in these folds, which have been thought to be under nervous control. Their purpose has been assumed to be the prevention of the flow of bile into the gall bladder, or its exit, depending upon the viewpoint of the observer. These valves are not found in all species,and it would seem, regardless of their action and importance in some animals that they connot be considered of major importance with regard to the general physiology of the gall bladder.

The glands of Luschka: Luschka described certain structures in the mucosa of the gall bladder which have been designated as true glands, it is however questionable that these are true glands, perhaps they are simply hernias of the mucosa thru defects of the fibrO-muscular coat. Several Theories have been promulgated with regard to their function.

Parietal sacculi: Little sacculer dilitations are found in the coats of the larger bile ducts, both intra and extrahepatic.

EMBRYOLOGY

While the embryology of the gall bladder has been worked out in relatively few species, it has been considered that the gall bladder arises from the same group of cells that give rise to a portion of the liver. However it probably has a more specific origin.[73] Bloom [12] believes that certain of the embryonic liver cords metamorphose, apparently under the influence of connective tissue to form the bile ducts. The most important embryological consideration, from a physiological point of view is that the gall bladder is formed from the group of primitive cells which also give origin to the liver, pancreas, stomach and duodenum. From the embryological standpoint it would seem that the gall bladder is of some importance, its phylogenesis also suggests that it is important because the autogeny of the gall bladder is extablished very early.

Some of the species studied do not have a gall bladder in adult life, Petromyzon, Pigeon, and the Rat.[93] The history of the gall bladder varies markedly in each of these three forms. In the Petromyzon there is a complete biliary apparatus which persists for a time then totally degenerates. In the Pigeon the gall bladder develops apparently in a normal manner, and then disappears. In the Rat the gall bladder never develops. It is obvious that with the present data no conclusions can be drawn from the comparative embryology of the gall bladder, with regard to its physiology. The question arises however, being derived from the gut, might not it reasonably be expected to manefest motor activity, absorption, and secretion, and might not the "Law of the Intestine" apply.[60]

If the gall bladder is of any importance functionally, it is resonable to assume that animals that do not posses the organ, must have developed some means of compensating for the lack of it. The anatomic variation in the dimensions of the common bile or hepatic ducts has been considered as a possible compensation. The Horse which does not posses a gall bladder, has a relatively short duct with a large diameter; the Ox which possesses a gall bladder , has a duct which, although narrower is much longer, and its relative capacity is almost as great as that of the horse; hence no definite conclusion can be made here.

GALL BLADDER FUNCTION

ABSORPTION

The function of concentration has been universally accepted since it was originally described by Rous and McMaster.[92] Their facts were simply these; 49.8 cc. of bile were concentrated by the gall bladder in 22 ½ hours to 4.6 cc. and by simply allowing the bile to flow through the gall bladder it was concentrated 2 to 4 times. This concentration is effected by the mucous membrane of the fundus and body, which is lined by a columnar epithelium, thrown into minute folds. Concentration is facilitated by the rich blood supply from the cystic artery and the large lymphatic system, especially that located in the sub-serosa. This region of the gall bladder has no glands. In the infundibulum mucous glands appear, becoming more prominent in the neck and cystic duct. Ivy [60] states that the gall bladder can secrete 20 cc. of mucous fluid a day. So it is easily seen that with the exception of this described portion of the gall bladder, the fundus and body, the extra-hepatic biliary system dilutes rather than concentrates the bile. Animals which have no gall bladder should excrete into the duodenum an even more dilute bile than that secreted by the liver. However, Boyden [13] has found that the Rat which has no gall bladder secretes a bile containing 3 times as much bilirubin as the mouse, which has a gall bladder, and found that the bile from a cat in which the gall bladder was congenitally absent, contained 2.2 times as much bilirubin as the liver bile of the normal cat.

The concentration of the bile is carried out mainly by absorption of water. At first the soluble salts, principally sodium chloride, are absorbed with the water at equal rates, but later the chloride is absorbed more rapidly, keeping the total osmotic concentration of the bile in the gall bladder the same as that of liver bile and serum.[88] During the process of concentration the bile becomes more acid.[88 78] Liver bile has a pH of about 7 to 8.5, gall bladder bile has a pH of about 5.5 to 7 a definite acidification.[90] This acidification of the bile of the gall bladder is of importance, because it is often stated in text books that gall stones are the result of acidification of the bile.[67] This is not true.[82] Indeed organized crystallizations resembling stones can be made by alkalinizing the bile.[82] It has been suggested that this acidification of the bile is one of the functions of the gall bladder, thereby preventing stone formation.[92 78] With this in mind administration of acids and alkali by mouth have been tried in an effort to change the pH of the gall bladder bile. Ottenberg and Kahn[84] found no change in the pH of the bile in man following the administration of acids or alkalies by mouth. Actually there is no striking difference in the pH of bile from stone-containing and normal gall bladders.[90]

Calcium is excreted into the bile by the liver, the liver bile containing relatively large quantities in amounts up to 60 mgm. per 100 cc.[79] It is concentrated in the gall bladder and also absorbed, in fact Mirvish[79] and his workers believe there is a "calcium circle", the calcium taken in by mouth enters the liver from the portal vein, a portion then goes into the general circulation, and a portion is excreted into the bile, the amount varying with the level of the blood calcium, this portion excreted by the bile is absorbed by the gall bladder by the lymphatics, to enter the gereral circulation, excesses only, then pass through the gut. They found no secretion of calcium by the normal gall bladder. Dostal, Hrdina, and Goff,[36] however, found that the bladder mucosa secreted calcium in large amounts. Johnston, Ravdin, Austin and Morrison[66] later have shown no calcium to be excreted or rather secreted by the normal gall bladder, but calcium may be secreted following injury to the mucosa, this is very possibly an explanation of Dostals findings in which case the cystic duct was obstructed. In man, liver bile contains 6.5 to 8.3 mgm. calcium per 100 cc., while gall bladder bile contains 6 to 60 mgm. per 100 cc. or even more.[79] Ravdin, Johnston, Riegal and Wright found the calcium varies, but as a rule is higher in concentration than the serum.[88] They also found increased concentration of base and bile salts and a lesser concentration of bicarbonate and chloride in a comparison of hepatic and gall bladder bile. The depression of freezing point, however, indicated only slight changes in osmodic pressure.

Bilirubin is absorbed in small amounts by the gall bladder wall, granules of it can be seen in epithelium of the gall bladder and upper cystic duct[4], but of course the chief effect of the gall bladder is to concentrate it. Liver bile contains about 5.4 mgm. bilirubin per 100 cc. according to Newman[82] and is concentrated about 5 to 40 times in the gall bladder, about 20 times as a rule. He believes it highly improbable that any bilirubin is secreted by the gall bladder, however, from the sparcity of the material on this subject it is rather difficult to draw any conclusions.

Cholesterol and Bile-Salts must be considered together. There has been considerable controversy on this subject, as it was suggested by Naunyon[81] some time ago that cholesterol was secreted by the gall bladder, this was contradicted by Aschoff[4] and many denials have since been made, this has resulted in a vast amount of work, some of which will be briefly considered here.

In twenty four hours man secretes approximately 0.4 Gram of Cholesterol and 5 Grams of Bile salts.[46] If any appreciable quantity were added the factor of concentration of cholesterol would be at the upper end of the series of substances mentioned, it is somewhat conclusive then that there is no significant secretion by the gall bladder as its factor of concentration is about mid-way between the factors of concentration for the other substances.

The Bile salts hold the Cholesterol in solution by forming a water soluble addition compound.[94] The normal gall bladder absorbs this addition compound in small amounts.

It is possible that more bile salts are absorbed than cholesterol,[91] but not in sufficient quantities to upset the solution of cholesterol.[49] Elman and Taussig[42] found that cholesterol determinations of gall bladder and hepatic bile obtained from the same source revealed a greater concentration in the gall bladder even after the inspisating effect of the gall bladder was allowed for, this is the only recent evedende that the gall bladder has the ability to excrete cholesterol into its lumen, they further noted that infections accelerated this activity. This work is in direct contradiction to that of Blaisdell and Chandler[11] who found no cholesterol in the gall bladder wall, not even in the epithelium, after ligation of the cystic duct, leading them to conclude that deposits of cholesterol in the wall of the gall bladder are dependent upon absorption of cholesterol from the bile. Dostal, Hrdina and Goff[36] found only negligable amounts of cholesterol secreted by the normal gall bladder. The general conclusions today are that the normal gall bladder does not secrete cholesterol.[82] No changes have been demonstrated in the bile salt cholesterol ratio with high fat and high protein diets.[35] Under normal conditions in the gall bladder, the absorption of water, cholesterol and bile salts is such that the bile salt and cholesterol ratio remains largely unchanged.[2]

Of the proteins, as was mentioned before mucous secretion by the mucous glands adds mucin to the bile but albumin and globulin are not found in normal bile.[82]

Fats, lecithin and soaps contributed by the liver are concentrated in the gall bladder.[82]

SUMMARY:

The gall bladder concentrates the bile about ten times by the removal of water and soluble salts, and other soluble substances are absorbed to some extent, but to a much greater degree merely concentrated.

The mucous membrane of the normal gall bladder adds nothing to the bile but mucous.

FILLING THE GALL BLADDER

No one has doubted that the gall bladder fills by means of the cystic duct. A thin, watery bile is secreted continuously into the hepatic ducts by the liver, the rate of flow varies with fasting and is decreased with anesthesia.[104] The maximal secretory pressure found by Winkelstein and Aschner[104] was 300 mm. of bile. This is in close range with that found by Mann[73] as well as the findings of McMaster and Elman.[72] For the filling of the gall bladder there is one necessary condition, the sphincter of Oddi must be closed, as this sphincter when unrelaxed offers sufficient resistance to shunt the flow of bile to the gall bladder. Whitaker[102] has shown that the gall bladder fails to fill when this sphincter has been cut.

The existence of this sphincter of the cholodochus both as an anatomical and physiological structure has been much discussed. It was first described by Gage according to Giordano and Mann,[48] and later compared by Oddi, who found it to reisit a maximal pressure of 50 mm. mercury, and it was he who first suggested that a spasm of this sphincter might occur as a result of irritation. Giordano and Mann have shown evidence to support the presence of this sphincter in animals with a gall bladder and also showed that animals without a gall bladder had a continuous flow of bile from the duodenal orifice, the flow was not stopped by irritation of the opening with gauze in animals which have no gall bladder as it was in those which did have.

Numerous efforts at transplanting the distal end of the common duct to disprove the presence of a sphincter have largely been unsucessful due to stenosis.[48] Berg[8] presented a sucessful case of transplant of the divided common duct in which he could produce notmal cholecystograms, but he does not deny the presence of a sphincter, as he demonstrated circular fibers at the previous site of the distal end of the common duct, in this case at the end of 175 days. He did feel, however, that his work did disprove any special neuro-muscular relationship between the gall bladder and the orifice of the common duct as suggested by Meltzer.[77] Burget[23] likewise gave evidence against reciprocal innervation of the gall bladder and sphincter, however he suggested that this activity might be interferred with as the duct passes rather obliquely through the wall of the intestine, activity of which would produce a sphincter like action on the duct.

Physiological existance has been conclusively demonstrated by Lueth[68] who showed this sphincter action was not due to the intestinal wall alone, further work with similar conclusions was done by Mann.[74]

The pressure necessary to overcome the sphincter has been found to range from 120 mm. water to 750 mm.[86 33] All agree that variations occur in different animals and in the same animal under varying conditions. Cole[29] has shown that this variation is controled by gastric and duodenal contents, the most important factor being the pH. He demonstrated that HCl

0.5 % caused a drop in pressure necessary to overcome the action of the sphincter and further that 0.5 % $NaOH$ increased this pressure, which was also increased by distention of the stomach. Further relations of sphincteric activity was suggested by Shapiro and Kasabach,[95] who worked with cases of Duodenal Ileus, their work will be further considered later.

Eisendrath[39] felt that the sphincter of the common duct was responsible for two cases of dilitation of the cystic duct, necessitating re-operation, this is unusual as the sphincter usually becomes inactive following cholecystectomy.[87]

The maximum secretory pressure of the liver seems low when compared to that of the kidney, but this is to be expected as its source is venous, not arterial.[82]

With the choledochal sphincter closed the ducts fill and bile passes into the gall bladder. Petter and Mann[86] found a slight sphincter like mechanism at the neck of the gall bladder capable of maintaining a slight pressure from both sides. This is in disagreement with Halpert[52] who believed the valves of Heister together with the shape and location of the gall bladder prevents any but one way passage of bile through the cystic duct, into the gall bladder. Johnston and Brown,[65] however, found no impediment to flow into or out of the gall bladder in anesthetized dogs, well preserved cadavers or fresh autopsy material, at pressures usually found in the biliary tract, but are in accord with

Potter and Mann, describing a pressure of 10 to 80 mm. water necessary to pass fluid into the gall bladder thru the cystic duct.

As the bile is concentrated in the gall bladder the pressure drops below that in the common duct and more bile runs in, this goes on during fasting, when the gall bladder has reached its limit of capacity the sphincter of the common duct relaxes allowing liver bile to enter the duodenum.[82] This conserves the more concentrated bile until needed.

With regular meals the gall bladder can hold all the bile secreted, because of its power to concentrate. The liver produces 500 to 1300 cc. of bile in 24 hours, this in its concentrated form will fill the gall bladder 1 to 3 times.

SUMMARY:

The gall bladder fills, by means of the cystic duct, during fasting hours by the interaction of liver secretory pressure and tone of the sphincter of the common duct.

GALL BLADDER EVACUATION

The emptying of the gall bladder has for some time been a controversial point. Halpert[52] working with rabbits believed the cystic duct to be a one way passage to the gall bladder. The valves of Heister acting to regulate this flow, the perpendicular position of the gall bladder and the fact that in some animals, the Rhesus monkey, the gall bladder is almost entirely embedded in the liver, led Halpert to believe that the muscle fibers found in the wall of the gall bladder were functionally to prevent over-distention, rather than to expel the bile, theorizing that bile is an essential secretion and disregarding the theory that bile is an excretion as well as a secretion. This work has not been duplicated.

Walsh[100] has shown the rabbit gall bladder contracts feebly, as compared to the contractions seen in the dog and cat gall bladders.

Complete absorption has been disproved by Hunt and Boyden[59] who tied off the cystic duct, without trauma to the gall bladder, its blood vessels or lymphatics and found it had not emptied in 48 hours. The bile salts and pigments were however, greatly concentrated indicating that the gall bladder absorptive power had not been interfered with to any great extent.

Numerous proofs that the gall bladder empties via the common duct have been given: It has been seen to contract during laporotomy, in response to fats injected by tube into the duodenum and at the same time "bladder bile" could be withdrawn from the tube.[47] During cholecystography on man, after the fatty meal the gall bladder can be seen to diminish in size, and the bile ducts can be seen to fill with the opaque bile, which was previously in the gall bladder. In animals, iodized oil injected into the gall bladder has been seen to pass down the ducts into the duodenum.[102]

The physiological stimulus for the expulsion of bile is the passage of food into the duodenum or even the jejunum, as for instance, after a gastroenterostomy.[96] A small psychic influence has been noted by Boyden,[14] McMaster and Elman,[72] and Puestow,[89] who worked with dogs.

Of the foods, the most effective are the fats such as milk and cream, the vegetable oils and egg yolk, the flow starts almost as soon as the food enters the duodenum.[14]

More recently Ivy and Oldberg presented their proof that "Cholecystokinin" prepared after the method of Ivy, Kloster, Lueth and Drewyer,[62] acting as a hormone causes gall bladder contraction. By cross circulation experiments on dogs with matched blood they were able to inject "Cholecystokinin" and produce gall bladder contraction in the attached dog. "Cholecystokinin" is not choline nor Histamine as it is uneffected by Atropine and causes no change in blood pressure tracings taken at the time of injection and during gall bladder contractions. Further they measured the pressure within the gall bladder following injection of "Cholecystokinin" and found pressures up to 240 mm. bile and the average pressure was 200 mm bile pressure maintained for 30 to 40 minutes in unanesthetized dogs. In their work, using Olive Oil and Egg yolk, they found it necessary to digest these materials with Pancreatin to produce good reseult, this was possibly because they used anesthetized dogs for this particular work.

Lueth and Ivy[69] in later experiments with "Cholecystokinin" found that gall bladder contraction produced by this means was independent of liver volume, diaphragm, thoracic and abdominal muscle action and two out of five animals responded equally well after section of the spinal cord at the level of the Third Cervical Vertebra, and they felt that had the blood pressure not fallen so markedly in the other three animals the results would have been 100%.

Over a long period of time many theories of gall bladder contraction have been advanced, this of course due to the lack of any unanimity of opinion. Various theories proposed have been: Increased intra-abdominal pressure due to respiratory movements; Swelling of the liver during vasodilitation; Pumping action of intestine during peristalsis; Recoil of distended gall bladder wall; Flushing action of Hepatic Bile as it enters and leaves the cystic orifice; Contraction of intrinsic musculature.

Early work probably led to the formation of the first mentioned theories, as sections of the gall bladder wall taken by early workers believed the muscle to be too thin to cause effective contraction.[16] Boyden[16] believes there is sufficient muscle present in the wall and that earlier studies were made on sections taken from the distended gall bladder.

Higgins and Mann[58] several years ago made some very valuable observations on the gall bladder contractions, being unsatisfied with Halperts theory and not convinced that the gall bladder, a hollow viscus would empty into the intestine, another hollow viscus by the application of a pressure common to both, the intra-abdominal pressure. This was the theory proposed by Winkelstein[104] who believed the bladder emptied in response to respiratory movements. Higgins and Mann, using Pike, Lepidosteus plastistomus, which have neither lungs nor respiratory movements, a thick abdominal wall and move only slightly, were able to show emptying of the gall bladder and bile in the intestine after introducing a fat meal by stomach tube. Their work was carefully controlled, using a similar amount of water instead of the fat they found the gall bladder in the fasting state and no bile in the intestine. They concluded that intra-abdominal pressure had little to do with emptying of the gall bladder. This work seems to conclusively discredit the first mentioned theory.

Lueth and Ivy[69] found in their work that the liver volume was not changed by the administration of "Cholecystokinin", discrediting the second theory. Further they found that no constant effect was produced on the intestine and they definitely showed that "Cholecystokinin" did not contract the duodenum or stomach. Thus it may be seen that if the pumping action of the intestine is a factor in emptying the gall bladder it is not a necessary one. Shapiro and Kasabach[95] report a definite increase in the evacuation time of the gall bladder in cases of Duodenal Ileus; and further that with relief from the Ileus the emptying time approached normal. This lends favor to the belief that intestinal motility though not essential to gall bladder evacuation is never the less of some aid. Increased emptying time has also been noted in experimental Duodenitis in which post-mortem examination revealed neither gall bladder nor duct pathology.[33]

The question of elastic recoil came up after Copher, Kodama and Graham[32] reported that they had been able to make a rubber bag, function in a manner similar to the normal gall bladder except for concentration. Their work was done with the neck of the bag opening to the outside and in this way the bag was free to fill but emptying was in all probability due to increases in the abdominal pressure, their experiment not fulfilling the requirements found normally, in which there is noopening to the outside. Burget[24] believes that the elasticity of the gall bladder wall may aid the flow of bile in a passive way, this is likely true to some extent but Whitaker[102] has shown that sectioning of the sphincter of the common duct does not cause the filled gall bladder to empty.

Taylor and Wilson[99] showed that Epinephrine given intravenously caused a fall in gall bladder pressure followed by a marked rise and an increase in amplitude of rythmic contractions--repeated injections abolished the initial fall in pressure.

Under the influence of any of these stimuli the gall bladder first pulls itself together, instead of hanging flaccid like a pear, rises, stiffens and becomes oval in shape. The fundus contracts, changing the shape to that of a pear with the thickened end uppermost, the whole bladder contracting to some degree. Contraction rings have been noted by Walsh[100] and Higgins and Mann.[58] During this phase the pressure within the gall bladder rises to about 200-230 mm. of bile.[33 63 72] McMaster and Elman[72] found a decreased resistance to the flow of bile at the papilla during this stage. At the papilla the bile is seen , in animals, to emerge in little spurts.[87] The expulsion of bile is sometimes associated with a peristaltic wave, but often takes place between these waves.[68] There is no doubt that the muscle of the ampulla can work quite independently of the duodenal wall.[82] Burget and Bockelhurst[22] demonstrated a special emptying mechanism in the guinea pig, a modified ampulla, which they thought forced the bile through the papilla. Newman[82] believes a similar mechanism is active in man, during the emptying phase, though not demonstrable.

The application of the "Law of the Intestine" to the evacuation of the gall bladder suggested to Meltzer[77] that the gall bladder and sphincter were reciprocally innervated, this has been confirmed by McMaster and Elman[72] experimentally. There has been much disagreement about this, but it must be remembered that although "Cholycystokinin" can empty the gall bladder via the blood stream, and that denervation experiments confirm the hormone-like action of this substance, the possibility of a double system has not been disprooved.

CLINICAL INVESTIGATION OF GALL BLADDER PHYSIOLOGY

Cholecystography is of greatest use in diagnosis of organic disease of the gall bladder and of gall stones. Graham and Cole[50] advanced the use of Tetraiodophenolthalein in the roentgenological examination of the gall bladder. This substance together with its other halogen derivitives wase used, as it was found that the liver excreted the substances and as a result they were concentrated in the gall bladder. The Phenol conjugation being an exclusive function of the liver parenchyma.[30] Tetraiodophenolthalein and its salts, especially Sodium, have been found to be the most satisfactory both from the standpoint of toxicity and ability to cast a shadow of the gall bladder. Sosman, Whitaker and Edson[96] in their series of cases at the Peter Bent Brigham Hospital found that the intravenous administration of the Sodium Tetraiodophenolthalein a very accurate and reliable test for non-functioning and poorly functioning gall bladders. They report 93.5% reliability in their cases. Further they found that the oral administration of the drug not only gave poorer results but this method of administration was more liable to reactions from the drug.

Cholecystography has disadvantages in the diagnosis of functional disorders. First that it tells little of the concentration; true the intensity of the shadow depends upon the degree of concentration, but a cholecystogram can only tell us that the gall bladder concentrates well in general terms. If the shadow is indefinite, it may be because the concentration is defective, or that too little bile has entered the gall bladder. This is of course a greater factor when the drug is given orally, negative results with this method should be followed by the administration of the drug intravenously.[96] Further it tells only roughly how the gall bladder empties, in some cases it would be of value to know the type of emptying, as well as the rate of the process. This method allows no analysis of the bile.

In view of the fact that the gall bladder varies greatly in size in different individuals, the degree of distention is difficult to judge, and a further sourse of error is included.

Best and Hicken[10] report a method of clinical and experimental investigation of the choledochal sphincter and its effect upon biliary duct stasis, in those cases in which stasis of the bile flow is a factor following the removal of all pathology, "biliary dyskinèsia" or as they suggest "biliary dyssynergia" a more discriptive term. Their method, a modification of cholecystography, is the introduction of lipiodine(Ciba) and Olive Oil at body temperature into the drainage tube located in the common duct. Roentgenograms are then taken immediately, and if there is retention of the material in the bile ducts subsequent rentgenograms are taken at 25 and 35 minute periods. Fluoroscopic studies can also be made in this manner. The Lipoidine and Oil do not cause a contraction of the sphincter, as in five of their cases they were able to demonstrate a relaxed sphincter.

Duodenal intubation has some advantages, it provides bile for analysis, this is of considerable value in diagnosis as was early shown by Lyons.[71] Some information is also obtained as to how the bile is expelled. To excite the flow of bile there are a choice of stimulants, Lyon found that 25% Magnesium Sulphate solution caused a completely local relaxation of the intestinal wall, including the choledochal sphincter. Magnesium Sulphate given by mouth, however has comparatively little effect.[71] Giving 25 cc. is sufficient if given by duodenal tube, this amount does not produce such a general cathartic effect. Olive oil is preferred by some,[82] as it floats on top of the bile and does not dilute it as the watery solutions do. The soaps produced are easily recognized microscopically and hence do not interfer with the analysis of the obtained bile.

Disadvantages of this method lie in the passage of the duodenal tube to a position at which the bile can be obtained, this frequently requires several attempts and is no less pleasant than cholecystography.

GENERAL CONCLUSIONS

The gall bladder which arises embryologically from the gut is shown to have a structure, which, anatomically speaking, specially adapts it for concentration of the bile produced in the liver. Concentration is largely by absorption of water and soluble salts, such as Sodium Chloride. With the exception of mucous, the gall bladder has no secretory activity, which might account for the concentration. Gall bladder bile is ten times as concentrated as that produced by the liver and found in the hepatic ducts.

The gall bladder fills by means of the cystic duct, during fasting hours, by an interaction of the liver secretory pressure and the tone of the sphincter located at the duodenal end of the dommon duct. The Valves of Heister do not offer sufficient resistance to prevent the flow of bile into or out of the gall bladder.

Normally the gall bladder empties, probably by contraction of its intrinsic muscle, at the response to food in the upper intestine, especially that food of a fatty nature. Many other stimuli may produce gall bladder evacuation.

Clinical study of these activities is made possible by the use of Cholecystography, employing an opaque material which is excreted by the liver into the bile. Such a substance is Sodium Tetraiodophenolthalein.

Another method used clinically to determine the function of the gall bladder is the study of the bile. This is done by duodenal intubation and the administration of a chologogue. The bile is collected by the tube and the bile is examined.

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