THE BILE EXPELLING MECHANISM.

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In the past two decades the literature has been filled with theories and isolated facts concerning the physiology of the gall bladder. The maze of conflicting experimental observations has resulted in widespread confusion as to the probable functions of this organ. Recent work has somewhat cleared the picture and now more definite conclusions can be drawn. We have been particularly interested in the peculiar bile expelling mechanism of the guinea pig, recently described by Burget and Brocklehurst (1). Before presenting the observations here to be described regarding the functions of this particular mechanism it might be well to consider the present status of gall bladder function.

The theories of gall bladder function may be classified into three general groups. The first of these denies that the gall bladder plays any significant role in digestion, some considering it quite functionless, and others attributing to it a purely absorptive role. The second theory is that the gall bladder is a passive organ and acts as a reservoir from which bile is expelled only by extrinsic agencies or by elastic recoil of its walls. The third theory attributes to the gall bladder the power to actively contract by its own musculature in response to certain stimuli.

Study of the comparative anatomy of the biliary vesicle has suggested to many that the gall bladder may be a superfluous organ. It has not been reported that the gall bladder exists in any lower form of animal life than fishes (2). At the other end of the series it presents a variety of conditions. In some twenty species of mammals and birds it has entirely disappeared. The horse, deer, rat and pocket gopher have no gall bladder. In

the pigeon it is present in the embryo only. In a third group, as in the two-toed sloth (Halpert, 3) the gall bladder persists but its musculature has almost entirely disappeared. Hutchinson (4) from studies of animals who died in the zoological gardens concluded that the gall bladder is practically functionless. This idea has also gained recognition from the statements that experimental animals survive cholecystectomy without noticeable change in nutrition or general condition. Mann observed a dog for three and one-half years after cholecystectomy and did not note any change in its general health (5). Gatewood (6) found normal gastric acidity in dogs after cholecystectomy. Rosenberg and Rost (7) did not find any changes in metabolism following removal of the gall bladder. Judd (8) (9) did not note any effect of cholecystectomy on the health of his patients. Carlson (10) called the gall bladder an "anomoly." This gave rise to such a widespread disbelief in the utility of the gall bladder that many surgeons have done unnecessary cholecystectomies. Only one year ago, in pointing out the fallacy of this attitude, Boyden (15) writes: "It is no longer uncommon to find reputable surgeons removing normal gall bladders with normal appendices when operating for hysterectomy or even in the course of exploratory laporatomies". Such practices are quite untenable with our present knowledge of gall bladder function. Whipple (11) and Delrez (12) pointed out that removal of the normal gall bladder results in marked digestive disturbances, although removal of a diseased gall bladder is not followed by such untoward results, since its functions have already been lost. Sweet (13) found that the cholesterol content of the blood was considerably increased after removal of the gall bladder and did not reach normal for a period of forty days. Jaundice appears much more rapidly than usual if obstruction arises after cholecystectomy (14). That the gall bladder stores,

concentrates, and actively expells bile for digestion, and that removal of the gall bladder is followed by dilatation of the extra-hepatic ducts will be pointed out later in this paper. In the face of such evidence, the theory of a non-functioning gall bladder is without physiological foundation.

In 1923, Boyd (16) made micro-dissections of the mucosa of the gall bladder and found a very abundant blood and lymph supply. On the basis of these findings he concluded that absorption is a primary function of this organ. The mucosa of the cystic duct is arranged in spirals, forming the so-called valves of Heister. Halpert (17) is of the opinion that the complicated bends in the neck of the vesicle and peculiar arrangement of the Heisterian valves is evidence of a mechanism which regulates inflow and hinders outflow of bile. He maintains (18) (19) that bile which enters the gall bladder does not leave it again by way of the cystic duct but is absorbed in toto by the mucous membrane and the bile constituents are then returned by way of the veins and lymphatics into the liver and general circulation respectively. He quotes Blond (20) as interpreting the results of cholecystography of the last five years in the light of total absorption by the gall bladder mucosa of all bile which enters the vesicle. This concept is far from being widely accepted. There can be no doubt that bile is greatly concentrated by the gall bladder, but this is no new idea. Rous and McMaster (21) have demonstrated that bile is greatly concentrated while in the gall bladder, so that the pigment content of gall bladder bile may be ten times that of liver bile. McMaster (22) further found that the bile of the rat (gall bladder absent) is about eight times higher in pigment than the liver bile of the mouse (gall bladder present). It would seem that Nature has compensated here for the lack of gall bladder to serve the function

of concentration. The utility of this function is the delivery of concentrated bile when the process of digestion is initiated. Situated, as it is, close to the diaphragm, it is highly desirable that storage be concentrated and not bulky. That bile actually leaves the gall bladder by way of the cystic duct has been conclusively demonstrated. Iodized oil placed in the gall bladder has been seen in the duct in human cholecystograms (23). The total absorption theory necessarily disregards the evidence that the gall bladder actually contracts, and that dilatation of the extra-hepatic ducts occurs after its removal. Concentration of bile is certainly a function of the gall bladder but probably not total absorption.

A popular theory of gall bladder function is that is serves as a simple reservoir or "tension bulb" for bile secreted during the intervals between feedings. Although Mayo (24) showed that the relation of the capacity of the human gall bladder to the amount of bile secreted is only about one to forty, the recognition of the concentrating ability of the vesicle has made this theory widely acceptable. Again we point to the findings in our experiment on the dilatation of the extra-hepatic ducts after cholecystectomy. Unless there is some other mechanism present to compensate for the loss of the gall bladder as a tension bulb, dilatation occurs after its removal (vide infra). Storage and regulation of pressure are undoubtedly part of the function of the gall bladder. Given the gall bladder full of concentrated bile, by what mechanism does the bile become evacuated?

Halpert (2) has pointed out that the intrinsic muscles of the gall bladder arise simultaneously with the muscularis mucosae of the primitive gut. This evidence that the musculature is only a "hypertrophied muscularis mucosae" has led many to believe that the gall bladder expels bile only

passively. Whitaker (25) and others have emphasized the large amount of elastic tissue in the vesicle wall. This, they believe, may be evidence of a passive elastic recoil when the gall bladder becomes distended. The mechanical pumping effect ("respiratory squeeze") of the diaphragm and liver was advanced by Winkelstein (26) (27) (28) as a probable means of gall bladder evacuation. Rost (29) reported that with anesthetized dogs he was able to see bile enter the duodenum synchronously with respiration. After cholecystectomy he found a more or less constant dribbling of bile. Higgins and Mann (30) objected to this theory on the grounds that in certain fishes, which breathe by gills and not by rhythmic diaphragm action, the gall bladder will empty soon after a meal of egg yolk. Using an artificial gall bladder made of rubber which he attached to the cystic duct of dogs, Whitaker (31) did not find any evacuation of iodized oil with respiration or even after a meal, although biliary secretion was augmented by the latter means. Respiratory squeeze of the diaphragm can hardly account for the rapid emptying of the gall bladder that has been shown to follow ingestion of food (2).

Evidence has been presented by Burget (32) (33) (34) to show that simple peristalsis and tonus changes in the duodenum play a part in the regulation of the discharge of bile. This is evidenced by a "milking" action on the intra-mural portion of the common duct. Although not denying the importance of this mechanism, Boyden (15) claims to have seen iodized oil leave the gall bladder when he gave food to cats in which the common duct had been severed. However this may be, evidence presented by Ivy (vide infra) has recently proven that the gall bladder can actively discharge bile. So this theory must be modified in that it does not explain all of the means of bile evacuation. That peristalsis in the duodenum plays its part cannot be questioned.

Active contraction of the intrinsic muscles of the gall bladder has been definitely demonstrated by Ivy (35) and his co-workers. Previous to this, Boyden (15) had applied the Graham method of cholecystography (36) (37) to humans and found that egg yolk and cream taken by mouth caused a decided emptying of the gall bladder. The initial response was very rapid - two to five minutes post cibum. Krause (38) reported that fats and fatty acids are the most active stimulants to the gall bladder, especially the unsaturated fats. Pure proteins have a lesser emptying effect; pure carbohydrates are practically ineffective. There has been no question that these foods caused an evacuation of bile from the vesicle. The actual mechanism of its expulsion remained a question for dispute. The efficacy of fats and proteins (which stimulate the pancreas) in emptying the gall bladder led Ivy (35) (48) to try the effect of secretin on gall bladder contraction. Burgsch and Horsters (39) had already obtained evidence of gall bladder contractions after giving secretin to dogs, but they had not ruled out a vasodilator effect. Ivy's work is convincing and carefully done. He showed that secretin caused active contraction of the gall bladder by hormone action. The latter was established by cross-circulation experiments. He states that "every agent which causes a fall in blood pressure causes contraction of the gall bladder". Histamine will cause a contraction of the gall bladder with a fall in blood pressure. However, his pure secretin does not produce a blood pressure depressor effect. This fraction of secretin which stimulates gall bladder contraction he names "cholecystokinin" (That which moves the gall bladder.) He reports that he saw rhythmic contractions of the gall bladder at the rate of two to four per minute. As much as 3.0 cc. of bile may be expelled with each contraction. The maximum power of gall bladder contraction was found to be 24.0 cm. of bile. Ivy was also able to

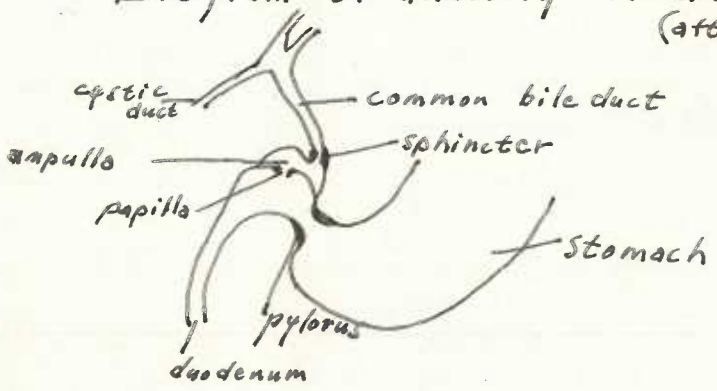
see a change in the gall bladder with the use of lipiodol and x-ray. Hydrochloric acid introduced into the duodenum causes evacuation of bile after a latent period of two to fifteen minutes (the time required for formation and circulation of the hormone). So it can be stated that under certain conditions at least, the gall bladder can expel bile by its intrinsic forces.

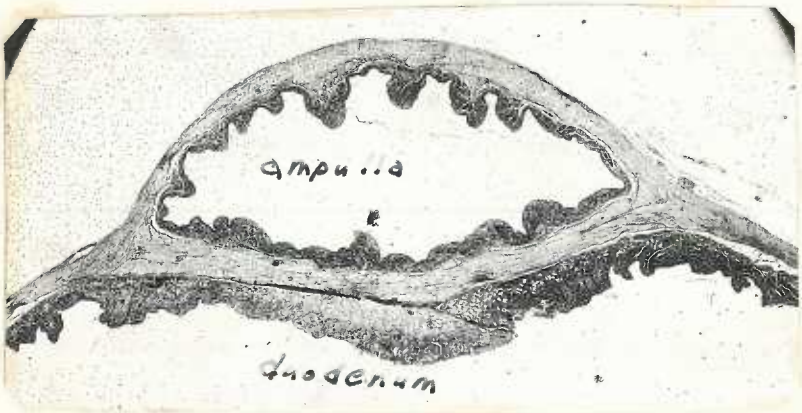
With an understanding of the physiological forces by which bile is emptied from the gall bladder, we can turn to the consideration of the mechanism which regulates its entrance into the duodenum. This brings us to the question of the sphincter of Oddi which has long been a source of dispute, both from an anatomical and a physiological viewpoint. Mann (40) studied the sphincter in ten species possessing a gall bladder and in four species without a gall bladder. He states that a definite arrangement of muscle fibers which might function as a sphincter was found in each case. He states further (14) that in certain instances what would appear to be a sphincter is only an accumulation of the intramural portion of the duct over that of the extramural portion by the addition of fibers from the circular coat of the duodenum. Meltzer (41) maintained that the gall bladder and sphincter were innervated in a reciprocal manner, so that contraction of one occurred during the relaxation of the other. It is generally held that this theory cannot be substantiated by experimental evidence. Many records have been made of the intra-duct pressure which this sphincter will withhold. Such measurements have averaged about 125.0 mm. of water. Burget (33) demonstrated that much of the function commonly attributed to the sphincter was really a property of the duodenal musculature. He transplanted the common duct into a nearby portion of the duodenum and found there was a sphincter action here by means of tonus changes in the duodenal musculature.

This is readily understood if one recalls the very oblique course which the duct pursues as it passes through the duodenal wall to empty into its lumen. A moderate amount of tonus in the duodenum was found to be sufficient to close the lumen of the duct. Increased pressure on the biliary side could overcome the resistance and bile entered the intestine.

Burget and Brocklehurst (1) have lately described a mechanism in the guinea pig which regulates the entrance of bile into the duodenum in a manner not described in any other species. The peculiar part of this mechanism consists of a contractile ampulla lying on the antero-superior aspect of the duodenum (and partially embedded in its wall) at the terminal end of the common duct.

Diagram of anatomy in Guinea Pig. (after Burget.)





Section Through Ampulla - Showing arrangement of muscle fibers.
(Used through courtesy of Dr. G. E. Burget.)

These authors found by microscopic examination of the distal 2 mm. of the common bile duct a compact coat of plain muscle which seems to form a true sphincter. They describe the muscularis of the contractile ampulla as being thick and compact, consisting of an outer longitudinal and an inner circular layer. The longitudinal coat is directly continuous with the duodenal musculature. "The circular layer of both the ampulla and duodenum split into halves at the edge of the ampulla, the inner half of each forming a muscular partition common to both cavities." Through this common wall, surrounded by a "papilla" formed of duodenal mucosa, is the opening into the duodenal lumen.

The activity of this ampulla as described by these authors, is quite striking. Both the ampulla and the sphincter lying just above it are highly irritable and contract strongly after mechanical or faradic stimulation. They found that there was a marked activity of both the ampulla and the sphincter during duodenal peristalsis instituted by digestive processes or from the asphyxia of sudden death of the animal. At the approach of the peristaltic wave the sphincter was seen to contract tightly, obstructing the lumen of the common duct above the ampulla. Contraction of the ampulla followed at once and the bile contents (as much as 0.2 cc.) were expelled into the duodenum. Both the sphincter and ampulla then relax and bile enters the latter at a rate dependent upon the pressure from the ducts above. The cycle is again repeated so that the mechanism acts in the nature of a "bile heart".

Distension of the ampulla by pressure exerted on the gall bladder was said in a few instances to result in a contraction of the sphincter and ampulla. If this observation were correct it would seem to throw much light on the physiological function of this mechanism. The conclusion would be

that when pressure on the biliary side of the sphincter an ampulla is increased the ampulla immediately relieves this pressure through its prowess of active contraction. The attention in the experiments here presented has been particularly directed towards this possibility. If the gall bladder actually acts as a pressure regulator removal of this organ would provide a simple means for increasing the pressure within the extra-hepatic ducts. In animals not possessing this possible compensatory mechanism of a contractile ampulla there should be dilatation (or hypertrophy with dilatation) of the extra-hepatic ducts after cholecystectomy. If the ampulla compensates for such increased pressure in the guinea pig, cholecystectomy should not cause a change in the ducts. The solution, then, lay in the removal of the gall bladder both from a series of animals without an ampulla, as the dog and rabbit, and in a group of guinea pigs.

The effect of cholecystectomy or ligation of the cystic duct on the condition of the common bile duct has been noted by several investigators. Oddi (42) was the first to note a dilatation of the cystic, hepatic and common bile ducts following cholecystectomy. Eisendrath (43) found that if a stub of the cystic duct were left in after cholecystectomy, the stub would dilate to twice its former size within one week. Hartman et al (44) and Mann (45) found dilatation of the common duct as well. Clinical reports indicate that a similar condition appears in humans after cholecystectomy (45) (46). Hartman (44) reviews thirty-three cases in which a return of gall bladder symptoms after cholecystectomy were attributed to a post-operative dilatation of the ducts. There has not been perfect uniformity of opinion as to occurrence of this dilatation. Haber and Clairmont (47) stated that no dilatation occurred if all of the cystic duct were removed. Other reports indicate that dilatation is variable in occurrence. Com-

sequently, our first thought is to establish whether or not cholecystectomy has any effect on animals not possessing a contractile ampulla.

METHOD: Cholecystectomy was performed on eight rabbits and six dogs. Under ether anesthesia and aseptic conditions a right rectus incision was made and the gall bladder caught up with an Allis forceps. With an aneurysm needle a ligature was placed about the cystic duct and vessels below the neck of the gall bladder. The neck of the gall bladder was caught with curved forceps and cut free. Dissection of the vesicle from its peritoneal covering was sometimes carried out from below upwards and sometimes from above downwards. The latter proved to be the easier method. The animals were then placed in their cages and given the routine diet of the animal laboratory. For the dogs this consisted of 400.0 to 500.0 cc. of milk and 130 to 150 grams of kibbled dog cake per day with 250 grams of fresh hamburger twice a week. The rabbits always had hay and rolled barley in their cages. At intervals varying from one to five months these animals were sacrificed with ether and measurements of their ducts were made at autopsy. The ducts were measured both externally and with a set of graduated probes. Measurements were made on an equal number of normal rabbits as an additional control.

PROTOCOLS

Cholecystectomized Dogs.

Animal Number	Measurement of Common Duct. At operation	At autopsy	Post-operative period	Amount of cystic duct left.
i	3mm. diameter (at autopsy the lower hepatic duct was 8 mm. wide)	5 mm.	6 weeks	none
ii	3.5 mm. (this animal showed the greatest dilatation in the series)	10 mm.	5 weeks	none
iii	3 mm.	5 mm.	5 weeks	none
iv	2.5 mm.	4 mm.	4 weeks	a stub 1.0 cm. long which dilated to 8 mm. diam. bile containing.
v	3 mm.	4 to 10 mm. (varied at levels)	4 weeks	none
vi	4 mm.	9 mm.	3 months	none.

Cholecystectomized Rabbits.

Animal Number	Measurement of Common duct at autopsy.	Post-operative period.	Weight of animal	Cystic duct left.
i	5 mm. near hepatic duct.	5 weeks	2.8 kilo.	none
ii	6.5 mm.	6 weeks	3.5 kilo.	0.5 cm.
iii	4 mm. (dilatation not marked in this animal)	6 weeks	3.6 kilo.	none.
iv	3.5 mm.	8 weeks	3.0 kilo.	none.
v	4.5 mm. (stub of cystic duct dilated and well filled with bile).	11 weeks	2.3 kilo.	1.0 cm.
vi	4.6 mm.	8 weeks	3.6 kilo.	none.
vii	3.5 mm.	12 weeks	3.0 kilo.	0.8 cm. dilated to 6 mm. wide and filled.
viii	4 mm.	12 weeks	3.4 kilo.	none.

Normal Control Rabbits

Animal Number	Measurement of Common duct at autopsy.	Weight of animal
i	2.5 mm.	3.2 kilo.
ii	3.5 mm.	4.0 kilo.
iii	2.5 mm.	3.0 kilo.
iv	3.0 mm.	3.0 kilo.
v	4.0 mm.	4.7 kilo.
vi	2.0 mm.	2.0 kilo.
vii	2.5 mm.	2.3 kilo.
viii	2.2 mm.	3.0 kilo.

Analysis of these results show that there was some dilatation noted at the autopsy of each cholecystectomized animal. In some cases the ducts had dilated to three times their normal size. This is definite evidence for the pressure regulating function of the gall bladder. Its removal causes increased intra-duct pressure which in the dog and rabbit, with no contractile ampulla or other means of compensation, results in dilatation of the

ducts. Cholecystectomy in the guinea pig should also result in increased intra-duct pressure. This gives us, then, an effective means of determining the efficiency of Burget's contractile ampulla.

Cholecystectomy was performed on sixteen guinea pigs. Since the vesicle in these animals is practically suspended from the liver by a mesentery the operation is a comparatively simple one and very little trauma results to the ducts. To avoid the trauma co-incident with measuring the ducts at operation a control series of ten animals was used. The control animals were from the same litters and were kept in the cages with the cholecystectomized animals under identical conditions. Autopsies were performed on both series at the same time. It is worthy of note that the growth and activity of the operated animals did not seem to vary in any way from that of the normal animals. Several of the cholecystectomized animals underwent two or three uneventful pregnancies or were pregnant when autopsied. All were in good condition when examined, with very few adhesions.

PROTOCOLS Cholecystectomized Guinea Pigs.

Animal Number	Post-operative period	Weight in grams	Diameter of common bile duct	Cystic duct left
i	4.5 months	757	2.2 mm.	0.5 cm.
	(the stub of cystic duct was atrophied and not filled with bile)			
ii	5 months	648	1.6 mm.	1.0 cm.
	(cystic duct stub 1.0 mm. in diameter, not dilated)			
iii	5 months	613	2.0 mm.	none
iv	3.5 months	490	1.8 mm.	none
v	3 months	425	1.5 mm.	0.5 cm. cord-like
vi	3 months	652	1.5 mm.	none
vii	4.5 months	708	2.2 mm.	none
viii	5 months	806	2.0 mm.	0.5 cm. not dilated
ix	6 months	761	2.0 mm.	none

Cholecystectomized Guinea Pigs, Cont.

Animal Number	Post-operative period	Weight in grams	Diameter of common bile duct	Cystic duct left.
x	5.5 months	710	1.8 mm.	none
xi	5 months	776	1.5 mm.	none
xii	6 months	731	2.0 mm.	8.0 mm. stub filled with bile but not dilated.
xiii	6 months	806	1.8 mm.	none
xiv	5.5 months	640	2.0 mm.	none
xv	6 months	743	2.2 mm.	none
xvi	6 months	809	2.0 mm.	all of cystic duct (and a slight stub of gall bladder present. No dilatation.)

Normal Control Guinea Pigs.

Animal Number	Weight in grams	Size of common duct
i	729	1.8 mm.
ii	521	1.5 mm.
iii	597	1.7 mm.
iv	759	2.4 mm.
v	652	2.2 mm.
vi	720	2.2 mm.
vii	816	2.0 mm.
viii	755	2.8 mm. (The ducts in this pig were the largest encountered in either series.)
ix	810	2.0 mm.
x	728	1.8 mm.

The size of the ducts in the cholecystectomised and in the control animals is seen to be essentially the same. That is to say, cholecystectomy does not result in dilatation of the ducts in the guinea pig. Similar

results were obtained with this animal by Burget and Brooklehurst (1) on seven animals which were autopsied 9 to 48 days after operation. They did not draw any definite conclusions because the number of animals was small and the post-operative period short. Histological specimens taken from the ampulla of some of our operated guinea pigs did not show any evidence of dilatation. Evidence of any possible muscular hypertrophy was inconclusive. No gross changes in the ampulla were apparent.

This is direct evidence that the contractile ampulla compensates for whatever pressure adjustment is usually relegated to the gall bladder. In consideration of the mechanism of this ampulla as described above, it is to be concluded that whenever the ampulla became over-distended by the increased pressure within the common duct, it adequately responded by contracting and expelling bile into the duodenum, thus relieving the pressure. This furnishes further evidence of the physiological importance of this bile expelling mechanism.

In conclusion, we have reviewed the present status of the functions of the gall bladder. Experiments are presented to show that pressure regulation is one of these functions. Cholecystectomy in the rabbit and dog (having the ordinary bile expelling mechanism) is followed by dilatation of the common bile duct. Burget's contractile ampulla takes over the pressure regulating function of the gall bladder in the cholecystectomized guinea pig.

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