

# Experimental Study of the Effect of Grafts in the Common Duct on Biliary and Hepatic Function \*

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FOR MORE THAN 50 years surgeons have been searching for suitable material to replace a diseased or damaged segment of the common bile duct.<sup>2, 3, 8, 12, 17</sup> Although initial successes have been reported, with the passage of time it has become evident that all attempts to bridge a gap in the common duct with an inert tube have been unsatisfactory. Failures generally have been attributed to stenosis, precipitation of bile or rejection of the implant. That an inert graft might produce a specific type of *functional obstruction* of the common duct was suggested by some studies on the effect of partial occlusion of the common bile duct by banding with cellophane. It was noted that in certain experiments progressive liver failure was produced without elevation of bilirubin, acholic stools or appreciable narrowing of the common duct and without obvious infection.<sup>13, 14, 16</sup> This raised the question as to whether a functional obstruction of the duct was caused by a stiffening of its wall without constriction of the lumen. It was postulated that such a functional obstruction might be due to interference with some type of neuromuscular mechanism if not actual peristalsis. In an attempt to obtain more information on this

point, the effect of short grafts in the common duct has been determined with particular reference to resting and emptying gallbladder pressures, response to cholecystokinin, hepatic function and histologic changes.

## Methods

Eighty-three experiments were performed on 58 goats and 16 dogs. All experiments were conducted under aseptic conditions using intravenous nembutal anesthesia. Goats were premedicated with atropine and placed on the operating table in the head down position because of a high incidence of fatal pulmonary complications.

In the experiments in goats, the common bile duct was divided either above or below the pancreatic duct and a short segment (1.0 cm. or less) of graft of fresh autologous vein, autologous artery or preserved homologous arteries sutured between the divided ends with fine silk. A similar procedure was performed in dogs except that the graft was always placed proximal to the pancreatic duct. In all experiments, the internal diameter of the graft was larger or equal to that of the common duct. In four goats and four dogs, Teflon grafts were used and in two dogs and two goats, the divided duct was reconstructed by immediate end-to-end suture. In a series of four experiments, the effects of total occlusion of the bile duct was studied.

Before and at varying periods after insertion of the grafts, the following liver function tests were performed: serum bilirubin,

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alkaline phosphatase (a modification of the King-Armstrong method), serum protein, thymol turbidity, serum amylase and serum glutamic transaminase (a modification of the method of Reitman and Frankel). All stools were tested for bile.

In 22 experiments, bile duct function was studied by pressure measurements and by cineradiography using the image intensifier. In a few of these experiments, this was done by means of a T-tube in the common duct, but in the majority the contrast material was injected into the gallbladder which had previously been sutured to an anterior abdominal wall. At varying periods between a few days and nine months, the animals were either operated upon or sacrificed. The bile ducts were examined and sections of liver taken for histologic study.

All experiments in which there was the slightest evidence of narrowing or constriction of the anastomosis were discarded from this study.

**Results**

**Group I. The Effect of a Graft of Autologous Vein, Autologous Artery or Preserved Homologous Artery on Bile Duct and Hepatic Function.** There were 20 experiments in the group; ten were discarded because of technical failures or questionable narrowing of the graft during the course of the study. Provided there was no evidence of constriction, there did not appear to be any difference with reference to the type of materials used for the graft. Preserved homologous artery proved the easiest to use and was employed in the latter experiments.

TABLE 1. *Experiments on Goats.\**

Exp. No.	Length of Survival	Gallbladder and Upper Bile Ducts	Bile in Feces	Alkaline Phosphatase	Thymol Turbidity	Transaminase	Site of Graft in Relation to Pancreatic Duct	Serum Amylase
1	5 das.	Slightly dilated	+	Elevated			Below	Elevated
2	8 das.	Dilated	+	Normal			Above	Elevated
3	10 das.	Normal	+	Normal			Above	Normal
4	16 das.	Normal	+	Normal			Above	Normal
5	5 wks.	Tense and dilated	+	Persistent elevation	Normal	Normal	Above	Normal
6	6 wks.	Tense and dilated	+	Persistent elevation after two weeks	Normal	Normal	Below	Elevated
7	8 wks.	Tense and dilated	+	Persistent elevation		Normal	Below	Elevated
8	10 wks.	Tense and dilated	+	Persistent elevation	Slight elevation	Normal	Below	Elevated
9	7 mos. alive and well	Gallbladder normal-upper bile ducts dilated	+	Intermittent elevation	Slight elevation	Normal	Below	Elevated
10	9 mos. alive and well		+	Persistent elevation	Slight elevation	Normal	Below	Elevated

\* Bilirubin normal in all experiments.

TABLE 2. *Experiments on Goats and Dogs\**

Exp. No.	Length of Follow up	Gallbladder and Upper Bile Ducts	Alkaline Phosphatase	Resting Pressure in G.B.	Radiologic Emptying of G.B. & C.B.D.	Response to Cholecystokinin
1	3 das.	Slightly dilated				
2	1 wk.	Dilated	Normal	Elevated	Delay in passing graft	
3	1 wk.	Dilated		Elevated	Delay in passing graft	
4	8 mos.	G.B. normal upper duct dilated	Elevated	Normal	Delay in passing graft	Delayed emptying
5	4 wks.	Slightly dilated	Elevated	Elevated	Some delay	Delayed emptying
6	6 wks.	Normal	Elevated	Elevated	Considerable delay in passing graft	Delayed emptying

\* Experiments 1-4—goats; 5, 6—dogs; bilirubin normal in all.

The results of this series of experiments is summarized in Table 1.

Four experiments were terminated between five and 16 days after operation. In two there was already slight dilatation of the proximal biliary tree although there was no elevation of bilirubin and there was bile in the feces. Alkaline phosphatase was elevated in one of these experiments. Four experiments were terminated between five and ten weeks after operation. In all of these the bile ducts proximal to the graft were slightly dilated. Again, however, there was normal bilirubin and bile in the stools. Alkaline phosphatase in all of these experiments was periodically but not consistently elevated.

Two experiments were carried beyond six months. Again there was evidence of proximal dilatation of the bile ducts but it was not strikingly different from that observed in the earlier experiments. Levels of bilirubin were normal and bile was consistently present in the feces. Alkaline phosphatase was elevated consistently in one experiment and intermittently in the other. One of these animals at 12 months appears com-

pletely well, but there is persistent elevation of serum alkaline phosphatase and slight elevation of thymol turbidity.

In all instances except one in which there was an elevation of serum amylase at some time during the experiment, the graft had been placed below the entrance of the common bile duct. Serum glutamic oxalic transaminase was normal throughout the course of all these experiments. In three animals carried beyond ten weeks, there was slight elevation of thymol turbidity.

**Group II. The Effect of Grafts of Homologous Artery on Intraluminal Pressure, Emptying Time and Response to Cholecystokinin of the Gallbladder and on Hepatic Function.** There were 24 goats and eight dogs in this group of experiments. A preliminary operation was performed in which the gallbladder was first sutured to the anterior abdominal wall so as to permit percutaneous cholangiography and studies of bile duct pressures. The animals were then re-operated upon after control studies had been performed and the grafts inserted. There was a high mortality among the goats with the dual operation and the multiple

TABLE 3. *Experiments on Goats and Dogs\**

Exp. No.	Length of Follow up	Gallbladder and Upper Bile Ducts	Alkaline Phosphatase	Resting Pressure in G.B.	Radiologic Emptying of G.B. & C.B.D.	Response to Cholecystokinin
1	3 wks.	Dilated	Elevated	Normal	Some delay	
2	4 wks.	Normal	Normal	Normal	Some delay	
3	4 wks.	Normal	Elevated	Normal	Some delay	Normal
4	4 wks.	Some dilation	Normal	Normal	Delayed	Normal
5	10 das.	Normal	Elevated	Normal	Some delay	
6	5 wks.	Normal	Elevated	Elevated	Normal	
7	7 wks.	Normal	Elevated	Normal		Delayed emptying
8	7 wks.	Normal	Elevated	Normal	Normal	Delayed emptying

\* Experiments 1-4—goats; 5-8—dogs; bilirubin normal in all.

anesthesias necessary for the determination of pressure and radiographic emptying of the gallbladder. Only six experiments were deemed suitable for evaluation, four goats and two dogs. The results are summarized in Table 2.

It will be noted that the findings are similar to those in Group I. Of particular interest, however, is the fact that there was delay in contrast material passing through the graft as early as one week after insertion of graft. The most consistent abnormality observed was delay in radiological emptying time of the gallbladder and common duct. There was also a delay in the response to cholecystokinin in the experiments in which this was studied.

**Group III. The Effect of Teflon Grafts in the Common Bile Duct on Intraluminal**

**Pressure, Emptying Time, Response to Cholecystokinin of the Gallbladder and Hepatic Function.** There were eight experiments on four goats and four dogs. The technical results were much better using teflon as has been reported by others.<sup>4, 7</sup> All experiments were suitable for evaluation. The results are summarized in Table 3. Despite the excellent technical results, it will be noted that there was an elevation of alkaline phosphatase in six experiments. In the two instances in which alkaline phosphatase was normal there was a delay in emptying of the gallbladder. It is of particular interest that these abnormalities were present in the short period in which these animals were observed, the longest being seven weeks.

TABLE 4. *Experiments on Goats and Dogs\**

Exp. No.	Length of Follow up	Gallbladder and Upper Bile Ducts	Alkaline Phosphatase	Resting Pressure in G.B.	Radiologic Emptying of G.B. & C.B.D.	Response to Cholecystokinin
1	6 wks.	Normal	Normal	Normal	Normal	Normal
2	3 mos.	Normal	Normal	Normal	Normal	Normal
3	10 wks.	Normal	Normal	Normal	Normal	Normal
4	3 mos.	Normal	Normal	Normal	Normal	Normal

\* Experiments 1, 2—goats; 3, 4—dogs; bilirubin normal in all.

TABLE 5. *Experiments on Goats and a Dog\**

Exp. No.	Length of Survival	Gallbladder and Upper Bile Ducts	Bilirubin	Alkaline Phosphatase	Radiologic Emptying of Gallbladder	Response to Cholecystokinin
1	5 das.	Very dilated				
2	6 das.	Very dilated	Elevated	Elevated		
3	7 das.	Very dilated	Elevated	Normal	None	
4	14 das. Sacrificed	No dilatation	Elevated	Elevated	None	No emptying
5	20 das.	Very dilated	Elevated	Elevated	None	No emptying

\* All goats but No. 4; pressure in gallbladder elevated in all.

**Group IV. The Effect of Division and Immediate End-to-End Suture on Intraluminal Pressure, Emptying Time and Response to Cholecystokinin of the Gallbladder and on Liver Function.** The results of the four experiments are summarized in Table 4. The animals were sacrificed respectively: one goat at six weeks, one dog at ten weeks, one goat at three months, and one dog at three months. All tests studied in the other groups were repeated and found to be normal. There was no dilatation of the proximal biliary tree. Determinations of bilirubin and alkaline phosphatase remained at normal levels. Resting pressure in the gallbladder and radiological emptying time of the gallbladder was normal as was the response to cholecystokinin. There

was no proximal dilatation of the bile ducts and histologic studies showed no abnormalities in the liver.

**Group V. The Effect of Ligation of the Common Duct.** By way of contrast, in four experiments the results of complete division and ligation of the common duct were studied. The results are summarized in Table 5. It can be seen that in all cases there was marked dilatation of the proximal biliary tree. Bilirubin was consistently and markedly elevated. There was marked elevation of resting gallbladder pressure and there was no emptying of the gallbladder, either spontaneously or in response to cholecystokinin. These animals were gravely ill and all succumbed within five to 20 days of operation.

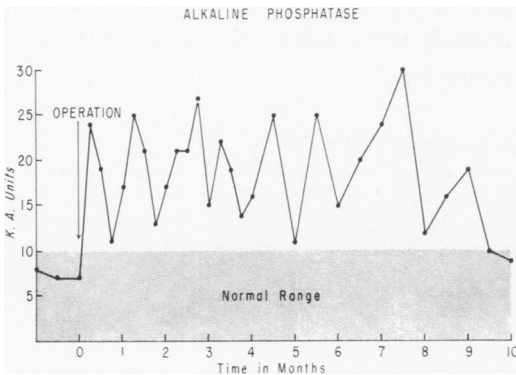


FIG. 1. Graph showing serum alkaline phosphatase levels following insertion of a segment of autologous artery into common bile duct of a goat.

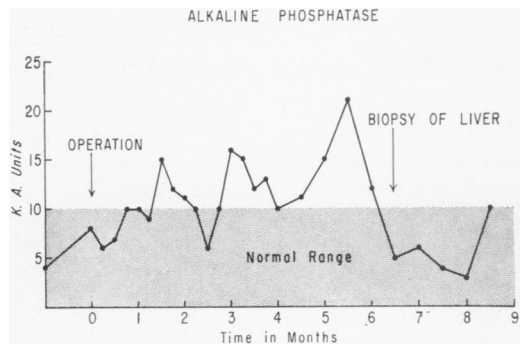


FIG. 2. Graph showing intermittent elevation of alkaline phosphatase following insertion of a graft of autogenous vein into common bile duct of a goat. Biopsy of liver is shown in Figure 11.

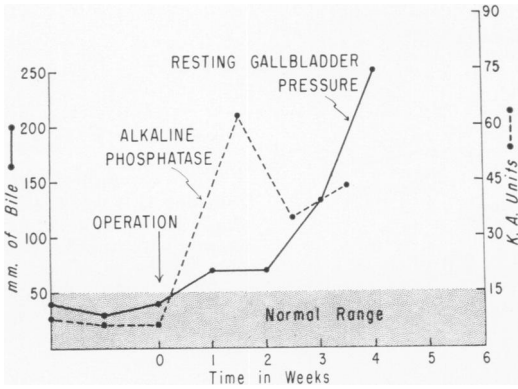


FIG. 3. Graph showing effect of graft in common bile duct on resting pressure in gallbladder and serum alkaline phosphatase of a dog.

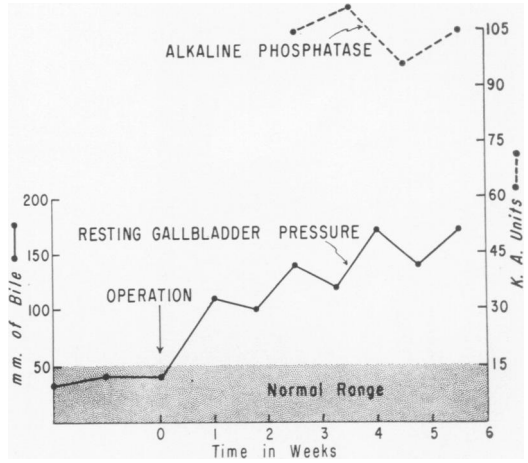


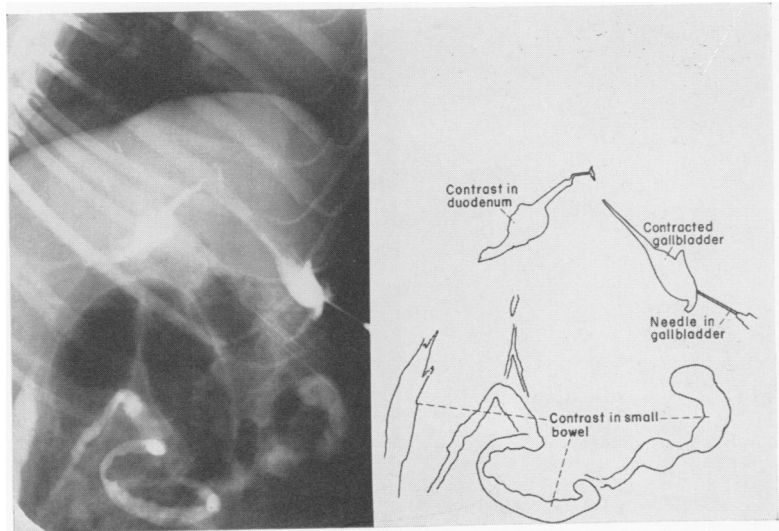
FIG. 4. Graph showing effect of graft in common bile duct on resting gallbladder pressure and serum alkaline phosphatase of a dog.

### Alkaline Phosphatase, Intraluminal Pressure and Emptying Mechanisms of the Gallbladder and Common Duct

Particular experiments are described in more detail to illustrate the course of the changes which follow the insertion of a graft into the common bile duct. Figure 1 illustrates the changes in alkaline phosphatase over a period of ten months. Note the marked fluctuation and the frequency with which nearly normal levels were obtained. Throughout this period, the animal appeared completely well. Four months

after operation, she delivered two kids and suckled them normally. It is obvious that an occasional sampling of serum alkaline phosphatase might place it in the normal range and give the impression of an entirely normal course. Figure 2 illustrates the same thing in an animal followed for eight months. The animal was re-operated upon at six and a half months when the alkaline phosphatase had returned to normal. There was proximal dilatation of the

FIG. 5. Radiographs from a dog showing normal emptying and contraction of the gallbladder in response to cholecystokinin.



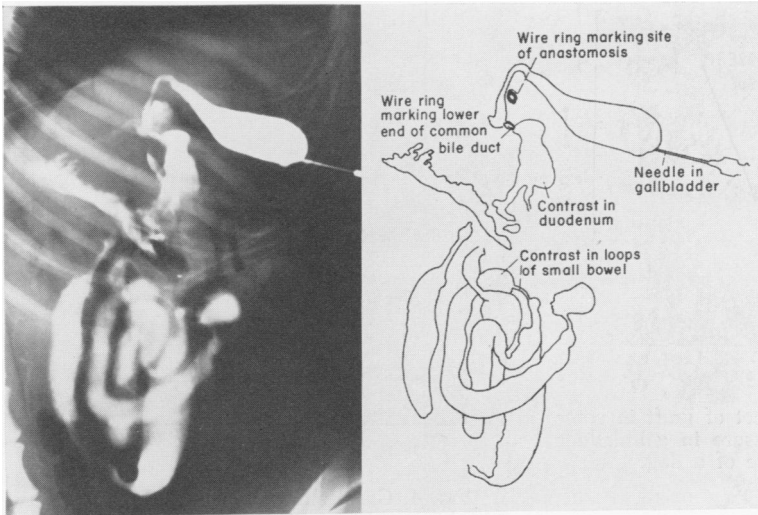


FIG. 6. Radiographs from dog two weeks after simple division and reanastomosis of common bile duct. There is a normal response eight minutes after injection of cholecystokinin.

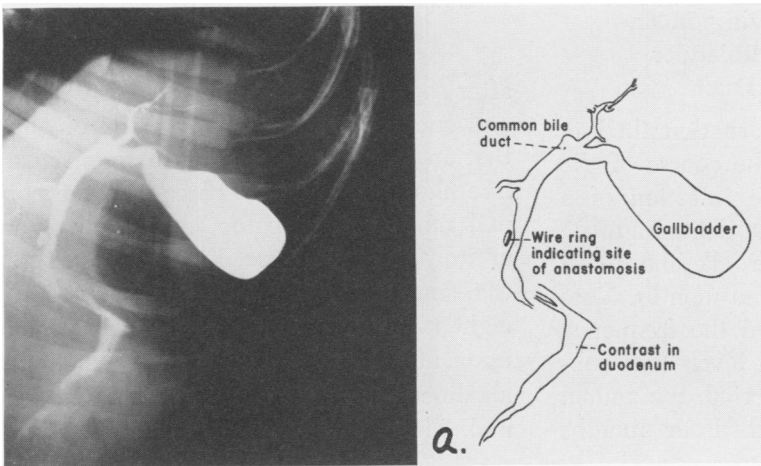


FIG. 7A. Radiographs from dog ten weeks after simple division and reanastomosis of the common bile duct. There is prompt spontaneous emptying of contrast media into a normal common duct.

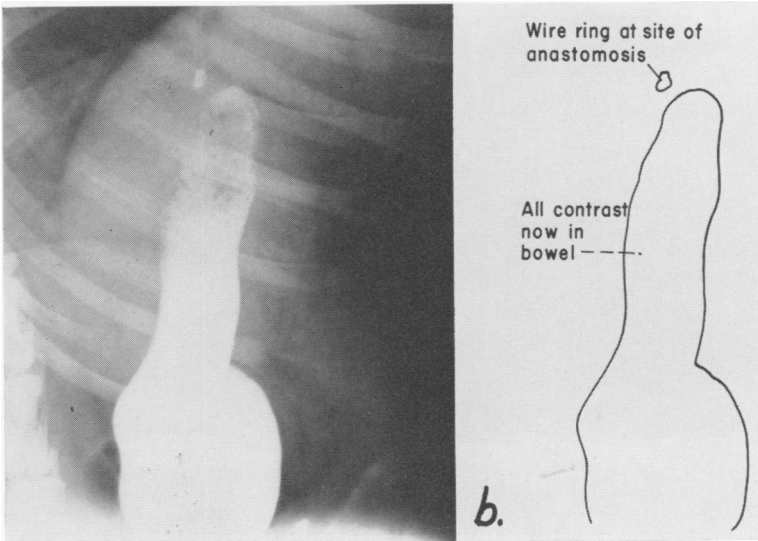


FIG. 7B. After six hours there is no contrast remaining in the gallbladder.

biliary tree and a biopsy of the liver showed distinct periductal fibrosis.

The effect of the grafts on intraluminal pressure in the gallbladder and the emptying mechanisms of the gallbladder and common duct are of particular interest. In Figures 3 and 4 the course of resting gallbladder pressures and serum alkaline phosphatase are demonstrated before and after

the insertion of a vascular graft in dogs. In both experiments, the animals appeared completely well.

Normal radiographic emptying of the gallbladder is shown in Figure 5 eight minutes after the administration of cholecystokinin. Note the contracted gallbladder, the narrow normal common duct and the rapid passage of the contrast material into the

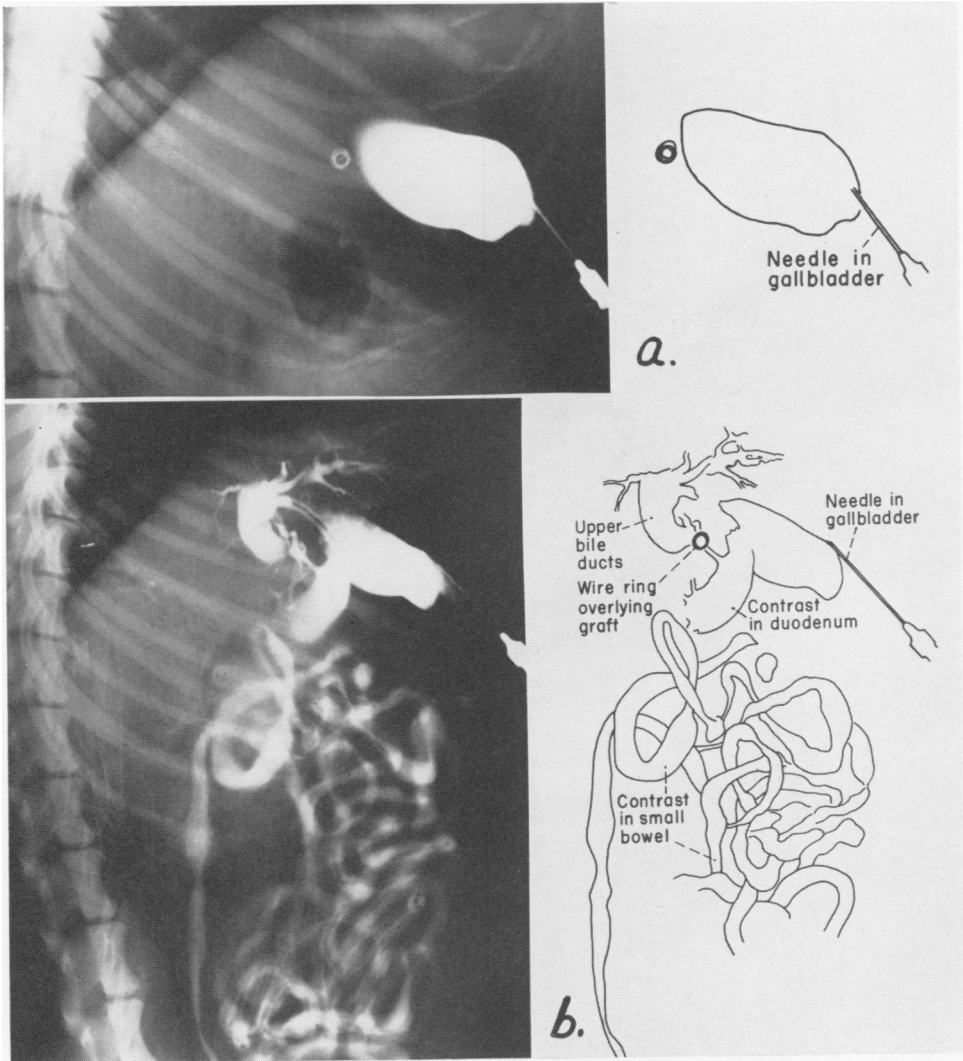


FIG. 8. Radiographs from dog two months after insertion of a graft of homologous artery into common duct: A. Gallbladder fails to empty even though the pressure was elevated; B. Fifteen minutes after cholecystokinin the pressure in the gallbladder was very high and a little contrast had passed into duodenum. The gallbladder fails to empty at the normal rate and the upper bile ducts are dilated. The radiograph has the appearance of stenosis at the site of graft but there was no evidence of stenosis on direct examination (see text).



small intestine. Figure 6 shows the response to cholecystokinin two weeks after division and end-to-end anastomosis of the common duct. Figure 7a shows normal spontaneous emptying of the gallbladder and common duct two months after an end-to-end anastomosis. Again note the rapid emptying and normal appearance of the bile ducts. At six hours (Figure 7b) all contrast media is in the colon.

In contrast, the results one month following the insertion of a graft of homologous artery are shown in Figure 8. Figure 8a shows no spontaneous emptying of the gallbladder although the resting pressure recorded at this time was markedly elevated. After cholecystokinin, the gallbladder empties into a dilated upper ductal system, Figure 8b. The site of the graft appears narrow and stenotic but actually

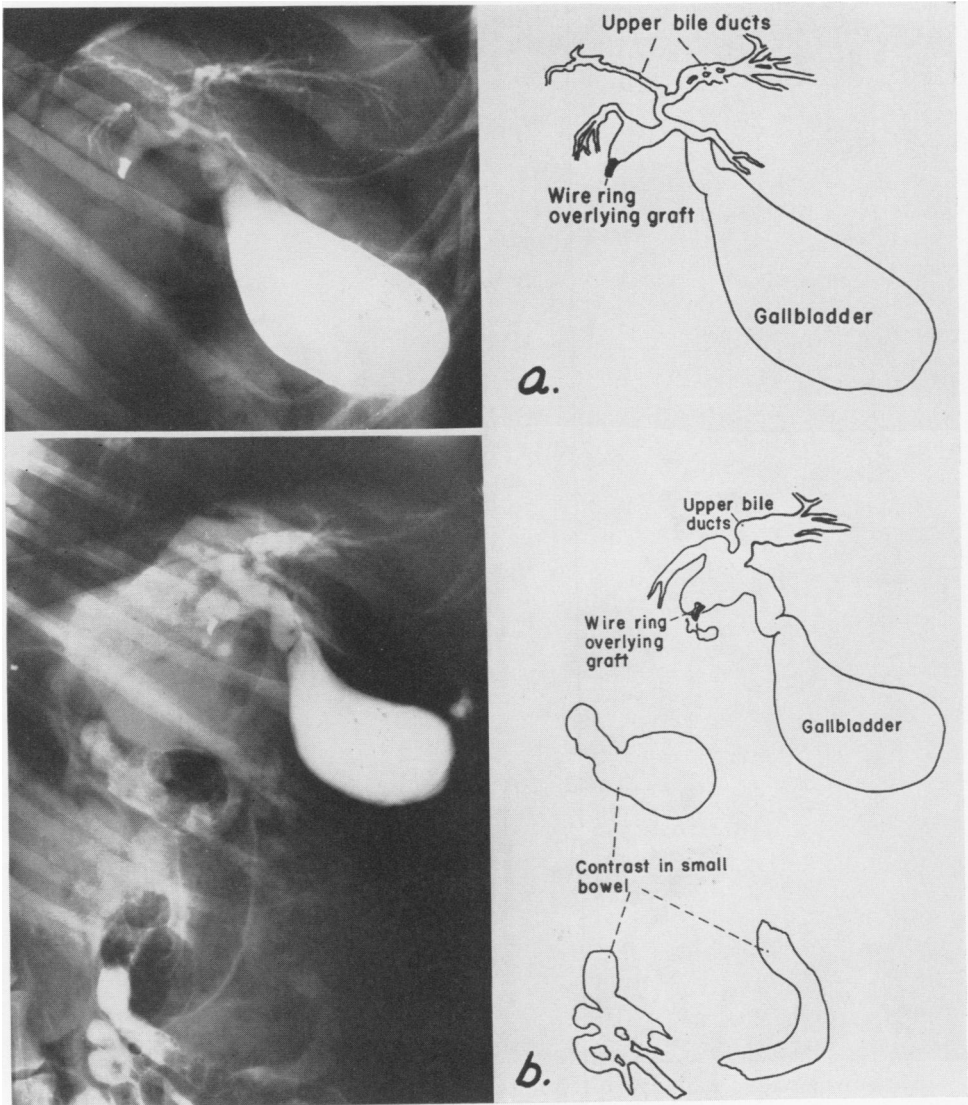


FIG. 9. Radiographs from dog two weeks after insertion of a vein graft showing: A. The gallbladder contracts poorly and the contrast media appear to be held up at the site of the graft; B. Four hours later only a little contrast has passed into the bowel and the proximal ducts are dilated.

measured 4.0 mm. in diameter which was the size of the graft and the common duct at the time of implantation.

The results only two weeks after the insertion of a vascular prosthesis are depicted in Figure 9. In this experiment, the gallbladder empties spontaneously, but the contrast media appears to be held up at the site of the graft (Figure 9a.). After cholecystokinin (Figure 9b), the media empties rapidly into the small intestine but the bile ducts now appear dilated proximal to this graft. Figure 9c shows contrast material still in the gallbladder twenty-four hours later.

The results two weeks after the insertion of a teflon prosthesis are shown in Figure 10. The gallbladder empties spontaneously into a normal appearing common duct. The graft is widely open (Fig. 10a). However, eight minutes after cholecystokinin there is prompt but inadequate emptying (Fig. 10b). Twenty minutes later there is still considerable contrast material in the gallbladder (Fig. 10c).

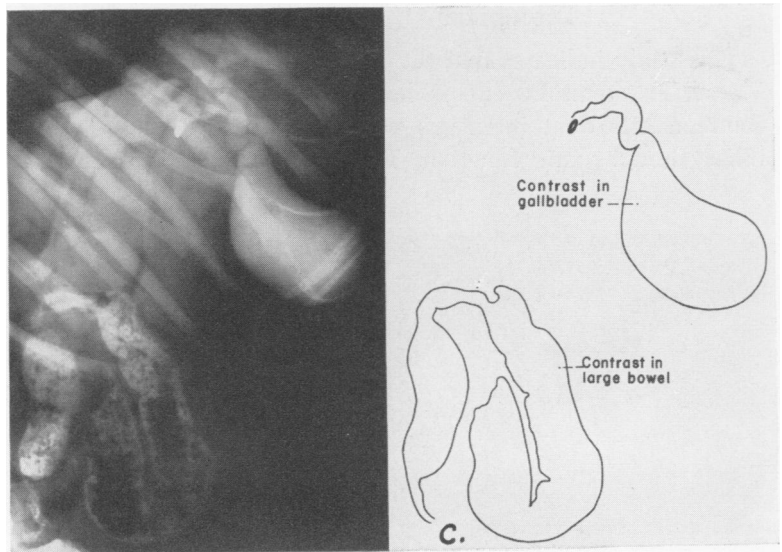
In all radiographic studies using the image intensifier, a particular search was made for evidence of peristalsis. In the entire group of 28 experiments in which

cineradiography was performed with repeated observations in some animals, no recognizable peristaltic wave was seen. In both the normal and obstructive ducts, however, duodenal contractions were noted. At times these were very active and appeared synchronous with emptying of the contrast material into the duodenum. Frequently, there seems to be slight dilatation of the common duct after constriction of the gallbladder. This is well shown in Figure 9a and b.

### Histologic Studies

Severe hepatic failure was not encountered in this series of experiments, in which only grafts that were widely open were included. Grossly the liver appeared normal. Histologic changes were minimal but could be demonstrated regularly in the animals followed for more than a few weeks. Figure 11 shows the type of changes found. This animal had been followed for six months and at the time of biopsy appeared to be completely well. The graft was widely open. There was bile in the stool and serum bilirubin was normal. There was an elevation of alkaline phosphatase and the resting pressure in the gallbladder was high.

FIG. 9C. Twenty-four hours later still a considerable quantity of contrast in the gallbladder.



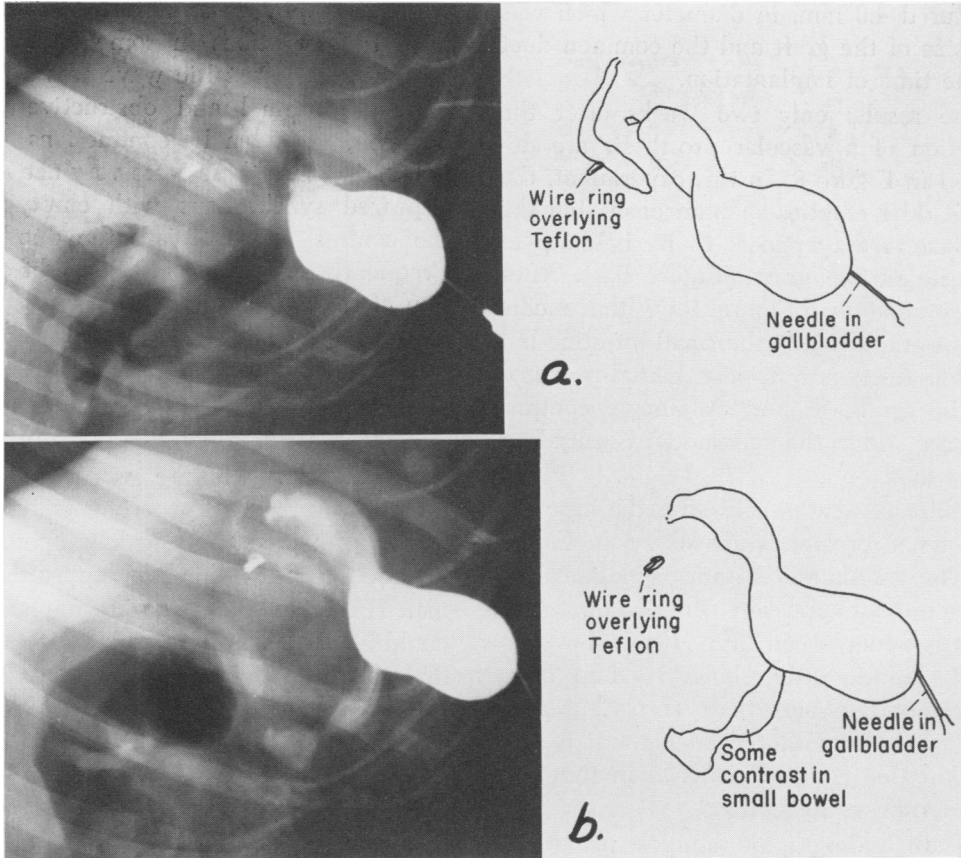


FIG. 10. Radiographs from dog two weeks after insertion of a teflon tube between the divided ends of the common bile duct; A. There is spontaneous emptying. The bile duct appears normal; B. Eight minutes after cholecystokinin there is prompt but inadequate passage into the small bowel.

**Discussion**

This study indicates that the insertion of a graft less than 1.0 cm. in length in the common bile duct interferes with normal biliary and hepatic function. This can be

detected within two weeks but becomes progressively more evident with the passage of time. Significant abnormalities consist of an elevation of alkaline phosphatase, increase in the resting pressures in the

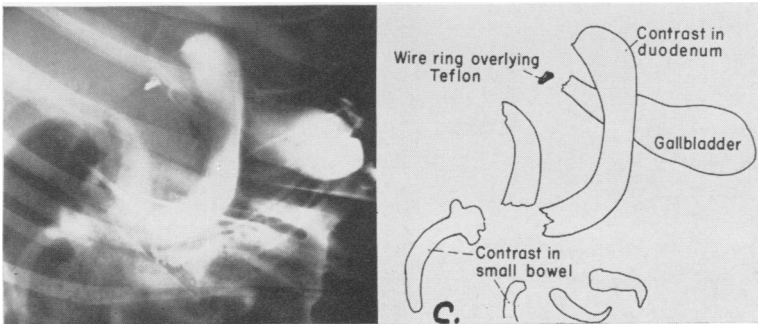


FIG. 10C. Twenty minutes after cholecystokinin the gallbladder has still failed to contract well although more contrast has passed into the small bowel.

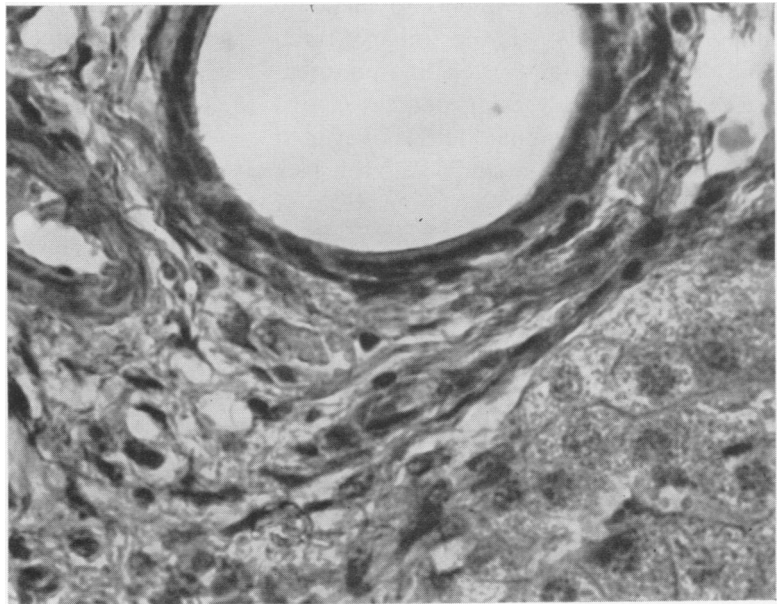
gallbladder, dilatation of the upper biliary tract, a delay in the normal emptying of the gallbladder and a delayed response to cholecystokinin. In these experiments which were deliberately selected because the grafts were widely patent, hepatic failure was not observed. However, there was evidence of mild but progressive hepatic injury histologically.

There is a striking similarity between attempts to replace segments of bile duct and segments of ureter.<sup>6, 10, 15, 18-20</sup> It is known that the ureter is an actively functioning neuromuscular structure with peristaltic activity and it is difficult to avoid the implication that there is a similar type of function in the common duct. Burnett and Shields<sup>1</sup> have reported peristalsis in the common bile duct in humans after cholecystectomy, but despite repeated efforts to demonstrate it in these experiments in both normal and grafted animals, definite peristaltic waves were never seen. Slight dilatation of the common duct with contraction of the gallbladder was noted occasionally and it appears likely that a synchronous relaxation of the wall of the

common duct at periods of increased biliary flow may be the contribution of the common duct to biliary and hepatic physiology. The insertion of an inert graft or any rigid ring such as scar tissue at the site of anastomosis even though the internal diameter of the ring is equal to that of the normal common duct may interfere with function. It appears from this study that increases in bile duct pressure above the normal contributes to a slowly progressive hepatic injury. That man may be more vulnerable to such increase in pressure than the dog or the goat is suggested by the poor results using Teflon grafts in the common duct reported by Myrin<sup>11</sup> despite the favorable results encountered experimentally. Also if as Burnett reports there is more definite peristalsis in the common duct of man, an inert prosthesis might be expected to be even more harmful than in the experimental animal.

The possibility at once presents itself of using some type of distensible prosthesis in the common duct. An inert but slightly expansile tube, particularly if responsive to the relatively low pressures encountered in

FIG. 11. Photomicrograph of liver of the goat: Section from a biopsy taken six and a half months after insertion of graft. There is considerable periductal fibrosis.



the common duct, might produce a more satisfactory graft. This problem is under further study in our laboratories at the present time.

A final word should be said about the reliability of the standard liver function tests as an indication of malfunction of the hepatobiliary tract. It has been shown by us and others that an elevation of the serum alkaline phosphatase is a much more sensitive indicator than serum bilirubin but it is far from being a reliable test. It frequently was only intermittently elevated when intraluminal pressures in the gallbladder were raised and radiographic emptying was delayed. The role of the gallbladder in preventing abnormal increases in biliary and intrahepatic pressure was pointed out years ago by Mann and Bolman<sup>9</sup> with reference to elevations of bilirubin. More recently, Halberg<sup>5</sup> has shown that the gallbladder plays a similar role with reference to elevations of serum alkaline phosphatase. After cholecystectomy there is less opportunity for distention in the extrahepatic system and an increase in intrahepatic pressure is more readily produced.

As the gallbladder was deliberately left in place in these experiments to facilitate radiographic study of the biliary tract, some of the variations in alkaline phosphatase may represent varying degrees of distensibility of the gallbladder. However, a striking feature of the study was the lack of correlation among the various tests of hepatic and biliary function. Thus in some instances, there were abnormally elevated bile duct pressures but alkaline phosphatase recorded simultaneously was in the normal range. At other times, there was an elevation of alkaline phosphatase in the presence of normal bile duct pressures. In all experiments in which radiographic emptying of the gallbladder was studied, some abnormalities were noted. Here again, however, there were inconsistencies. At times the

contrast medium was held up at the site of the anastomosis, at other times there was delayed emptying, but the contrast material eventually passed freely through the graft. In one experiment, the contrast material was held up at the sphincter of Oddi.

It is evident that more sensitive tests of abnormalities of hepatobiliary function are needed. The recent report of Hallberg<sup>5</sup> that a combination of serum alkaline phosphatase and ornithine carbamyl transferase provide information not obtained by either test alone is of particular interest and warrants further study.

### Summary

It has been shown that grafts in the common bile duct interfere with hepatobiliary function as determined by resting pressures in the gallbladder, radiographic emptying time of the gallbladder and common duct, response to cholecystokinin and elevations of serum alkaline phosphatase. This occurs without stenosis or narrowing of the lumen. Peristalsis could not be demonstrated but a slight dilatation of the common duct was noted at the time of contraction of the gallbladder. Distensibility of the common duct appears to be an essential mechanism whereby abnormal elevations of intrahepatic pressure at times of increased biliary flow are prevented.

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#### DISCUSSION

DR. HARWELL WILSON (Memphis): I had the privilege of reviewing Dr. Dunphy's manuscript prior to the meeting. It is interesting to note that in his report the results were far superior in four dogs where Teflon had been used as compared to the experiments carried out on goats.

Dr. Roger Sherman, in our Department, has been interested in the past 14 months in replacing the common bile duct with an experimental inert plastic and Dr. Sherman's results in the dog using this plastic tend to confirm the better results in the dog reported by Dr. Dunphy.

(Slide) This photograph shows the inert plastic graft which has been used to replace the common duct approximately 2½ months before. As was found in a number of Dr. Dunphy's experiments, there is marked proximal dilatation of the common and hepatic ducts in this animal, although there is no narrowing or stricture at the site of

anastomosis and the serum bilirubin and alkaline phosphatase levels are normal.

(Slide) This is a 3.0 cm. graft of an inert plastic material being used to replace the common duct. There is no narrowing at the site of anastomosis. The proximal duct is of the same size as it was before operation, there being no proximal dilatation, although this animal was operated upon 4 months prior to the time of this photograph. Again, alkaline phosphatase and serum bilirubin levels are normal and the animal appears to be perfectly healthy.

(Slide) This shows an interesting curve regarding alkaline phosphatase levels in dogs. All these animals, immediately following the replacement of the common duct with a graft, showed a marked elevation of the alkaline phosphatase level. However, in all of our experiments after approximately 4 weeks, the alkaline phosphatase level returned to normal and one animal that has been observed for about 15 months still has a