The Relation Between Carcinoma of the Gallbladder and an Anomalous Connection Between the Choledochus and the Pancreatic Duct

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An anomalous connection between the choledochus and the pancreatic duct may be associated etiologically or pathogenetically with congenital biliary dilatation and carcinoma of the dilated bile duct. During the past 10 years, a total of 14 cases of carcinoma of the gallbladder with an anomalous connection between the choledochus and the pancreatic duct were encountered. These cases were studied in reference to their clinical features and histological findings. An experimental model of pancreatic juice inflow into the gallbladder of mongrel dogs was produced and the histological changes of the mucosa of that organ was observed. The intent was to elucidate the relationship between carcinoma of the gallbladder and this anomaly. The results of this clinical and experimental study suggest that reflux and stasis of pancreatic juice in the gallbladder induce chronic cholecystitis with intestinal metaplasia. This may be important in the pathogenesis of well-differentiated carcinoma of the gallbladder.

INVESTIGATORS HAVE BEEN interested in the etiological association of the anomalous connection between the choledochus and the pancreatic duct (called "this anomaly" hereafter) with congenital biliary dilatation since Babbitt (1969)[1] and Irwin (1973)[2] described it. Recently, some Japanese authors have reported tumors that were formed in the biliary tract and not in the dilated bile duct.[3–9] Over the past 10 years, we have encountered 14 cases of carcinoma of the gallbladder with this anomaly. We analyzed the clinical features of these cases and their histological findings.

We made an experimental model of pancreatic juice inflow in the gallbladder of mongrel dogs, and observed histological changes of the mucosa, hoping to elucidate the relationship between carcinoma of the gallbladder and this anomaly.

Clinical Study and Methods

This anomaly is generally understood to be a congenital condition of the bile duct in which the common channel is abnormally lengthened, with the connection between the choledochus and the pancreatic duct located outside of the duodenal wall, free of the influence of the

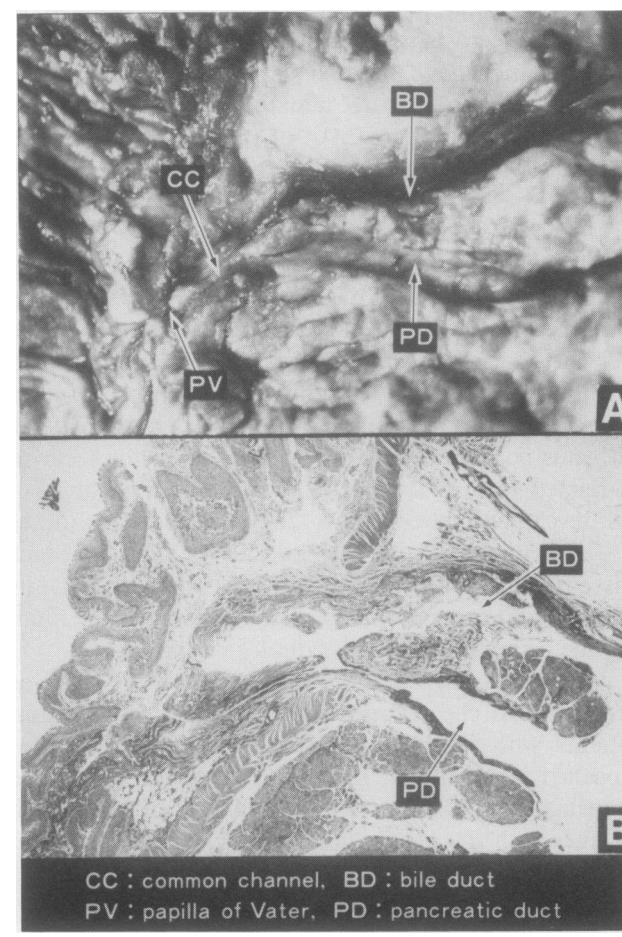

FIG. 1. Most common normal connection between the choledochus and the pancreatic duct. Pancreatobiliary common channel is located inside the tunica muscularis of the duodenum. *A*, macroscopic; *B*, loupe.

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sphincters of Boyden (Figs. 1 and 2).[10] There is a constant reflux of pancreatic juice into the bile duct. We decided to diagnose this anomaly in adults whose cases satisfy two of the following three diagnostic points: (1) the choledochus and the pancreatic duct are seen on direct cholangiograms to connect above the notch made by the sphincter of Boyden; (2) the common channel on direct cholangiograms is 1.5 cm long or more; and (3) amylase levels in the bile are 10,000 IU or more. We encountered a total of 40 cases of this anomaly during the last 10 years, from 1975 to 1984, among which there were 14 cases of carcinoma of the gallbladder. These cases were studied in reference to the clinical features, methods of treatment, prognosis, and histological findings.

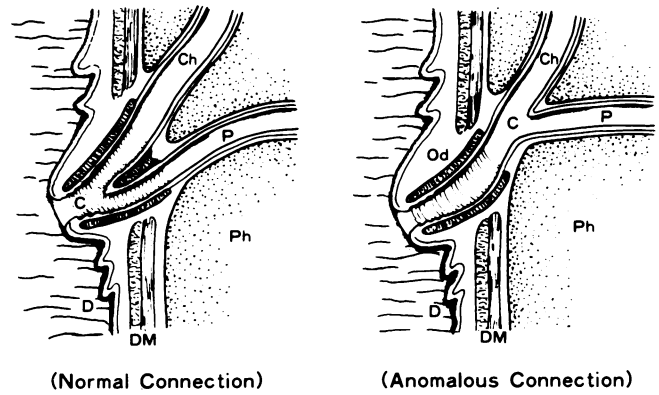


FIG. 2. Normal and anomalous connection between the choledochus and the pancreatic duct.

Results

The ages of the patients (9 women and 5 men) with carcinoma of the gallbladder associated with this anomaly ranged from 34 to 73 years, with a mean of 53.9. The patients' main complaints were abdominal pain (9 cases), jaundice (4 cases), fever (3 cases), and loss of weight (1 case). The common bile duct was dilated in three cases (Cases 2, 5, and 14), and gallstones were found in only two of the 12 cases examined for gallstones (16.7%). The biliary amylase levels, which were determined in 12 cases, were all extremely high (1530–567,000 IU).

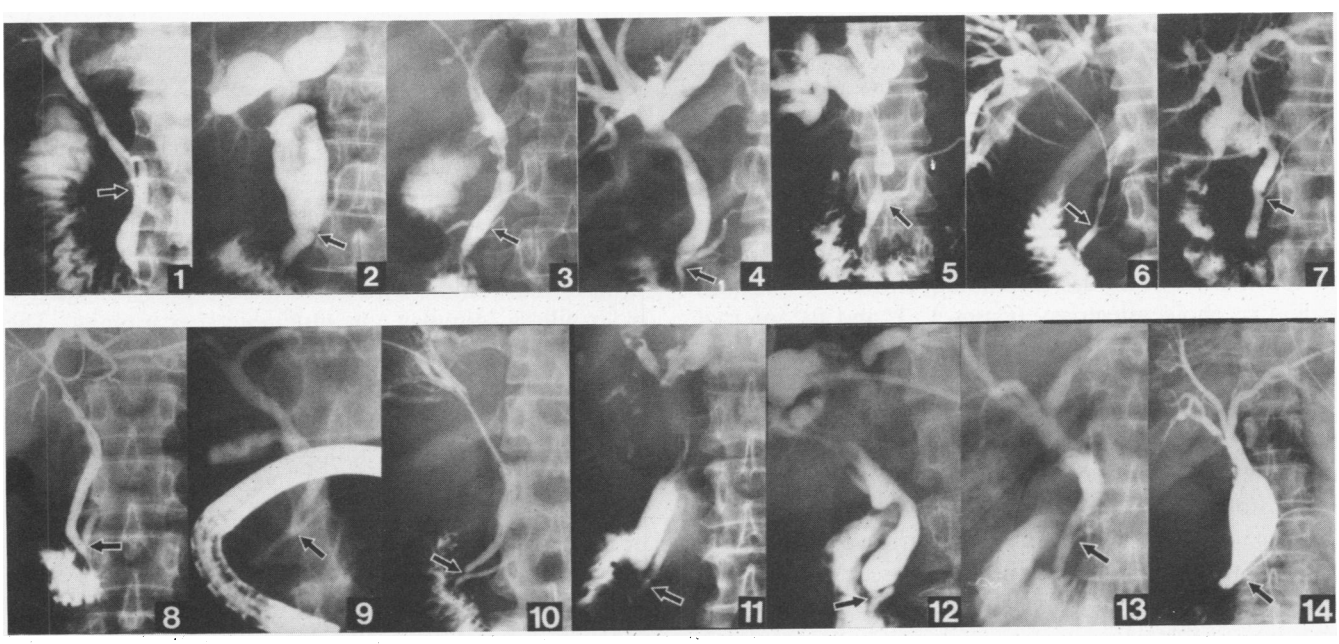


FIG. 3. Direct cholangiograms of gallbladder carcinoma with an anomalous connection (arrows) between the choledochus and the pancreatic duct. (1) Operative cholangiogram showing a dilated long common channel (Case 1). (2) Operative cholangiogram demonstrating a fusiform dilatation of the common bile duct and of the intrahepatic duct, and a dilated long common channel (Case 2). (3) Postoperative cholangiogram through a transhepatic cholangiodrainage tube demonstrates an irregular common bile duct wall and a long common channel (Case 3). (4) Percutaneous transhepatic cholangiogram showing a dilated left intrahepatic duct and a long common channel (Case 4). (5) Direct cholangiogram through percutaneous transhepatic cholangiodrainage tube: a complete obstruction of the common hepatic duct and a dilated long common channel (Case 5). (6) Direct cholangiogram through percutaneous transhepatic cholangiodrainage tube, demonstrating a complete obstruction of the common hepatic duct and of the common bile duct (Case 6). (7) Postoperative cholangiogram through transhepatic cholangiodrainage tube showing a long common channel (Case 7). (8) Postoperative cholangiogram through transhepatic cholangiodrainage tube: a long common channel and a dilated pancreatic duct (Case 8). (9) Direct cholangiogram through endoscope showing a long common channel (Case 9). (10) Postoperative cholangiogram through transhepatic cholangiodrainage tube: an incomplete obstruction of the common hepatic duct and the common bile duct (Case 10). (11) Direct cholangiogram through percutaneous transhepatic cholangiodrainage tube showing an incomplete obstruction of the hepatic duct (Case 11). (12) Direct cholangiogram through percutaneous transhepatic cholangiodrainage tube showing a compression of the hepatic duct (Case 12). (13) Operative cholangiogram demonstrating a long common channel (Case 13). (14) Operative cholangiogram showing a long common channel and a fusiform dilatation of the common bile duct (Case 14).

TABLE 1. *Clinical Features of Gallbladder Carcinoma with this Anomaly*

Case	Age (years)	Sex	Chief Complaint	Bile Duct Dilatation	Gall-stone	Length of Common Channel (cm)	Amylase Level in Bile (IU)	Macroscopic Classification of the Tumor	Treatment	Prognosis after Surgery (Months)
1	45	M	Abdominal pain, fever	−	+	5.3	?	Diffuse	PC	DWD (14)
2	60	F	Abdominal pain	+	−	2.8	98,000	Papillary	CC CJ	AFD (78)
3	59	F	Abdominal pain	−	−	3.4	253,000	Diffuse	PC	DWD (15)
4	46	F	Abdominal pain Jaundice, fever	−	−	2.0	85,500	Papillary	CC	DWD (22)
5	52	F	Jaundice, loss of weight	+	?	5.0	32,000	Nodular	PTCD E	DWD (7)
6	47	M	Abdominal pain, jaundice	−	−	3.0	567,000	Diffuse	PTCD	DWD (5)
7	50	F	Abdominal pain	−	−	4.5	510,000	Nodular	CC CJ	DWD (19)
8	62	M	Abdominal pain	−	+	1.5	90,000	Diffuse	PTCD E	DWD (2)
9	34	M	Fever	−	−	2.3	300,000	Diffuse	PC	DWD (5)
10	50	F	Jaundice	−	−	1.6	273,000	Diffuse	PTCD E	DWD (6)
11	66	F	Jaundice	−	?	1.5	14,000	?	PTCD	DWD (2)
12	73	M	Fever, general fatigue	−	−	1.5	?	Diffuse	Longmire	DWD (2)
13	38	F	Abdominal pain	−	−	2.4	1,530	Nodular	CC, CJ PCo	AFD (4)
14	72	F	Abdominal pain	+	−	3.2	45,600	Papillary	CC	AFD (1)

Key: PC = palliative cholecystectomy; CC = curative cholecystectomy; CJ = choledochojejunostomy; PTCD = percutaneous transhepatic cholangiodrainage; PCo = partial colectomy; E = exploration; AFD = alive, free of disease; and DWD = dead with disease.

The common channel measured on direct cholangiograms was from 1.5 to 5.3 cm long (Fig. 3). Carcinomas of the gallbladder were macroscopically classified as diffuse in seven cases, nodular in three, and papillary in three. In cases of diffuse carcinoma, treatment was with palliative cholecystectomy (Cases 1, 3, and 9), internal biliary drainage with a percutaneous transhepatic cholangiodrainage (PTCD) tube (Cases 6, 8, and 10), or a Longmire-Sandford's operation (Case 12). Two of the three patients with nodular carcinomas (Cases 7 and 13) underwent a curative cholecystectomy with choledochojejunostomy, and the other (Case 5), internal biliary drainage with a polyethylene catheter. Two of the three patients with papillary carcinomas (Cases 2, 4, and 14) received curative cholecystectomy with hepatic wedge resection (Table 1).

Prognostic study showed that nine patients died within 15 months after surgery, and that three patients are alive now. Only one of these three patients is alive for long-term, 6 years and 6 months after her operation. She is free of disease (Table 1).

Histological findings from the 11 cases for which they were available are shown in Table 2. Of the 11 tumors examined, five were diagnosed as well-differentiated adenocarcinomas and four were poorly-differentiated ones. Cases 6, 11, and 12 were categorized as adenocarcinoma by cytological examination of the bile, and Cases 8 and 13 as adenosquamous cell carcinoma (Fig. 4). All tumors were clearly invasive carcinomas. The five well-differentiated adenocarcinomas had the characteristics of intestinal tumors with goblet cells (Fig. 5), suggestive of papillary, tubular, or mucinous carcinomas. The presence of argyrophil cells among the neoplastic cells was disclosed by a Grimelius stain in four cases (Fig. 6). Of the cases of poorly-differentiated adenocarcinomas, argyrophil cells were found within the cancerous areas in only Case 5. In the noncancerous areas of all gallbladders, chronic cholecystitis with epithelial hyperplasia or atrophy was found. In Cases 1, 4, 7, 9, and 14, goblet cells and pseudo-Brunner glands were detected. Argyrophil cells and Paneth cells (Fig. 7) were also detected in the mucosa of five gallbladders. Papillary hyperplasia with intestinal metaplasia was especially marked in Case 14 (Fig. 8).

Experimental Study

Materials and Methods

We performed the following experiment in 15 mongrel dogs: the caudal side of the right pancreas was anastomosed with the gallbladder (Fig. 9) to make pure pancreatic juice flow into the gallbladder. These dogs were

TABLE 2. *Histological Findings of the Gallbladder Carcinoma with this Anomaly*

Case	Histological Diagnosis	Degree of Chronic Cholecystitis	Metaplastic Lesions								
			Noncancerous Area					Cancerous Area			
			Pseudo-Brunner Gland	Goblet Cell	Argyrophil Cell	Paneth Cell	Epidermoid Cell	Goblet Cell	Argyrophil Cell	Paneth Cell	Epidermoid Cell
1	Tubular adenocarcinoma	++	++	+	−	−	−	+	−	−	−
2	Poorly differentiated adenocarcinoma	++	−	−	−	−	−	−	−	−	−
3	Tubular adenocarcinoma	++	−	−	−	−	−	+	+	−	−
4	Tubular adenocarcinoma	++	++	+	−	−	−	+	+	−	+
5	Poorly differentiated adenocarcinoma			Not examined				−	++	−	−
6	Well-differentiated adenocarcinoma (cytologic diagnosis)						Not examined				
7	Papillary adenocarcinoma	+	+	+	+	+	−	++	+	−	−
8	Adenosquamous cell carcinoma			Not examined				−	−	−	++
9	Poorly differentiated adenocarcinoma	++	−	++	++	+	−	−	−	−	−
10	Poorly differentiated adenocarcinoma	+	−	−	−	−	−	−	−	−	−
11	Adenocarcinoma (cytologic diagnosis)						Not examined				
12	Adenocarcinoma (cytologic diagnosis)						Not examined				
13	Adenosquamous cell carcinoma	++	−	−	−	−	−	−	−	−	++
14	Papillary adenocarcinoma	++	+	++	++	+	−	++	−	−	−

++ = marked; + = moderate; and − = none.

killed 3, 6, or 9 months after the anastomosis. Changes with time of the mucosa of the gallbladder were investigated histologically (Table 3).

Results

There were no histological differences among the mucosa of the gallbladder depending on timing. However, we found marked lymphoid cell infiltration in 11 dogs, and observed follicular formation with germinal centers among four of them (Fig. 10). There was hyperplasia of the mucosal epithelium in 13 dogs (Fig. 11), increased mucin synthesis in 12, and metaplasia in seven. These mucosal epithelial cells assumed a tall columnar shape, with the nucleus located at the base and clear cytoplasm. Particularly in six dogs (Nos. 1, 4, 5, 8, 11, and 13), goblet cells were numerous (Fig. 12). To our regret, however, we have so far been unsuccessful in producing experimental carcinoma of the gallbladder. In the bacterial study of the gallbladder, we detected a few Gram-positive cocci in only one dog, No. 11; in the other dogs, cultures were negative.

Discussion

The abnormal connection between the choledochus and the pancreatic duct is a rare malformation of the pancreaticobiliary ductal system. In 1969, Babbitt[1] disclosed that this anomaly was found in patients with choledochal cysts. Since then, investigators have examined the association of this anomaly with congenital biliary dilatation in more cases.[6,11,12] However, this anomaly was rarely found in patients without choledochal cysts.[3] The anomaly is a condition that is present when the common channel is abnormally long and when the connection between the choledochus and the pancreatic duct is outside of the duodenal wall, beyond the influence of the sphincters of Boyden.[10] It is, however, impossible to check the sphincter mechanism of this connection in all clinical cases.

Diagnosis of this anomaly is usually made based on the length of the common channel and the type of connection as seen on a direct cholangiogram.[13] There are natural variations in the length of the common channel measured in this way, depending on the age

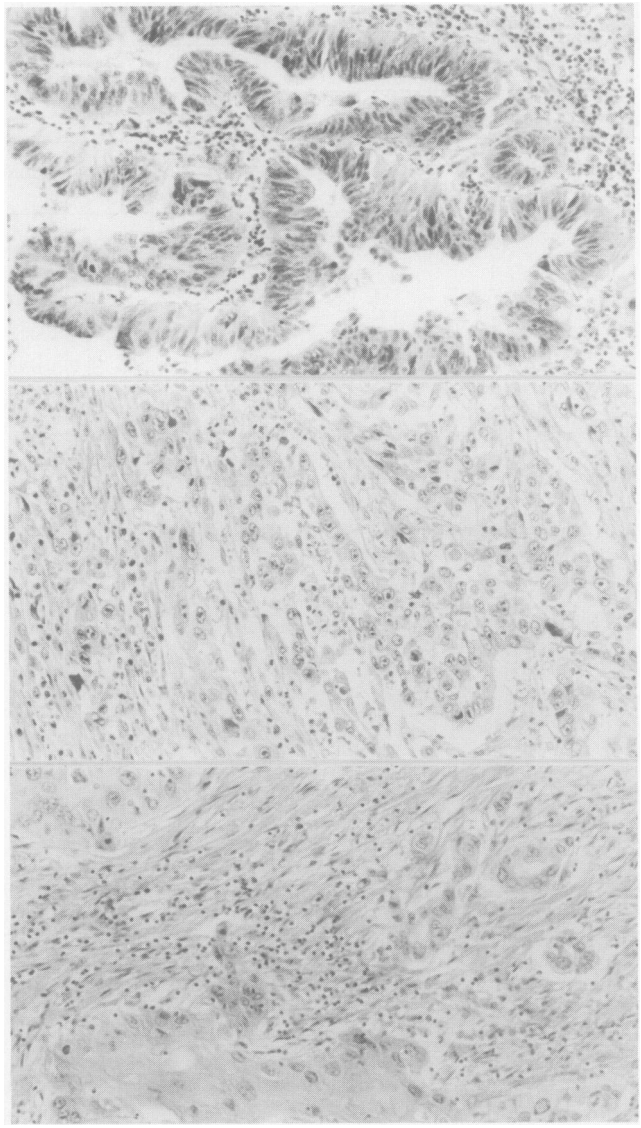


FIG. 4. *Top,* Tubular adenocarcinoma, ×360 (Case 4). *Middle,* poorly differentiated adenocarcinoma, ×180 (Case 9). *Bottom,* Adenosquamous cell carcinoma. Squamous components and glandular components are seen, ×180.

and the physique of the patient. Measurements made *via* cholangiograms involve unavoidable inaccuracy because of variation in the angle of the penetration of the channel through the duodenal wall. Jones found that sphincters varied in length from 6 to 30 mm in some cases.[14] Keeping these facts in mind, we took into consideration both morphological and functional aspects in diagnosing this anomaly. In practice, we observed the notch of the bile duct and the length of the common channel which were seen on direct cholangiograms, and assayed the amylase in the bile to clarify the functioning of the sphincter. In this study, we compared the clinical features of our 14 cases with those in cases reported in

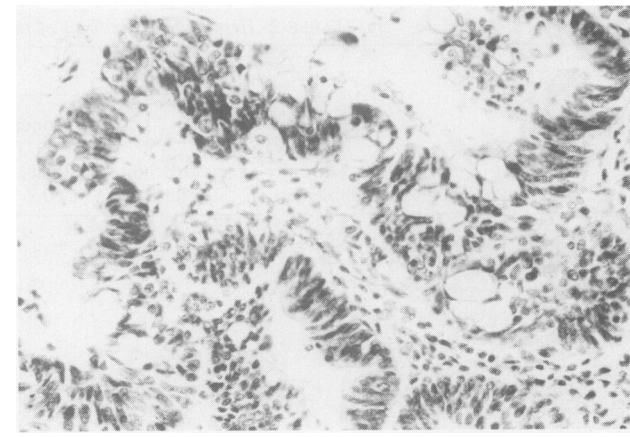


FIG. 5. Many malignant goblet cells (Case 4), ×360.

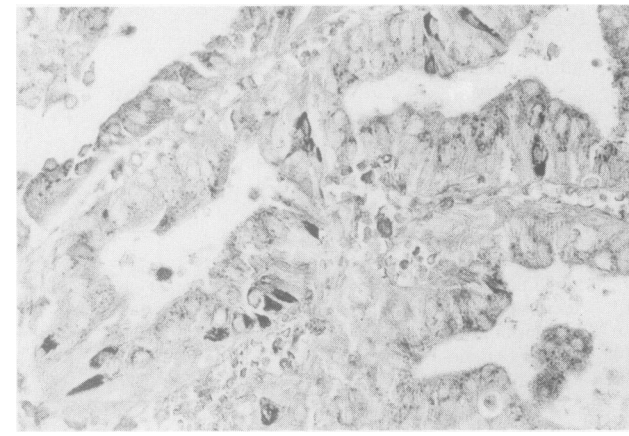


FIG. 6. Tubular adenocarcinoma (Case 4). Scattered argyrophil cells are recognized, ×360.

Japan of carcinoma of the gallbladder, in which incidence of this anomaly was not investigated.[15] Though there were no notable differences between the two groups with

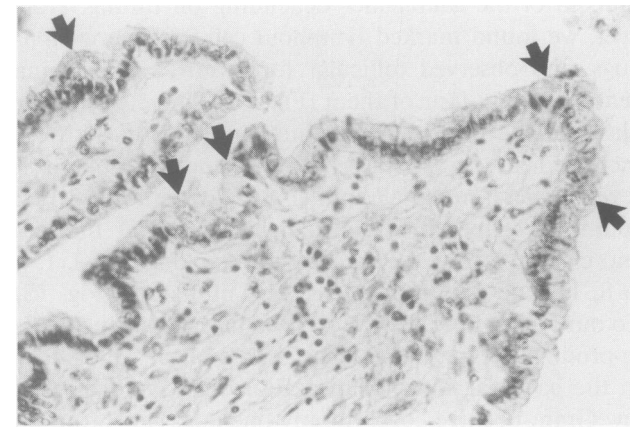
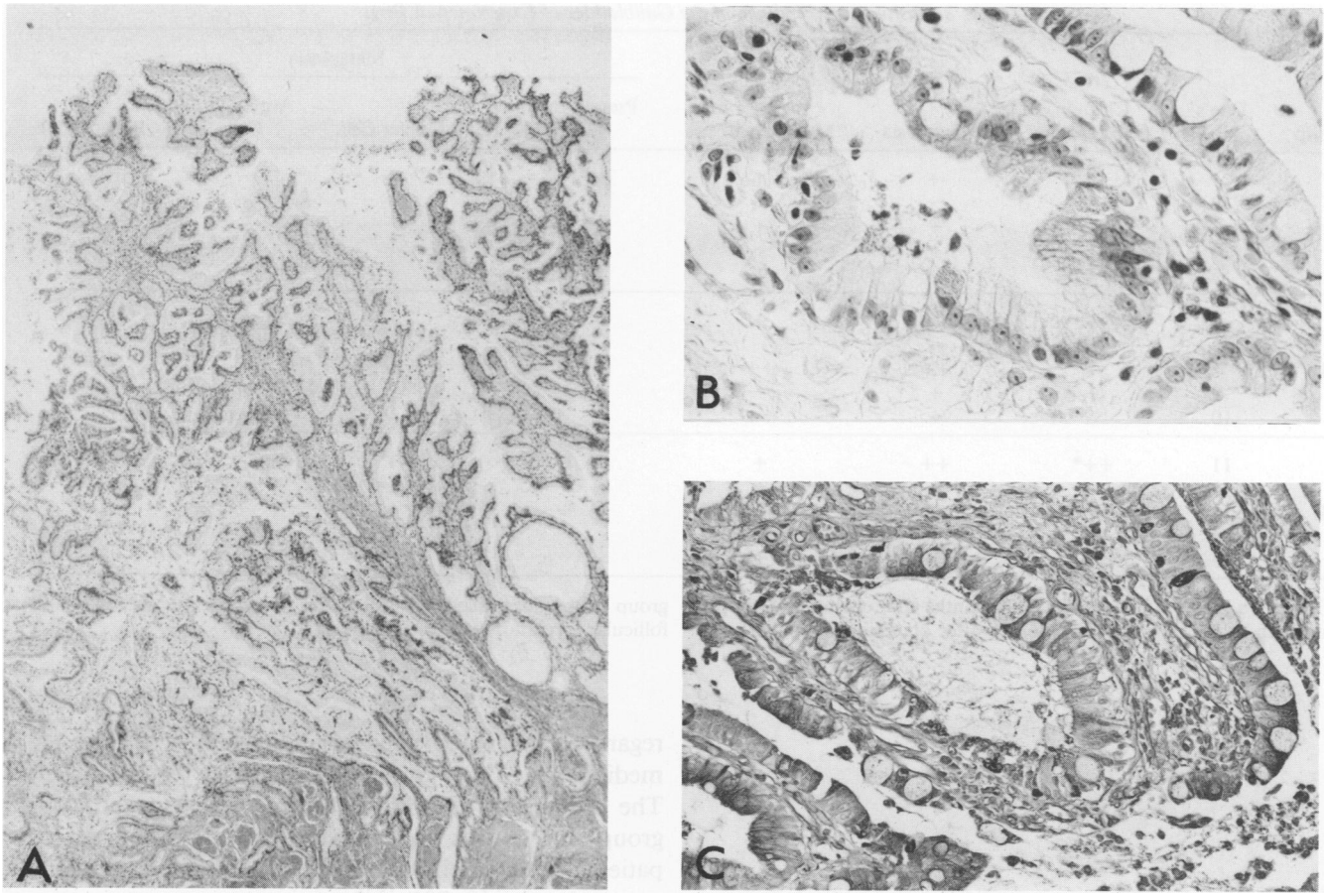


FIG. 7. Metaplastic epithelium with Paneth cells (arrows) in the noncancerous area, ×360 (Case 7).



FIGS. 8A–C. Papillary hyperplasia with intestinal metaplasia of mucosal epithelium of the gallbladder in the noncancerous area (Case 14). *A*, Papillary hyperplasia, ×360; *B*, Goblet cells and Paneth cells, ×360; *C*, Argyrophil cells, ×180.

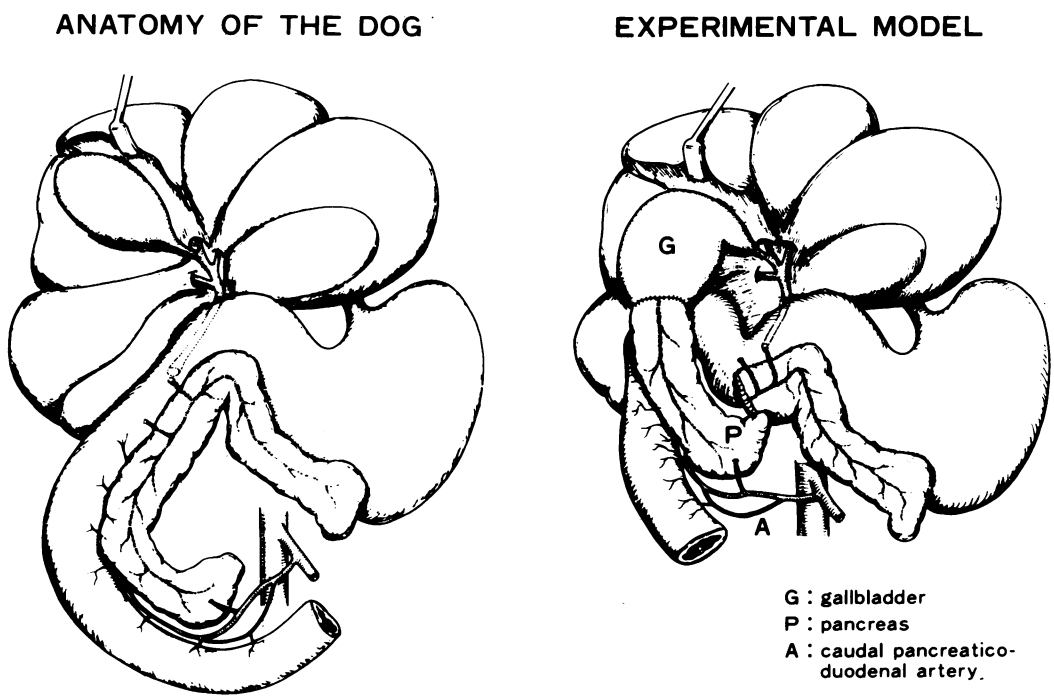


FIG. 9. Scheme of experimental study.

TABLE 3. *Histological Findings of the Gallbladder of Experimental Dogs*

Group	Dog's No.	Chronic Cholecystitis	Hyperplasia	Increase in Mucin Synthesis	Metaplasia			
					Pseudo-Brunner Gland	Goblet Cell	Argyrophil Cell	Paneth Cell
I	1	++*	+	+	+	+	−	−
	2	−	−	−	−	−	−	−
	3	+	+	+	−	−	−	−
	4	+	+	+	+	+	−	−
	5	++*	++	+	+	+	−	−
II	6	+	+	+	−	−	−	−
	7	−	−	−	−	−	−	−
	8	+	++	++	−	+	−	−
	9	+	+	+	−	−	−	−
	10	+	+	++	−	+	−	−
III	11	++*	++	+	+	+	−	−
	12	+	+	−	−	−	−	−
	13	+*	++	+	+	+	−	−
	14	+	+	+	−	−	−	−
	15	+	+	+	−	−	−	−

Group I: a group of the dogs killed 3 months after operation. Group II: a group of the dogs killed 6 months after operation. Group III: a group of the dogs killed 9 months after operation. *Observed lymph follicular formation with germinal centers.

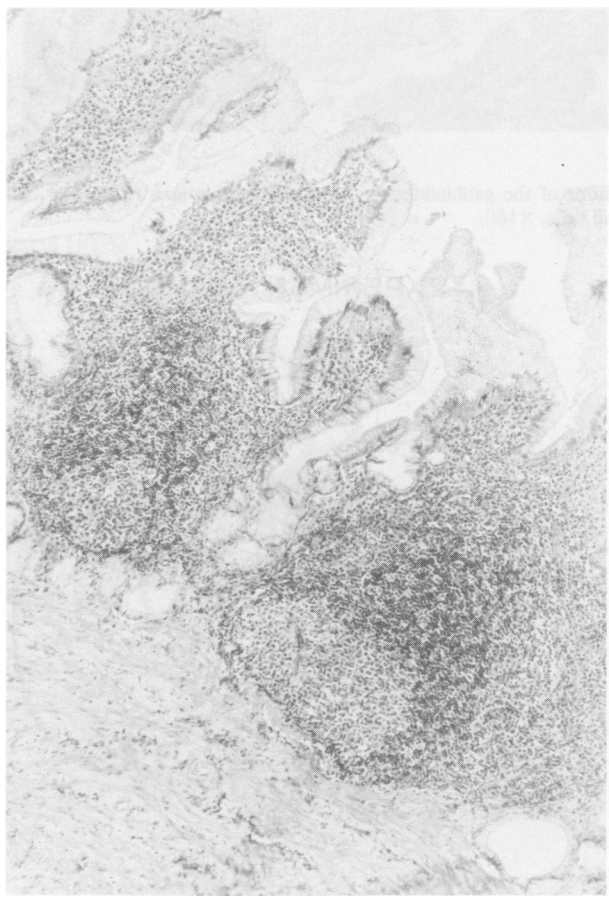


FIG. 10. Lymph follicular formation with germinal centers observed in the lamina propria mucosa of dog 5, ×90.

regard to sex or chief complaints of the patients, the median age of our group was about 10 years younger. The proportion of complication with gallstones in our group (16.7%) was much lower than that proportion in patients with carcinoma of the gallbladder, generally reported to be 60–70%.[15,16]

The high frequency of gallstones in patients with carcinoma of the gallbladder has provided the basis for a widely-accepted hypothesis that mechanical irritation by gallstones,[17] along with chronic inflammation, gives rise to regeneration of the mucosa and mucosal metaplasia, creating an environment suitable for the oncogenesis of differentiated carcinoma of the gallbladder.[18–20] To examine this, we checked to see if our nine cases had metaplasia or chronic inflammation involving cancerous or noncancerous areas. In the cancerous areas, malignant goblet cells were found in all of the differentiated adenocarcinomas (5 cases), and argyrophil cells in four cases. In the noncancerous areas, goblet cells and pseudo-Brunner glands were detected in five cases. From these observations, we inferred that mucosal metaplasia developed as a result of chronic cholecystitis, providing an environment suitable for carcinogenesis.

The atypical epithelium of the gallbladder with cholelithiasis has been the subject of much study.[18–21] Thomas[16] and Arnaud[22] advocated prophylactic cholecystectomy to protect the patient against cancerous changes of the gallbladder. However, the incidence of cholelithiasis was fairly low in our cases with this anomaly. We think that in cases of carcinoma of the gallbladder with this anomaly, it will be found that

cholelithiasis is not often related to the carcinoma. That is, there is probably some other factor that causes inflammation of the gallbladder.

In many cases of carcinoma of the gallbladder complicated with congenital biliary dilatation or this anomaly, cancerous lesions appear in the dilated bile duct or in the gallbladder, where bile stasis occurs. Järvi and Laurén[20] and Sonobe et al.[23] demonstrated that in cases with heterotopic pancreatic tissue in the gallbladder, the mucosa of the organ was affected by the chronic inflammation. Furthermore, free flow of pancreatic juice in the common bile duct produced recurrent bouts of cholangitis.[24] In most of our experimental dogs, we produced cholecystitis with metaplasia, and hyperplasia of the mucosa of the gallbladder, by making possible the free flow of pancreatic juice into the gallbladder. The mucosa of the gallbladder was somewhat influenced by the pancreatic juice. These clinical and experimental observations suggest that reflux and stasis of pancreatic juice in the gallbladder may induce chronic cholecystitis, and then give rise to mucosal metaplasia. This metaplasia in the gallbladder may be a precancerous condition

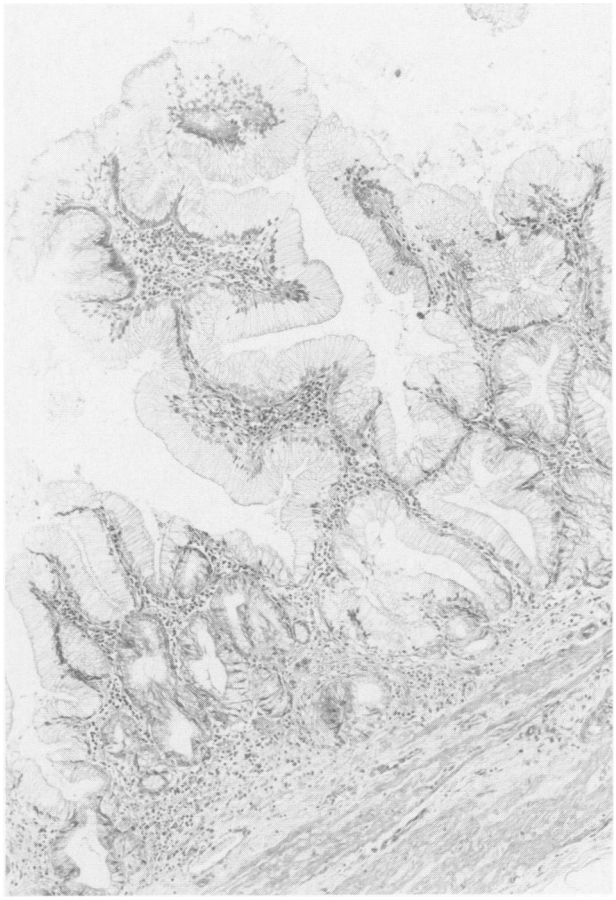


FIG. 11. Hyperplasia of the mucosal epithelium of dog 5, ×90.

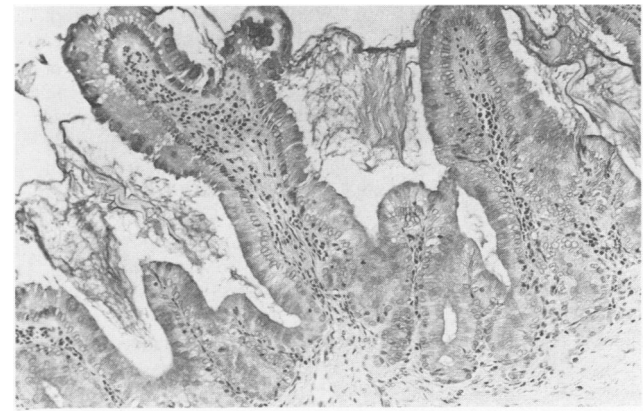


FIG. 12. Goblet cells are detected in dog 10, × 180.

eventually leading to differentiated carcinoma, just as intestinal metaplasia of the gastric mucosa is regarded as a preliminary to gastric cancer by many authors.[25,26]

We think that it is important to remove the place that causes bile stasis and to stop backflow of pancreatic juice into the bile duct in managing patients with this anomaly. In other words, prophylactic cholecystectomy and reconstruction of the biliary tract, such as hepaticojejunostomy, are both necessary.

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