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## Pancreaticogastrostomy: Effect of Partial Gastrectomy on the Pancreatic Stump in Rabbits

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## Abstract

To assess the influence of digestive juice on the pancreatic stump when pancreaticogastrostomy was performed after pancreatoduodenectomy, the pancreatic stump was anastomosed to the intact stomach (group I), the stomach after partial gastrectomy (group II), or the jejunum (group III) in rabbits, and the nature of the digestive juice at the anastomotic site as well as the histologic changes of the pancreatic tissue were investigated. The digestive juice was highly acidic in group I, slightly acidic in group II, and almost neutral in group III. Histological examination of the pancreatic stump revealed extensive coagulative necrosis and delayed replacement with granulation tissue in group I, while there was less prominent liquefactive necrosis and early replacement with granulation tissue in groups II and III. Intraperitoneal abscess formation around the anastomotic site and atrophic fibrosis of the pancreas (similar to the changes after pancreatic duct ligation) occurred in 27.8% and 46.2% of group I rabbits, respectively, but no such changes were detected in groups II and III (both  $P < 0.05$ ). These results indicate that the highly acidic gastric juice had a widespread corrosive effect on the anastomosed pancreatic tissue, and that partial gastrectomy may be necessary to prevent anastomotic leakage and pancreatic duct obstruction after pancreaticogastrostomy.

**KEYWORDS:** pancreatoduodenectomy, pancreaticogastrostomy, pancreaticojejunostomy, gastrectomy

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## Pancreaticogastrostomy: Effect of Partial Gastrectomy on the Pancreatic Stump in Rabbits

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To assess the influence of digestive juice on the pancreatic stump when pancreaticogastrostomy was performed after pancreatoduodenectomy, the pancreatic stump was anastomosed to the intact stomach (group I), the stomach after partial gastrectomy (group II), or the jejunum (group III) in rabbits, and the nature of the digestive juice at the anastomotic site as well as the histologic changes of the pancreatic tissue were investigated. The digestive juice was highly acidic in group I, slightly acidic in group II, and almost neutral in group III. Histological examination of the pancreatic stump revealed extensive coagulative necrosis and delayed replacement with granulation tissue in group I, while there was less prominent liquefactive necrosis and early replacement with granulation tissue in groups II and III. Intraperitoneal abscess formation around the anastomotic site and atrophic fibrosis of the pancreas (similar to the changes after pancreatic duct ligation) occurred in 27.8% and 46.2% of group I rabbits, respectively, but no such changes were detected in groups II and III (both  $P < 0.05$ ). These results indicate that the highly acidic gastric juice had a widespread corrosive effect on the anastomosed pancreatic tissue, and that partial gastrectomy may be necessary to prevent anastomotic leakage and pancreatic duct obstruction after pancreaticogastrostomy.

**Key words:** pancreatoduodenectomy, pancreaticogastrostomy, pancreaticojejunostomy, gastrectomy

**F**or anastomosis of the remnant pancreas to the gastrointestinal tract after pancreatoduodenectomy (PD), pancreaticogastrostomy with partial gastrectomy

has increasingly been performed recently, although pancreaticojejunostomy is also common (1). The first clinical application of pancreaticogastrostomy was in 1946, with the pancreatic stump being inserted into the remnant stomach according to the method of Waugh and Clagett (2). In 1975, Mackie *et al.* (3) reported that pancreaticogastrostomy is safer than pancreaticojejunostomy. In 1988, Icard and Dubois (4) analyzed 134 cases of pancreaticogastrostomy reported after the experience by Waugh *et al.*; there were 6 operative deaths (4.5%) and 1 anastomotic leakage (0.7%), and they concluded that pancreaticogastrostomy was a safe operative procedure. In all of their patients, the pancreatic stump was inserted into the remnant stomach after partial gastrectomy. On the other hand, Traverso and Longmire (5, 6) reported the use of pylorus-preserving pancreatoduodenectomy (PPPD) to prevent the small stomach syndrome in 1978, while in 1985 Flautner *et al.* (7) performed PPPD and pancreaticogastrostomy (*i. e.*, pancreaticogastrostomy without partial gastrectomy) in 25 patients with chronic pancreatitis and reported no anastomotic leakage. However, Takakura *et al.* (8) reported anastomotic leakage related to pancreaticogastrostomy without partial gastrectomy in 5/11 patients (45.5%) treated for pancreaticobiliary cancer. In addition, the safety of pancreaticogastrostomy after PPPD in patients with normal pancreatic tissue has not yet been established (9).

It has been suggested that the presence of digestive juice around the anastomosis may have a strong influence on the pancreatic stump, especially when the stump is inserted into an intact stomach containing highly acidic gastric juice. In the present study, we inserted the pancreatic stump into the stomach (with or without partial gastrectomy) or the jejunum in rabbits, and investigated the nature of the digestive juice at the anastomotic site and

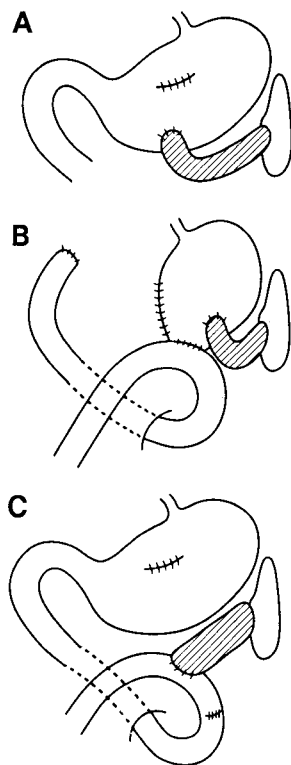
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the histologic changes of the pancreatic body and tail over time after anastomosis.

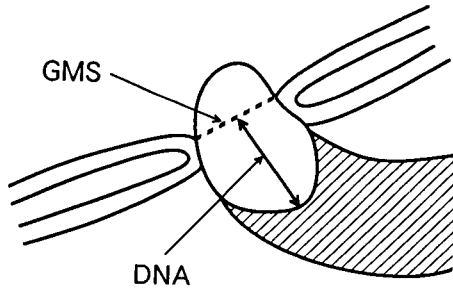
## Materials and Methods

**Animals.** Mongrel Japanese rabbits weighing 3–4 kg were purchased from Japan Ram (Kannabe, Japan) and housed in an air-conditioned (24 °C) room with a 12 h light/dark cycle for 1 week for acclimatization. The rabbits were allowed free access to water and a commercial balanced diet (Labo R Stock<sup>®</sup>, Nihon Nosan, Yokohama, Japan). They were treated in accordance with the Laboratory Practice Guidelines of Okayama University Medical School.



**Fig. 1** Anastomosis of the pancreatic stump to the stomach or the jejunum. (A) Group I: pancreaticogastrostomy with insertion of the pancreatic stump into the posterior wall of the intact stomach. (B) Group II: pancreaticogastrostomy with insertion of the pancreatic stump into the posterior wall of the partially resected stomach. (C) Group III: pancreaticojejunostomy with insertion of the pancreatic stump into the jejunum. The pancreatic body and tail are represented by the hatched area.

**Operation.** After a 24 h fast, all the rabbits were subjected to laparotomy under pentobarbital anesthesia. The greater omentum was resected around the pyloric region, and the pancreatic head and body were exposed. The pancreas was freed at the junction of the head and body, while avoiding damage to the bile duct, portal vein, and duodenal vessels, and the organ was ligated and cut at this site. Then the caudal pancreatic stump was inserted into the stomach or the jejunum as shown in Fig. 1. Pancreaticogastrostomy was performed with the intact stomach in group I, pancreaticogastrostomy with the remnant stomach was done after distal gastrectomy in group II, and pancreaticojejunostomy was done in group III. To cleanse the stomach, the anterior wall was incised, and the lumen was emptied and irrigated with saline in all 3 groups. In group III, an incision about 1 cm long was made in the jejunal wall approximately 20 cm distal to the pyloric ring for pancreaticojejunostomy. Next, a small forceps was inserted through the incised wall of the stomach or the jejunum, and a full-thickness incision was made in the posterior wall of the stomach or the jejunal wall on the side opposite the mesentery. This incision was smaller than the cut surface of the pancreatic stump. Then the pancreatic stump was inserted 5 mm into the gastrointestinal lumen using the forceps and taking care not to place tension on the remnant pancreatic tissue, after which the full thickness of the gastric or jejunal wall was anastomosed to the lateral pancreatic parenchyma using 4 interrupted sutures of 6-0 monofilament polyglyconate (Maxon). Finally, the suture ligating the pancreatic stump was removed and the incision in the wall of the stomach or the jejunum was closed. For partial gastrectomy, the stomach was cut along a line drawn between the mid-points of the greater and lesser curvatures using an Auto Suture (Multifire GIA 80 Titanium<sup>®</sup>, United States Surgical, Norwalk, CT), and the pylorus was ligated. Reconstruction of the gastrointestinal tract was performed according to the Billroth II method. As a positive control, a pancreatic duct obstruction model was created by ligating the junction of the pancreatic head and body with 3-0 nylon. All rabbits received about 250 ml of lactated Ringer's solution intravenously during and just after surgery. Postoperatively, all rabbits were fasted and given saline (60 ml/day) and 10 % glucose (60 ml/day) by subcutaneous injection. Cefotaxime sodium (Cefotax<sup>®</sup>; Roussel Uclaf, Paris, France) at 0.05 mg/kg/day and gabexate mesilate (FOY<sup>®</sup>; Ono Pharmaceutical, Osaka, Japan) at 3 mg/kg/day were also administered up to 7



**Fig. 2** Depth of necrotic area (DNA) in the remnant pancreas along the long axis measured using the gastrointestinal mucosal surface (GMS) as the baseline. The pancreatic body and tail are represented by the hatched area.

days postoperatively to prevent postoperative infection and acute pancreatitis.

**Repeat laparotomy.** Laparotomy was again performed on postoperative day (POD) 3, 7, and 14 in all three groups. After observation of the peritoneal cavity and the area around the anastomotic site, the stomach or the jejunum was ligated orad and aborad to the anastomosis and then removed en bloc with the pancreatic body and tail as well as the spleen. Then the gastric or jejunal wall was incised, the anastomotic site was examined, and the digestive juice around the site was collected and immediately stored at 4°C. Rabbits which died were necropsied and the status of the peritoneal cavity and the anastomotic site was evaluated. The rabbits with pancreatic duct ligation underwent laparotomy on POD 7, and the pancreatic body and tail were removed. Rabbits which died of debility due to diarrhea were excluded from the analysis.

**Measurements.** Digestive juice samples were centrifuged at 3,000 rpm for 30 min at 4°C, and the pH of the supernatant was determined using a 44 pH meter (Beckman Instruments, Fullerton, CA, USA). In addition, amylase activity was measured in the supernatant using an alpha-amylase EPS (Boehringer Mannheim, Mannheim, Germany) and a Hitachi Automatic Analyzer 7070 (Hitachi, Tokyo, Japan). The amylase activity is expressed as a logarithmic value ( $p$ [AMY]).

**Histologic assessment.** The pancreatic stump was examined macroscopically and fixed in 10% formalin for 3 days. Then sections containing the anastomotic site and the long axis of the pancreatic body and tail were

prepared and stained with hematoxylin and eosin (H&E) for histological evaluation of the pancreatic stump. To assess digestive juice invasion into the pancreatic stump, the depth of necrosis along the long axis of the pancreatic body and tail was measured from the gastric or jejunal mucosal surface (Fig. 2). In the rabbits with pancreatic duct ligation, the pancreatic tissue distal to the site of ligation was evaluated after H&E staining.

**Statistical analysis.** All data are expressed as the mean  $\pm$  SD. Inter-group differences were first compared using one-way analysis of variance, and any significant differences thus found were further tested using Scheffe's F-test. The incidence of intraperitoneal abscess formation and pancreatic fibrosis were compared using the chi-square test. Differences were judged to be statistically significant at  $P < 0.05$ .

## Results

**Intraperitoneal changes.** None of the 18 rabbits in group II (6 on POD 3, 6 on POD 7, and 6 on POD 14) or the 20 rabbits in group III (6 on POD 3, 8 on POD 7, and 6 on POD 14) showed anastomotic complications. In group I (6 on POD 3, 10 on POD 7, and 6 on POD 14), however, 3 of the 10 rabbits sacrificed on POD 7 had intraperitoneal abscess formation around the anastomotic site and necrosis of the pancreatic tail. Abscesses were also observed in 2 rabbits from group I which died on POD 8 and 11, respectively. In total, 5 of the 18 rabbits (27.8%) from group I sacrificed and necropsied on or after POD 7 had abscesses, an incidence significantly higher ( $P < 0.05$ ) than in either group II (0/12) or group III (0/14). No abscesses were observed in the 10 rabbits from the pancreatic duct ligation group.

**Digestive juice at the anastomotic site.** The pH of the digestive juice was significantly lower ( $P < 0.001$ ) in group I than in either group II or group III on POD 3, 7, and 14 (Table 1). It was also significantly lower in group II than in group III on POD 7 and 14 ( $P < 0.01$  and  $P < 0.05$ , respectively). Thus, the digestive juice was highly acidic in group I, slightly acidic in group II, and almost neutral in group III. The  $p$ [AMY] was significantly lower ( $P < 0.001$ ) in group I than in either group II or group III on POD 3, 7, and 14. It was also significantly lower ( $P < 0.01$ ) in group II than in group III on POD 7 and 14. Thus, amylase activity was relatively well maintained in groups II and III,

Table 1 pH and  $p$ [AMY]<sup>a</sup> of digestive juice collected around the anastomotic site

	pH			$p$ [AMY]		
	POD 3	POD 7	POD 14	POD 3	POD 7	POD 14
Group I	1.02 ± 0.19 (6)	0.96 ± 0.28 (10)	1.02 ± 0.41 (6)	1.69 ± 0.41 (6)	1.12 ± 0.20 (10)	1.21 ± 0.38 (6)
Group II	6.87 ± 0.26* (6)	4.92 ± 1.73* (6)	5.22 ± 2.13* (6)	5.24 ± 0.77* (6)	3.73 ± 1.20* (6)	3.88 ± 1.03* (6)
Group III	6.82 ± 0.60* (6)	7.46 ± 0.47*** (8)	7.64 ± 1.02*** (6)	4.88 ± 0.26* (6)	5.31 ± 0.27*** (8)	5.29 ± 0.31*** (6)

a :  $p$ [AMY] represents the log value of amylase activity in the digestive juice; POD: postoperative day.

\*:  $P < 0.001$  vs. group I; \*\*:  $P < 0.01$  vs. group II; \*\*\*:  $P < 0.05$  vs. group II

( ): number of rabbits

but was almost entirely lost in group I at all postoperative assessments.

**Macroscopic features of the pancreatic stump.** In group I, the pancreatic stump was abraded and depressed, with narrowing of the stump seen in all rabbits on POD 7 (Fig. 3A). The cut surface of the stump was completely covered by gastric mucosa on POD 14. In contrast, the inserted pancreatic stump was not covered by gastric mucosa or was still protruding on POD 7 in the majority of rabbits from groups II and III (Figs. 3B and 3C, respectively). In group III, the inserted stump still protruded even on POD 14 in some rabbits. No ulceration was noted around the anastomotic site in any of the rabbits.

**Histologic features of the pancreatic stump.** In group I, histologic examination on POD 3 revealed abrasion of the pancreatic stump to the serosal muscular layer and coagulative necrosis, with the pancreatic cells being discolored due to nuclear necrosis caused by exposure to digestive juice although the morphology of these cells was normal (Fig. 4a). Inflammatory cell infiltration was only observed in the area adjacent to the normal pancreatic tissue deep to the anastomosis, but was not seen in the necrotic tissue. Replacement of the necrotic tissue by granulation tissue was slight on POD 7, and was still not complete on POD 14 when the pancreatic stump was covered with gastric mucosa (Fig. 4b).

In group II, histologic examination on POD 3 revealed atrophy of the vesicular bodies and nuclei of the cells in the pancreatic stump, indicating liquefactive necrosis (Fig. 5a). Inflammatory cell infiltrates were seen among the necrotic cells as well as replacement of the dead

Table 2 Depth of pancreatic necrosis (cm)

	POD 3	POD 7	POD 14
Group I	1.08 ± 0.35 (6)	0.97 ± 0.15 (10)	0.86 ± 0.23 (6)
Group II	0.37 ± 0.26* (6)	0.38 ± 0.18* (6)	0.32 ± 0.19* (6)
Group III	0.30 ± 0.07* (6)	0.23 ± 0.06* (8)	0.26 ± 0.09* (6)

\*:  $P < 0.001$  vs. group I; POD: See Table 1.

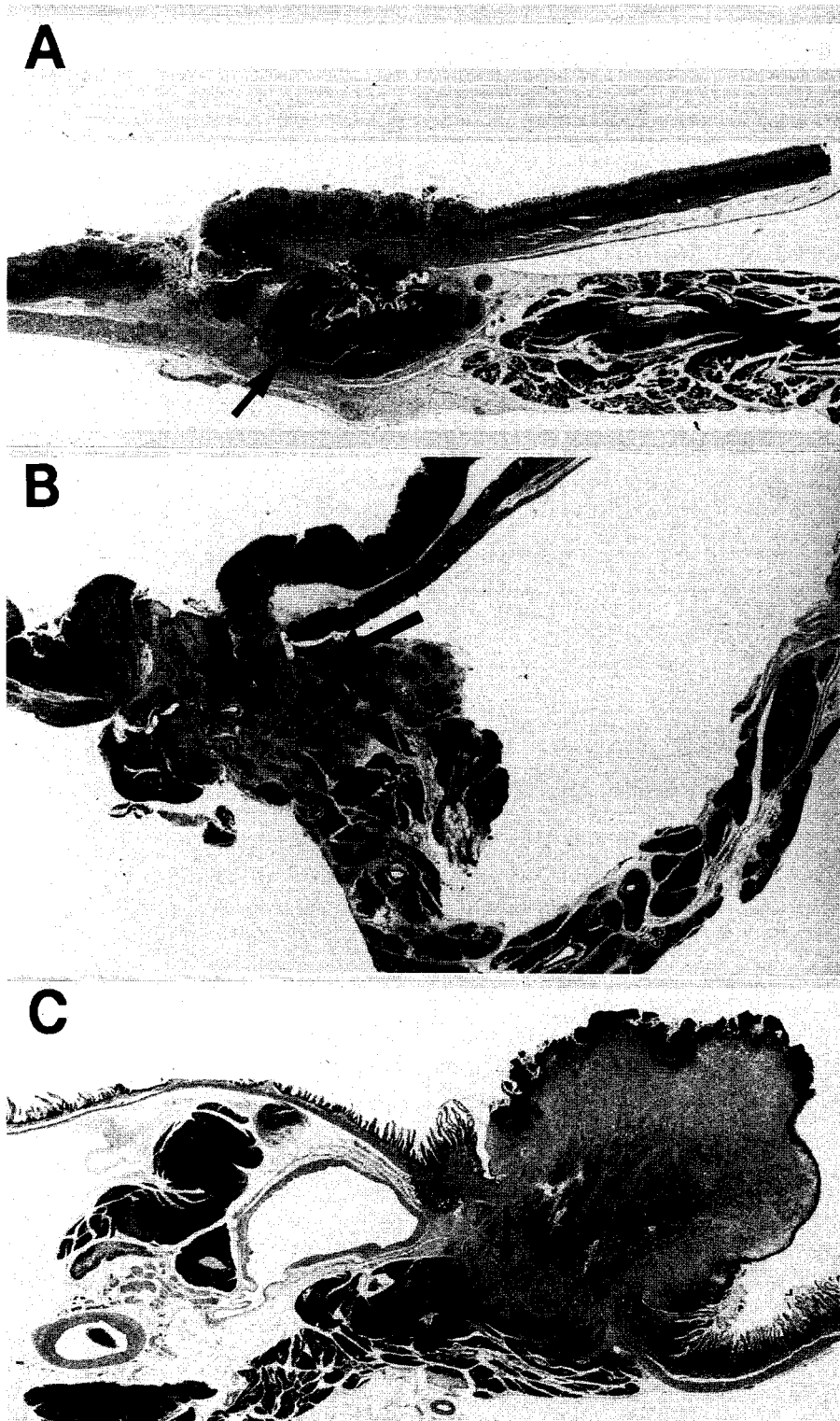
( ): number of rabbits

cells by granulation tissue. On POD 7, necrotic tissue and inflammatory cell infiltrates were no longer observed, and there was almost complete replacement by granulation tissue, indicating that the reaction against digestive juice invasion had ceased. Similar histologic findings were noted on POD 14 (Fig. 5b).

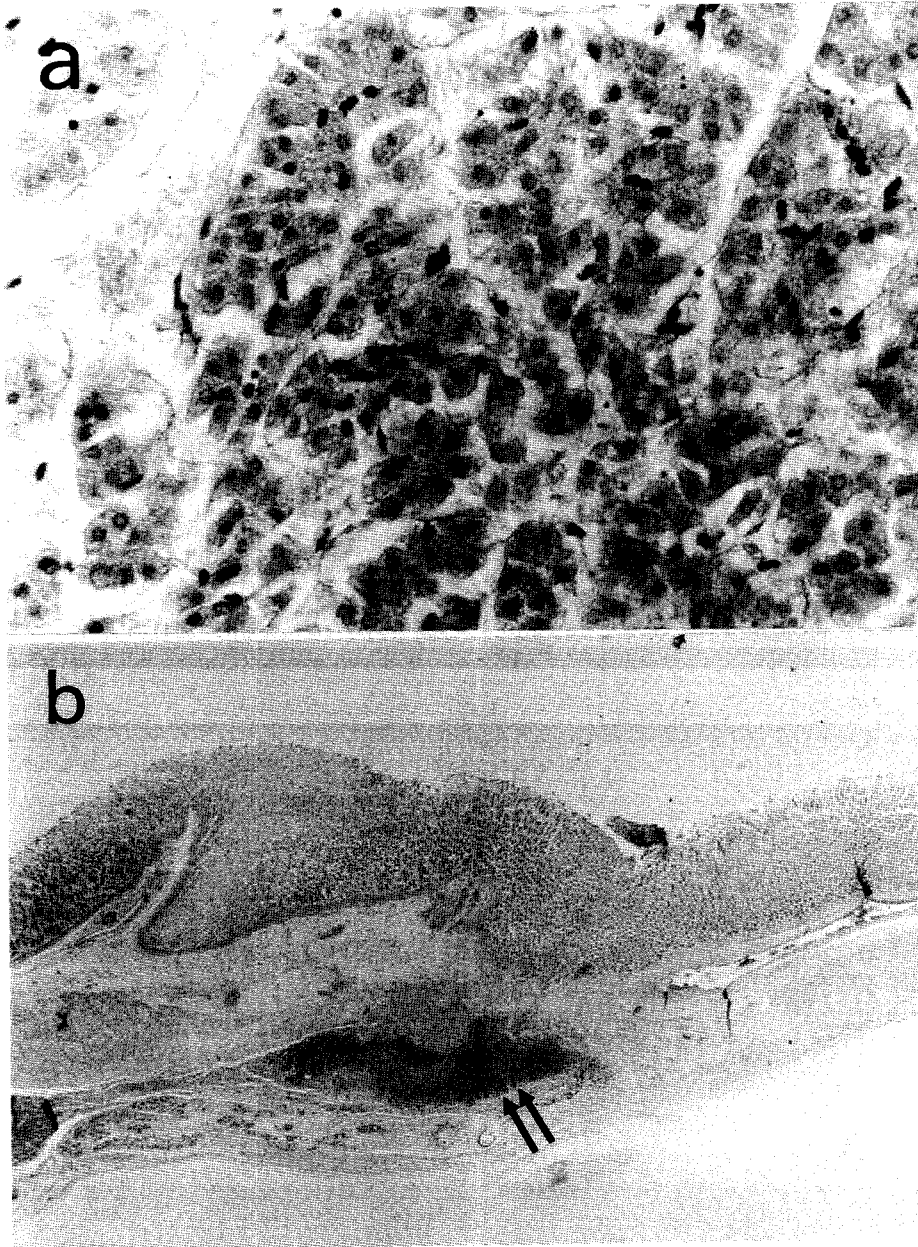
In group III, the findings were similar to those in group II, and the pancreatic cells showed liquefactive necrosis. Active inflammatory cell infiltration and replacement by granulation tissue were noted from POD 3 onwards, and the necrotic tissue was almost completely replaced by granulation tissue on POD 7.

**Depth of pancreatic necrosis** The depth of pancreatic necrosis was significantly greater ( $P < 0.001$ ) in group I than in either group II or group III at all postoperative assessments (POD 3, 7, and 14), although almost no increase was seen after POD 3 (Table 2).

**Histologic changes in the pancreatic body and tail.** After pancreatic duct ligation, there were



**Fig. 3** Anastomotic sites seen under the magnifier on postoperative day (POD) 7 stained with hematoxylin and eosin (H&E). The necrotic tissue (arrows) was deeper in group I (A) than in group II (B) or group III (C).

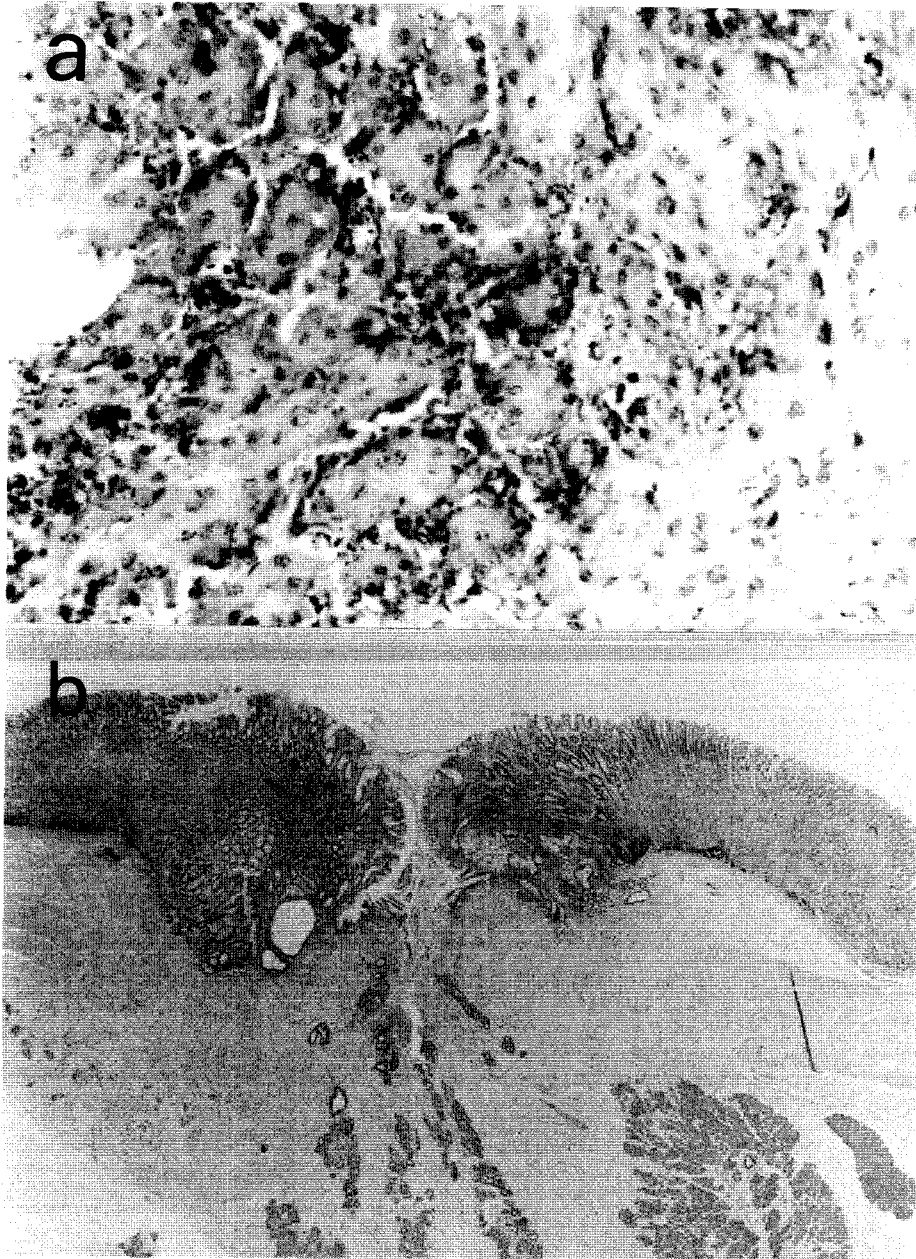


**Fig. 4** Necrotic tissue at the anastomotic site in group I. (a) The pancreatic stump shows coagulative necrosis on POD 3 (H&E; original magnification x400). (b) Necrotic tissue (double arrow) remains even on POD 14 (H&E; original magnification x10). POD, H&E: See Fig. 3.

moderate to severe histologic changes such as interlobular and perilobular fibrosis, atrophy of acinar cells, and loss of the lobular architecture (Fig. 6a). In groups II and III, there was no evidence of such changes in the pancreatic

body and tail. However, 6 of the 13 abscess-free rabbits (46.2%) from group I sacrificed on POD 7 and 14 (7 on POD 7 and 6 on POD 14) showed fibrosis, atrophy, loss of parenchymal architecture, and pancreatic duct dilatation

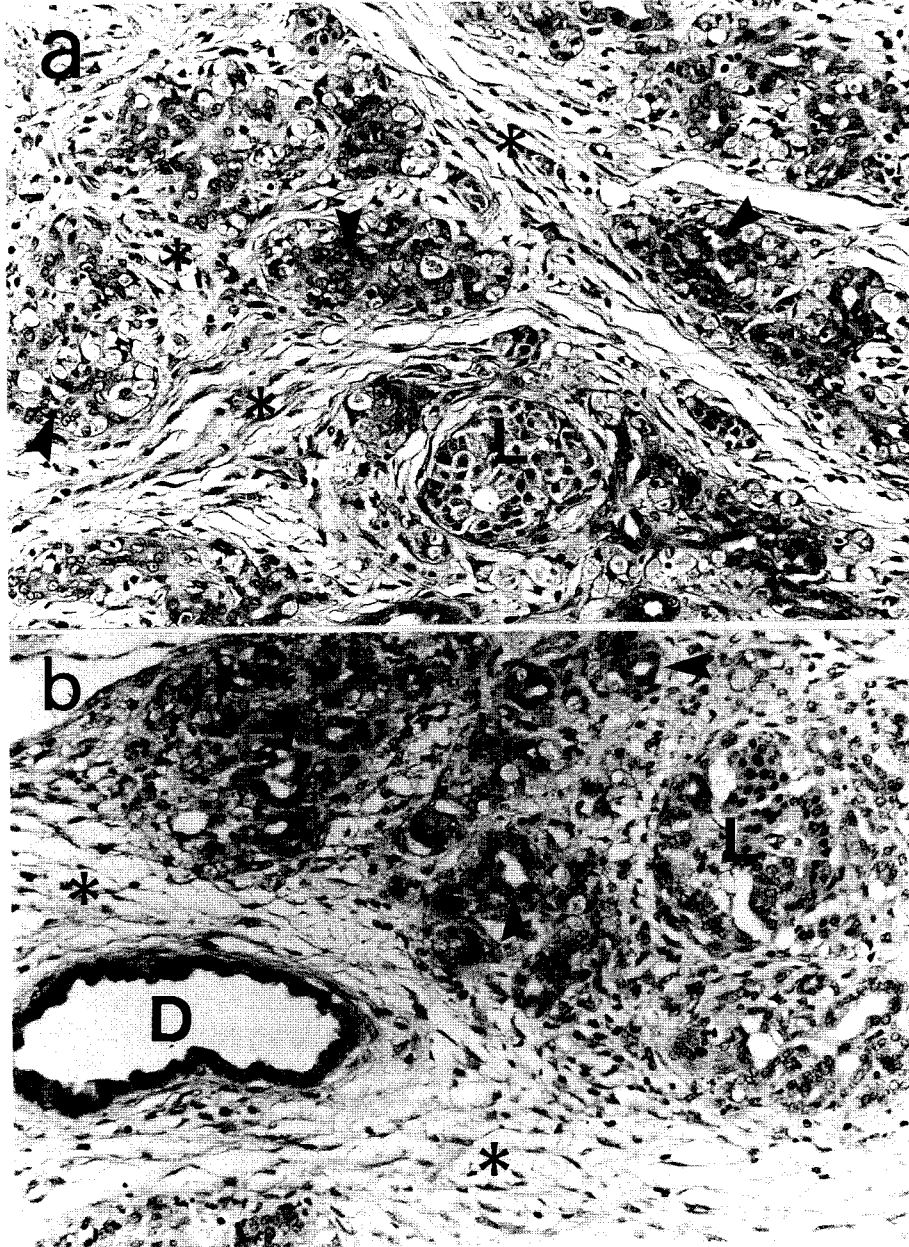




**Fig. 5** Necrotic tissue at the anastomotic site in group II. (a) The pancreatic stump shows liquefactive necrosis on POD 3 (H&E; original magnification x400). (b) The necrotic tissue is completely replaced by granulation tissue on POD 14 (H&E; original magnification x10). POD, H&E: See Fig. 3.

(Fig. 6b), findings very similar to the changes detected in the pancreatic duct ligation model. The incidence of parenchymal atrophic fibrosis was significantly higher in group I ( $P < 0.05$ ) than in either group II (0/12) or

group III (0/14). In the rabbits from group I with abscess formation, coagulative necrosis was noted throughout the pancreatic tail.



**Fig. 6** Changes of the pancreatic tissue on POD 7. (a) Interlobular and perilobular fibrosis (\*), atrophy of acinar cells, and loss of lobular architecture (arrowheads) are detected in the pancreatic body and tail after pancreatic duct ligation (H&E; original magnification x100). (b) Similar changes and dilatation of the pancreatic duct (D) are also observed in the body and tail of the pancreas in some group I rabbits (H&E; original magnification x100). Note the well-preserved islets (L) in (a) and (b). POD, H&E: See Fig. 3.

## Discussion

In a study using dogs, Tripodi and Sherwin (10)

found no endocrine or exocrine impairment following insertion of the pancreatic stump into the intact stomach, suggesting that this technique is safe. In contrast, Telford *et al.* (11) reported that the pancreatic stump

became totally replaced by cicatricial tissue after insertion into the intact stomach, resulting in pancreatic duct obstruction. Recently, Greene *et al.* (12) compared insertion of the pancreatic stump into the intact stomach or the jejunum, and found that pancreatic duct obstruction was more common after insertion into the jejunum. However, none of these experimental studies compared pancreaticogastrostomy after partial gastrectomy with anastomosis to the intact stomach.

The present study showed that the digestive juice around the anastomotic site was neutral after pancreaticojejunostomy and the amylase activity of pancreatic juice was maintained. In contrast, after pancreaticogastrostomy was performed with the intact stomach, the digestive juice around the anastomotic site was highly acidic and pancreatic amylase activity was almost entirely lost. However, when the pancreatic stump was anastomosed to the stomach after partial gastrectomy, the digestive juice around the anastomotic site was only slightly acidic and amylase activity was well maintained, findings similar to those after pancreaticojejunostomy.

Liquefactive necrosis of the pancreatic stump was caused by neutral digestive juice containing pancreatic proteolytic enzymes after pancreaticojejunostomy or pancreaticogastrostomy with partial gastrectomy, and the necrotic tissue was replaced by granulation tissue following inflammatory cell infiltration in the early stage after surgery (granulation was complete by POD 7) (13). Since the new granulation tissue was highly vascular, it was considered likely that the pancreatic stump would fuse with the serosa of the jejunal or gastric wall from the early postoperative period. In contrast, in the case of pancreaticogastrostomy without partial gastrectomy, coagulative necrosis of the pancreatic stump was caused by the low pH of the digestive juice around the anastomotic site, and infiltration of inflammatory cells into the necrotic tissue as well as replacement by granulation tissue were delayed. Furthermore, there was widespread invasion of corrosive digestive juice into the pancreatic body. These histologic changes suggested that fusion of the pancreatic stump with the gastric wall was likely to be delayed. Mackie *et al.* (3) and Icard and Dubois (4) have speculated that proteolytic enzymes in the pancreatic juice are inactivated by gastric acid, and this has been proposed as an advantage of pancreaticogastrostomy since it was thought likely to have a protective effect on the anastomotic site. However, the present study demonstrated a different outcome.

The main complication observed in the present study was intraperitoneal abscess formation around the anastomotic site, which was noted in 27.8% of the rabbits undergoing pancreaticogastrostomy without partial gastrectomy. The necrotic pancreatic tissue around the abscess generally showed extensive morphological changes suggesting coagulative necrosis, and these histologic changes were considered to have been induced by the leakage of highly acidic gastric juice. Since such abscess formation was not observed after pancreaticogastrostomy with partial gastrectomy or after pancreaticojejunostomy, the increased incidence of anastomotic leakage in the rabbits without partial gastrectomy may have been due to more extensive and prolonged coagulative necrosis of the pancreatic stump. Although clinical experience suggests that pancreaticogastrostomy with partial gastrectomy has a lower risk of anastomotic leakage than pancreaticojejunostomy, the present study did not demonstrate any difference (1, 4, 14-17).

Narrowing or obstruction of the pancreatic duct in the pancreatic stump could not be observed histologically or radiologically because of the extensive destruction of the stump and the fine pancreatic duct in rabbits. However, histologic changes like parenchymal atrophic fibrosis that were detected in our pancreatic duct ligation model were also recognized in 46.2% of the rabbits undergoing pancreaticogastrostomy without partial gastrectomy (18). In contrast, such changes did not occur after pancreaticogastrostomy with partial gastrectomy or after pancreaticojejunostomy. This difference in the extent of atrophic fibrosis of the pancreatic body and tail may have been related to the occurrence of extensive coagulative necrosis of the pancreatic stump in the early postoperative period after anastomosis to the intact stomach. More specifically, it may be that when the pancreatic stump is anastomosed to the jejunum or the stomach after partial gastrectomy, granulation tissue forms in the early postoperative period and liquid elements such as pancreatic juice can then pass through the stump. In contrast, when the pancreatic stump is anastomosed to the intact stomach, coagulative necrosis is extensive and the necrotic tissue is replaced by cicatricial fibrosis, resulting in pancreatic duct obstruction (11, 12). Based on the present findings, partial gastrectomy may be necessary to prevent pancreatic duct obstruction after pancreaticogastrostomy.

Following pancreaticogastrostomy with partial gastrectomy or pancreaticojejunostomy, the portion of the pancreatic stump protruding into the gastrointestinal

lumen was lost through liquefactive necrosis and the remnant cut surface became covered with highly vascular granulation tissue. It has been reported clinically that gastrointestinal bleeding may occur suddenly after pancreaticogastrostomy with partial gastrectomy or after pancreaticojejunostomy; such hemorrhage is considered to be due to the rupture of granulation tissue capillaries and may not be preventable by elaborate hemostasis of the pancreatic stump during surgery (4, 19). It is difficult to endoscopically investigate and/or manage bleeding from the pancreatic stump following pancreaticojejunostomy, whereas one advantage of pancreaticogastrostomy with partial gastrectomy is that endoscopic hemostasis can be performed if bleeding occurs (20).

In the present study, resection of half of the stomach was done to reduce gastric acidity. Inadequate resection might allow the gastric juice to remain highly acidic and cause the same changes of the pancreatic stump as occurred in the animals without partial gastrectomy. Thus, it is considered important to perform sufficient resection to markedly reduce the gastric acid output.

Based on the results of our study, pancreaticogastrostomy without partial gastrectomy may be associated with an increased risk of anastomotic leakage and exocrine dysfunction of the remnant pancreas. After PPPD, an anastomotic method is needed which does not involve exposure of the pancreatic stump to highly acidic digestive juice, such as pancreatic duct-to-gastric mucosa anastomosis, pancreaticogastrostomy with tubing, or pancreaticojejunostomy (5, 21-23). However, pancreaticogastrostomy with partial gastrectomy also appears to be a safe method of pancreatic drainage. Although it is associated with the small stomach syndrome and an increased risk of hemorrhage from the pancreatic stump, it reduces the risk of anastomotic leakage and pancreatic exocrine dysfunction.

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