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Short-Term Effects of Bile Diversion on Postgastrectomy Gastric Histology

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Twelve partially gastrectomized subjects who have consecutively undergone total biliary diversion for severe bilious vomiting were studied before and after operation in order to assess the effects of surgery on gastric histology and enterogastric reflux. Before and six months after operation, the following protocol was performed: (1) blood examinations including serum basal gastrin; (2) endoscopy with multiple gastric biopsies; and (3) quantitation of bile acids in the gastric aspirate. Of the preoperative symptoms, bilious vomiting and heartburn completely disappeared postoperatively in all the subjects. Fasting bile reflux was significantly reduced (bile reflux was annulled in six and considerably lowered in the remaining six subjects), and erythema of the gastric mucosa completely disappeared in all the subjects after diversion. Among histological findings, while a significant regression of foveolar hyperplasia was found both in the perianastomotic area and in the body of gastric remnant, none of the other aspects identifiable in postgastrectomy gastric mucosa (chronic gastritis changes included) were affected by diversion. These results show that biliary diversion is effective in correcting reflux, bilious vomiting, erythema, and foveolar hyperplasia of the gastric mucosa and confirm the suggested relationship between bile reflux and gastric foveolar hyperplasia.

KEY WORDS: alkaline reflux gastritis; atrophic gastritis; bile reflux; enterogastric reflux; foveolar hyperplasia; postgastrectomy syndrome; Roux-en-Y gastrojejunostomy.

Gastric mucosal changes after partial gastrectomy and their significance in the ultimate development of gastric remnant carcinoma have been widely investigated (1–7). Enterogastric reflux, abundant after gastrectomy, has been considered the main factor responsible for such changes (8–10).

Different degrees of chronic atrophic gastritis have been reported as a common histological finding in the postgastrectomy mucosa and were considered to be reflux-related (8–10), although such a relationship has never been demonstrated (11, 12). More recently, attention has been focused on hyperplasia of the foveolar epithelium (13–20), which is mostly confined to the perianastomotic area (16, 17, 21), and whose relationship with bile reflux has been shown independent of the degree of gastritis (21). This latter histological finding may be important since an enhanced proliferative activity of the epithelial cells resulting in hyperplasia could increase the probability of malignant transformation characteristic of that particular epithelium (22). This might be especially true in the mucosa of the

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TABLE 1. EPIDEMIOLOGICAL DATA OF OPERATED SUBJECTS AND EFFECTS OF BILIARY DIVERSION OPERATION ON SYMPTOMS AND ENDOSCOPIC FINDINGS

				Symptoms							
				Bilious vomiting		*Epigastric pain/discomfort*		*Heartburn*		*Gastric erythematous changes**	
Patient	*Age*	*Sex*	*Type of operation*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	57	M	Roux-en-Y + vagotomy	Yes	No	Yes	No	Yes	No	2	0
2	58	F	Roux-en-Y	Yes	No	Yes	Yes	No	No	1	0
3	42	M	Roux-en-Y + vagotomy	Yes	No	Yes	Yes	Yes	No	2	0
4	44	M	Roux-en-Y	Yes	No	Yes	Yes	Yes	No	2	0
5	36	F	Roux-en-Y + vagotomy	Yes	No	Yes	Yes	Yes	No	2	0
6	57	M	Roux-en-Y + vagotomy	Yes	No	Yes	No	Yes	No	2	0
7	41	M	Roux-en-Y	Yes	No	Yes	No	No	No	2	0
8	58	F	Roux-en-Y	Yes	No	Yes	Yes	Yes	No	2	0
9	63	M	Roux-en-Y	Yes	No	Yes	No	Yes	No	1	0
10	52	F	Roux-en-Y + vagotomy	Yes	No	Yes	No	No	No	1	0
11	58	M	Roux-en-Y	Yes	No	Yes	No	Yes	No	2	0
12	47	M	Roux-en-Y + vagotomy	Yes	No	Yes	No	Yes	No	2	0

*0, no erythematous changes; 1, erythematous changes of the perianastomotic area; 2, erythematous changes both of the perianastomotic area and gastric stump.

gastric remnant exposed to different mutagenic stimuli such as increased concentrations of nitrites, nitrosocompounds, and bile salts which have been reported after partial gastrectomy (23–26).

The present study was undertaken to assess the effects of bile diversion on postgastrectomy gastric histological changes and more specifically to verify whether the foveolar hyperplastic changes, which were previously suggested to be reflux-related (21), would regress after operations preventing enteric contents (bile and pancreatic enzymes) from reaching the gastric stump.

MATERIALS AND METHODS

Patients. Twelve subjects (eight men and four women, mean age 51.1 years, range 36–63) who have consecutively undergone total biliary diversion in the last four years were prospectively studied. All were operated for severe, debilitating bilious vomiting (one to four episodes a week). Each of them had undergone a B-II partial gastrectomy 2–31 years before (mean 10.8) for gastric (three patients) or duodenal (nine patients) ulcer.

Before diversion each underwent the following protocol: (1) blood examinations including serum basal gastrin; (2) barium meal; (3) endoscopy with multiple gastric biopsies; and (4) quantitation of bile acids in the gastric aspirate.

Symptoms were registered and Visick's grading (27) assessed. None of the patients had gallstones or had ever been operated upon for gallstones. None had recurrent peptic ulcer or barium meal abnormalities. None were alcohol abusers. Total biliary diversion was achieved with a 50-cm Roux-en-Y with vagotomy (six patients) or without vagotomy (six patients) (Table 1). Six months after operation, the whole study protocol was repeated (with the exception of barium meal). In four subjects an additional endoscopy was also performed 10–12 days after surgery.

Laboratory Methods. All esophagogastroscopies were performed by one of us (P.B.). A total of 12 grasp biopsies were taken in each patient. Four biopsies were taken in the perianastomotic area within 0.5 cm of the edge of the anastomosis (perianastomotic set I), four in the perianastomotic area at a distance of 1.5–2 cm from the edge of the anastomosis (perianastomotic set II), and four in the body of the gastric remnant (gastric body set) (Figure 1).

All the specimens were oriented, fixed in phosphate-buffered formol, and embedded in paraffin. Sections 5 μm thick were stained by hematoxylin and eosin and Alcian blue (pH 2.5) –periodic acid Schiff. All histological exam-

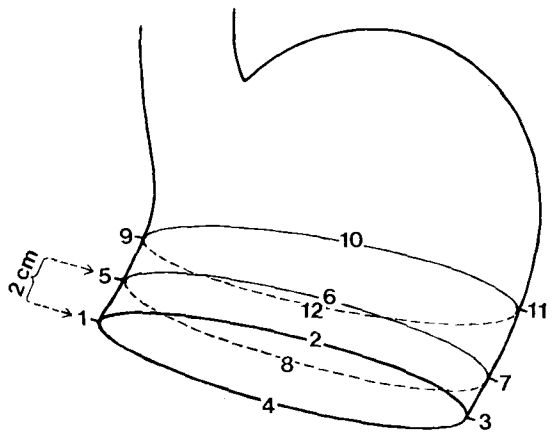

Fig 1. Sites of biopsies in the gastric remnant.

inations were carried out "blind" by one of us (A.A.). The state of the gastric mucosa was defined according to Whitehead et al (28). Chronic gastritis was classified as either superficial or atrophic. Chronic atrophic gastritis was graded with respect to gastric gland atrophy as mild, moderate, and severe (28). The degree of mucosal inflammation did not affect gastritis grading. A histological score for chronic gastritis was given for easier and more complete statistical analysis (0: no gastritis; 1: superficial gastritis; 2, 3, and 4: mild, moderate, and severe atrophic gastritis, respectively). The presence and type of metaplasia (intestinal and pseudopyloric) and cystic dilatation of the glands (defined as a distension two times or more the normal diameter of a gland) were also recorded. Gastric mucosa hyperplasia and dysplasia were defined according to the criteria outlined at the Workshop of the International Study Group on Gastric Cancer (ISGGC) held in San Miniato in 1982 (29). On this basis, hyperplasia is considered to be a proliferative lesion of nonprecancerous nature and dysplasia a precancerous lesion. Perianastomotic biopsy sets I and II were assessed cumulatively and separately from the gastric body set.

At 9 AM, after overnight fasting, gastric aspirates were obtained through a 16 F nasogastric tube. The position of the tube in the gastric stump, approximately 3 cm above the anastomosis, was checked fluoroscopically. The initial aspirate was discarded. Three samples were then collected by 10-min gentle suction with a syringe, in order to assess the fasting bile reflux (FBR) according to Hoare et al (30). Total bile acid concentration in each of the three diluted gastric aspirates was estimated enzymatically according to Mashige et al (31), using a commercial kit (Enzabile, Nyegaard, Oslo, Norway). This technique involves the oxidation of bile acids by the enzyme 3α-hydroxysteroid dehydrogenase with concomitant reduction of NAD^+ to NADH. The reducing equivalents of NADH are transferred by the enzyme diaphorase to nitrotetrazolium blue with subsequent formation of formazan, which is measured at 540 nm using a spectrophotometer. All assays were carried out in duplicate. The concentration of total bile acids in the samples was multiplied by the volume aspirated over half an hour, doubled, and expressed in micromoles per hour (FBR). Maximal bile acid concentration (bile acid concentration in the most bile-concentrated aspirate, MBC) and mean bile acid concentration (the mean of bile acid concentrations of the three different aspirates, mBC) were also considered and expressed in micromoles per liter.

Statistics. Statistical analysis was performed using Wilcoxon's rank sum test for paired values and according to the binomial model (32). When not otherwise specified, this latter was used.

RESULTS

Of the preoperative symptoms (Table 1) bilious vomiting and heartburn completely disappeared after surgery in all subjects, whereas epigastric pain/discomfort persisted in five (preoperative vs postoperative: nonsignificant differences for epigastric pain/discomfort, $P < 0.01$ for vomiting and heartburn). However, Visick's grading was considerably improved postoperatively in each patient (six had postoperative Visick's grading of I and six of II). Pre- and postoperative basal gastrin concentrations were not significantly different (Wilcoxon's rank sum test for paired values).

Erythema of the gastric mucosa, which was very evident and constantly present preoperatively, completely disappeared both in the perianastomotic area and in the gastric stump in all subjects after biliary diversion (Table 1). The regression of mucosal erythema apparently took place in the immediate postoperative course since no erythematous changes were found in any of the four subjects who underwent an additional endoscopy 10–12 days after diversion.

FBR was significantly ($P < 0.01$) reduced by biliary diversion. Postoperatively it was 0 in six subjects, and dramatically decreased in the remaining six (Table 2). Moreover, in these latter six subjects, bile acid concentrations (both MBC and mBC) were lower than preoperatively (Table 2).

Histological findings before and six months after operation (Figures 2 and 3) are reported in Tables 3 and 4. In the perianastomotic area (perianastomotic sets of biopsies) chronic gastritis remained unchanged in 11 subjects and improved in one (Table 3). In the body of the gastric remnant (gastric body set of biopsies) it was unchanged in 11 and worsened in one subject (Table 4). Foveolar hyperplastic changes in the perianastomotic area, present in all the subjects before diversion, completely disappeared in nine and became less evident in the remaining three (preoperative vs postoperative: $P < 0.01$) (Table 3). Two of the latter subjects with postoperative (milder than preoperative) hyperplastic changes were in the group of six subjects with decreased postoperative reflux and one was in the group without reflux.

Six subjects had foveolar hyperplastic changes in the body of the gastric remnant before diversion: in four they completely disappeared after diversion and in two they became less evident (preoperative vs postoperative: $P < 0.05$) (Table 4). One of the latter two patients had postoperative reflux, and one was without reflux. Pseudopyloric metaplasia was not significantly affected by biliary diversion (preoperatively nine and three subjects with pseudopyloric metaplasia in the perianastomotic area and in the gastric remnant, respectively; postoperatively seven and none, respectively). The same was true for intestinal metaplasia (preoperatively

TABLE 2. EFFECTS OF BILIARY DIVERSION OPERATION ON REFLUX (FASTING BILE REFLUX, FBR; MAXIMAL BILE ACID CONCENTRATION, MBC; AND MEAN BILE ACID CONCENTRATION, MBC)

	FBR (μmol/hr)		*MBC (μmol/liter)*		*mBC (μmol/liter)*	
Patient	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	506.0	0.1	190.0	4.9	131.7	1.6
2	59.5	0	402.5	0	362.2	0
3	500.0	0.2	185.3	15.5	128.5	8.8
4	2.7	0.4	166.0	40.8	69.8	10.2
5	26.3	0	2153.0	0	204.5	0
6	17.5	0.7	1084.0	44.6	759.0	11.1
7	13.2	0	290.0	0	208.0	0
8	13.0	4.1	1384.6	100.0	860.2	58.0
9	26.2	0	2200.0	0	200.5	0
10	66.8	0	1892.0	0	180.4	0
11	24.3	0	176.6	0	158.1	0
12	16.2	0.9	1799.0	5.5	603.3	3.6

three subjects with intestinal metaplasia in the perianastomotic area and three in the gastric remnant; postoperatively five and two, respectively) and intramucosal glandular cysts (preoperatively six and two subjects with intramucosal cysts in the perianastomotic area and in the gastric remnant, respectively; postoperatively four and none, respectively).

DISCUSSION

This study has shown that the postgastrectomy gastric histological picture is selectively and drastically modified by biliary diversion. Whereas chronic atrophic gastritis was unaffected, foveolar hyperplasia disappeared (in most subjects) or was greatly reduced. Total biliary diversion in the prospectively studied present series also appeared an effective procedure in the treatment of postgastrectomy biliary reflux and bilious vomiting.

Although activated pancreatic enzymes and lysolecithin in the refluxate have been proposed as cooperating aggressive factors (12, 33–35), bile acids are commonly considered the most harmful agents, they can be easily assessed, and their quantity may be assumed as an approximate index of the quantity of the whole refluxate.

Present results show that biliary reflux was annulled in 50% of the subjects and dramatically reduced in all the others. In each of the latter subjects not only a significant reduction of the absolute hourly quantity of reflux (FBR) was shown, but also bile acid concentration in the gastric aspirate (MBC and mBC) was lower than preoperatively. Since bile acid damage to gastric mucosa seems mainly due to bile concentration-dependent detergent activity, the marked reduced concentration in all the subjects, rather than the FBR reduction, may be important in the regression of mucosal lesions. This dilution of bile acids seems obviously due to the reduced quantity of refluxate in a grossly unchanged quantity of gastric secretion. These findings, consistent with previous reports concerning both fasting and postprandial enterogastric reflux (12, 15), could explain why bilious vomiting and heartburn disappeared postoperatively in all the subjects of the present series.

At variance with bilious vomiting and heartburn, the improvement of which was related to the reduction of reflux and of foveolar hyperplasia, epigastric pain/discomfort was not significantly affected by diversion. This symptom was present preoperatively in all the subjects studied and persisted after operation in 41.7% of them. However, the characteristics of this symptom (mostly fasting pain intensified by meals and relieved by bilious vomiting) were modified postoperatively (exclusively postprandial pain and fullness lasting up to 4–5 hr). No significant relationship was shown in this small group between this symptom and postoperative reflux or foveolar hyperplasia, since reflux was absent after operation in two of the five subjects with postoperative epigastric pain/discomfort (and markedly reduced in the other three) and foveolar hyperplasia was lacking in four of them. This finding is in agreement with previous reports on postdiversion persistence of symptoms in a certain percentage of operated subjects (36–38). In seven subjects studied and followed-up for longer periods

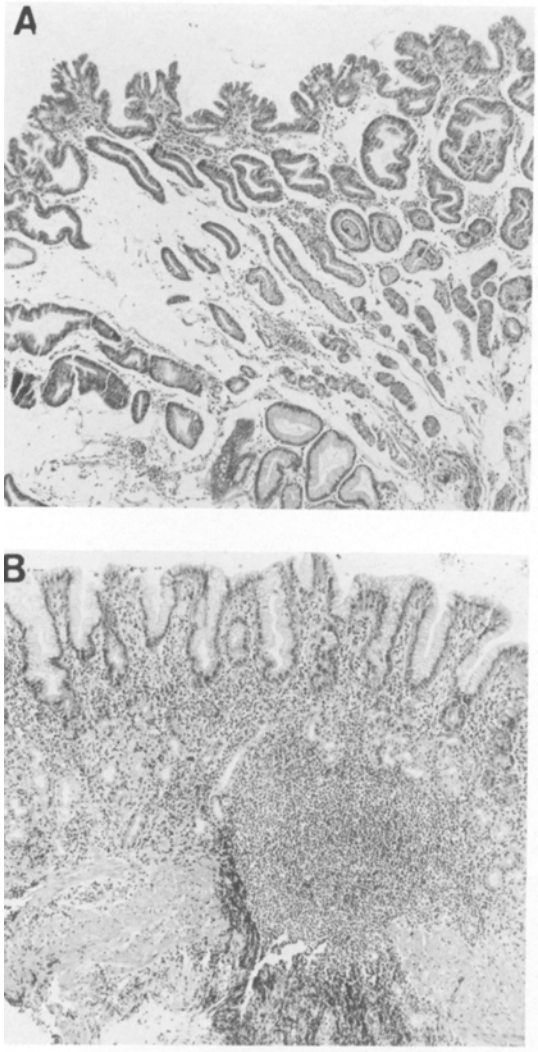

Fig 2. Patient 7. Perianastomotic area (perianastomotic set I of biopsies—biopsies within 0.5 cm of edge of anastomosis). (A) Before total biliary diversion. Severe foveolar hyperplasia, reduced number of gastric body glands (moderate atrophic gastritis) partly replaced by pyloric-type glands, mild inflammatory infiltration within edematous lamina propria are seen (H&E, ×60). (B) After total biliary diversion. Foveolar hyperplasia is no longer evident. Moderate chronic atrophic gastritis and a prominent lymphoid follicle are shown (H&E, ×75).

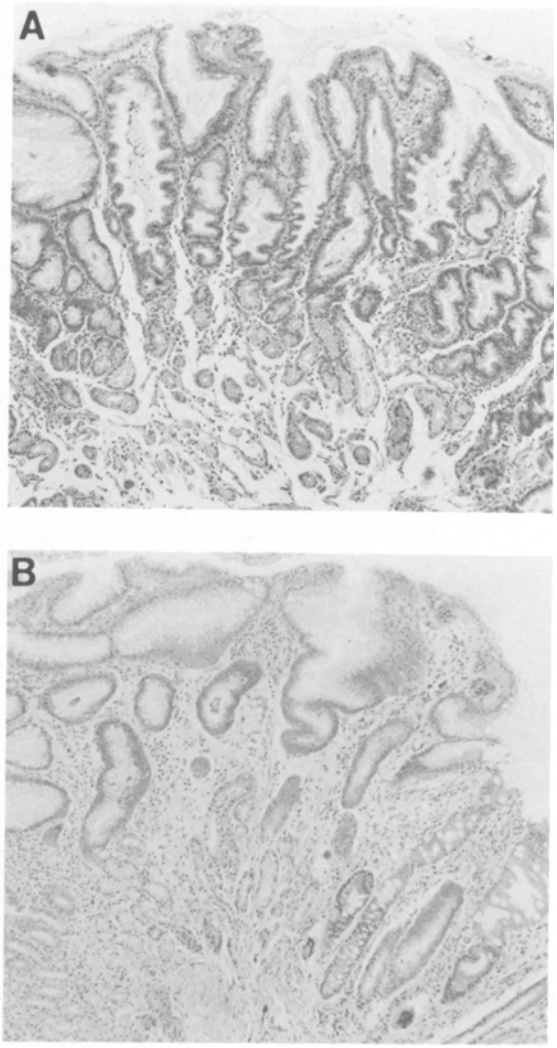

Fig 3. Patient 8. Perianastomotic area (perianastomotic set I of biopsies—biopsies within 0.5 cm of edge of anastomosis). (A) Before total biliary diversion. Severe foveolar hyperplasia, reduced number of gastric body glands (moderate atrophic gastritis) with mild inflammatory infiltration and pseudopyloric metaplasia are seen (H&E, ×60). (B) After total biliary diversion. Hyperplastic foveolar changes are less pronounced although still evident. Chronic atrophic gastritis with pseudopyloric metaplasia appears unchanged. Some metaplastic intestinal glands are seen on the right (H&E, ×75).

(1–3.5 years after operation), no further modification in postdiversion symptoms was observed.

The marked reduction of reflux certainly affects the endoscopic appearance of postgastrectomy gastric mucosa. As previously reported (8, 12, 15, 18, 36), erythema, which was very evident and characteristic of the gastric mucosa before, completely disappeared after diversion. This striking regression seems to take place very soon after diversion since, in all four subjects who underwent endoscopy 10–12 days after surgery, mucosal erythema had completely regressed. None of the typical features of postgastrectomy endoscopic appearance (mucosal erythema, edema, and friability) were present in any of the subjects six months after diversion, so that often it was not easy to distinguish between preanastomotic gastric and postanastomotic jejunal mucosa. The causative role of reflux (39) on post-

TABLE 3. EFFECTS OF BILIARY DIVERSION ON HISTOLOGICAL FINDINGS (PERIANASTOMOTIC SETS I AND II OF BIOPSIES)

Patient		*Chronic gastritis**	*Foveolar hyperplasia†*	*Pseudopyloric metaplasia‡*	*Intestinal metaplasia‡*	*Intramucosal cysts‡*
1	before operation	3	2	P	A	A
	after operation	3	0	P	A	P
2	before operation	2	2	P	A	P
	after operation	2	0	A	A	A
3	before operation	2	2	P	A	A
	after operation	2	0	A	A	A
4	before operation	2	3	P	P	P
	after operation	2	0	P	A	A
5	before operation	2	2	A	A	A
	after operation	2	0	A	A	A
6	before operation	2	2	A	A	A
	after operation	2	0	P	A	A
7	before operation	3	3	P	A	P
	after operation	3	0	P	A	P
8	before operation	3	3	P	A	P
	after operation	3	2	P	P	A
9	before operation	3	2	A	P	A
	after operation	3	1	P	P	A
10	before operation	2	2	P	A	P
	after operation	2	0	A	P	A
11	before operation	3	3	P	P	A
	after operation	2	0	A	P	P
12	before operation	2	2	P	A	P
	after operation	2	1	P	P	P

*0 = no gastritis; 1 = superficial; 2 = mild atrophic; 3 = moderate atrophic; 4 = severe atrophic.
†0 = absent; 1 = mild; 2 = moderate; 3 = severe.
‡A = absent; P = present.

gastrectomy endoscopic abnormalities was, therefore, confirmed by present findings.

Evidence from the literature is conflicting concerning the histological consequences of enterogastric reflux and their possible regression after diversion (12, 30, 40–42). Histological changes classifiable as chronic atrophic gastritis have been reported to develop gradually after surgery and, although it has been suggested that they could be related to enterogastric reflux (8–10), such a relationship has never been proved and has even been denied by some authors (43). Recently, gastric histological findings classifiable as foveolar epithelium hyperplastic changes, mostly limited to the perianastomotic area, were demonstrated (13–20) and a relationship with enterogastric reflux was suggested (13, 15, 19, 44) and later proved (21). Hyperplastic epithelial changes represent a nonspecific tissue reaction that can be observed in a variety of clinicopathological entities (45–47). However, the histological picture combining hyperplastic foveolar changes with gastric gland atrophy, mild inflammation, pseudopyloric metaplasia, and occasional cyst formation appears to be distinctive of the perianastomotic area before bile diversion (21) (Figures 2A and 3A). Severity of prediversion hyperplastic changes, as previously reported (17, 21), decreased from the anastomosis to the gastric body (Tables 3 and 4).

Present results show that, among all the histological aspects identifiable in postgastrectomy gastric mucosa, only foveolar hyperplastic changes seemed to be significantly affected by biliary diversion. This confirms previous data (21), suggesting a possible role of enterogastric reflux in determining foveolar hyperplasia.

The regression of hyperplastic changes and the diversion from the gastric stump of potentially cocarcinogenic substances (bile salts) might be important in view of the reportedly increased cancer risk in the resected stomach (1–7). An actively proliferating epithelium might be more sensitive to mutagenic stimuli such as the increased concentration of nitrites, nitroso compounds, and bile salts which has been reported after gastrectomy (22–26).

The trend to further regression of hyperplastic changes and the unchanged severity of atrophic gastritis was also confirmed by further histological follow-up already performed in seven of the subjects studied (followed-up for 1–3.5 years). More-

TABLE 4. EFFECTS OF BILIARY DIVERSION OPERATION ON HISTOLOGICAL FINDINGS (BODY SET OF BIOPSIES)

Patient		*Chronic gastritis**	*Foveolar hyperplasia†*	*Pseudopyloric metaplasia‡*	*Intestinal metaplasia‡*	*Intramucosal cysts‡*
1	before operation	1	0	A	A	A
	after operation	1	0	A	A	A
2	before operation	2	0	P	A	A
	after operation	2	0	A	A	A
3	before operation	1	0	A	A	A
	after operation	1	0	A	A	A
4	before operation	2	1	A	A	P
	after operation	2	0	A	A	A
5	before operation	1	0	A	A	A
	after operation	1	0	A	A	A
6	before operation	1	0	A	A	A
	after operation	2	0	A	A	A
7	before operation	2	1	A	A	A
	after operation	2	0	A	A	A
8	before operation	2	2	P	P	A
	after operation	2	1	A	A	A
9	before operation	2	2	A	P	A
	after operation	2	1	A	P	A
10	before operation	2	1	A	A	A
	after operation	2	0	A	A	A
11	before operation	2	2	P	P	P
	after operation	2	0	A	P	A
12	before operation	2	0	A	A	A
	after operation	2	0	A	A	A

*0 = no gastritis; 1 = superficial; 2 = mild atrophic; 3 = moderate atrophic; 4 = severe atrophic.
†0 = absent; 1 = mild; 2 = moderate; 3 = severe.
‡A = absent; P = present.

over, the irreversibility of chronic atrophic gastritis after longer follow-up periods has been previously reported (11, 30). This, by itself, does not necessarily imply a lack of relationship between postgastrectomy chronic atrophic gastritis and reflux, since atrophic gastritis could simply represent an irreversible histopathological stage. However, this finding might also suggest other causes for the atrophic changes such as the suppression after gastrectomy of antral gastrin secretion and its trophic action (48, 49).

On practical grounds, because of the irreversibility of atrophic gastric changes, vagotomy was not performed in the last Roux-en-Y operations of the present series in subjects previously widely resected (at least 65% gastrectomy), with atrophic gastritis both in the perianastomotic and in the gastric body sets of biopsies, and a neutral gastric pH at pH monitoring.

In conclusion, biliary diversion is effective in the treatment of enterogastric reflux, bilious vomiting, heartburn, erythema, and hyperplastic foveolar changes of the gastric mucosa. On the contrary, diversion of bile seems ineffective in correcting the other gastric histological changes (including atrophic gastritis) frequently found after partial gastrectomy. This suggests a role for reflux in determining postgastrectomy foveolar hyperplasia but not chronic atrophic gastritis.

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