

Marginal Ulcer

A Difficult Surgical Problem

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One hundred sixty-six patients with documented recurrent or marginal ulcers following previous ulcer operation were seen at Duke Medical Center and the Durham VA Hospital from 1950 through 1980. Patients with the diagnosis of gastrinoma were excluded from the series. Evaluation of initial operation for recurrent ulcer showed that the highest recurrence rate occurred following non-acid-reducing operations. Analysis of the symptom-free interval following initial ulcer operation showed a significantly longer interval prior to recurrent ulcer development following gastroenterostomy than other procedures, while resection and Billroth I reanastomosis showed a significantly shorter symptom-free interval than did other procedures. Endoscopy proved 85% sensitive in making the diagnosis of marginal ulcer, while upper GI series was 71% sensitive. Surgical treatment of 132 patients resulted in a 20.4% recurrence rate of second marginal ulcer, with a 2.3% mortality rate and a 10.6% morbidity rate. Second operation for recurrent ulcer in 24 patients yielded no deaths, a 12.5% morbidity rate, and a 29.2% recurrence rate. Average follow-up for the series was 12.3 years, and ultimate outcome of treatment showed, of patients not lost to follow-up, a 58.2% satisfactory to excellent rating, while 42.8% of patients had an unsatisfactory result of treatment.

ALTHOUGH THE INCIDENCE of peptic ulcer has probably declined in the past decade and effective medical therapy has become available, duodenal ulcer remains a significant clinical problem. Fortunately, most duodenal ulcer patients respond well to medical or surgical treatment, but a small number of patients continue to be disabled by ulcers following surgical therapy. This retrospective analysis of 166 patients with postoperative recurrent, marginal, or anastomotic ulcer during the past 30 years was done to learn more about this difficult clinical problem.

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Methods

All patients were seen at either the Durham Veterans Administration Hospital or Duke University Medical Center for at least one episode of recurrent or marginal ulcer from the years 1951 through 1980. Recurrent or marginal ulcer is an ulcer occurring in a patient previously treated surgically for peptic ulcer disease. Most recurrent ulcers were located at or near anastomotic sites of gastroenterostomy (marginal ulcer), or were recurrent duodenal or antral ulcers after vagotomy and drainage or Billroth I procedures. We have excluded from this series any patients with gastrinoma or reflux alkaline gastritis. Follow-up data on patients were obtained either by subsequent admissions or mailed patient questionnaires, or by obtaining outside medical records or contact with referring physicians. Statistical analysis of data was performed using Chi square or Student's t-test.

Results

Original Ulcer Disease

Patient records were analyzed for details concerning the initial presentation of peptic ulcer disease and the original ulcer operation. The original size of the patient population with ulcer disease from which this group of 144 males and 22 females was derived is unknown, as many patients had initial treatment elsewhere. Table 1 shows the anatomic distribution of initial ulcers. More females than males had gastric ulcers, while six patients had both gastric and duodenal ulcers initially, and two patients had jejunal ulcers after previous operations for

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TABLE 1. Location of Original Ulcer

	Duodenal	Gastric	Pyloric	Gastric and Duodenal	Jejunal	
Male	117	16	4	6	1	144
Female	10	9*	2	0	1	22
						166

* p < 0.01.

disease other than peptic ulcer. Figure 1 illustrates the chronologic distribution of first-ulcer operations from the marginal ulcer population, emphasizing the decline in the number of patients requiring operation for peptic ulcer who later developed a recurrence. The population was also analyzed for associated disease, as shown in Table 2.

Initial ulcer operation was divided into four general categories: resection only, vagotomy and drainage, vagotomy and resection, and drainage only (Table 3). There was a declining use with time of resection alone as treatment for ulcer disease. Resections composed 80% of operations in the 1950s, compared with 33% in the 1970s. Gastroenterostomy alone was commonly performed prior to 1930 but was abandoned because of the high incidence of recurrence.¹ No patient in this series received this operation after 1950. Vagotomy and resection and vagotomy and drainage composed a greater percentage (24% and 42%, respectively) of procedures in the 1970s than in the 1950s (0% and 8%).

Symptom-Free Interval

The time from the initial operation until the development of recurrent ulcer symptoms was recorded (Table 4). There was a significantly longer symptom-free interval for patients developing a recurrence after drainage procedure only, as has been shown in other series.²⁻⁸ In addition, patients receiving vagotomy and resection, or resection with Billroth I anastomosis exhibited a significantly shorter symptom-free interval when compared with those receiving Billroth II procedures. The average symptom-free interval for all patients was 3.7 years.

First Marginal Ulcer

Marginal ulcer was documented by one or more of the following: appropriate and positive findings on upper GI series, endoscopy, surgical exploration, or pathology specimen. The distribution of patient age at the time of the first marginal ulcer is shown in Figure 2, reflecting the expected peak in the fourth through sixth decades. The average age was 48.0 ± 1.05 (mean ± SEM) years for males, 56.0 ± 3.37 years for females, and 49.0 ± 1.04 years for the entire group, ranging from 18 to 83 years. Figure 3 demonstrates that, while the treatment of marginal ulcers in our hospitals peaked in the late 1960s, a substantially decreased frequency occurred subsequently. An average of 12 patients per year underwent surgical treatment for marginal ulcer from 1975 to 1979.

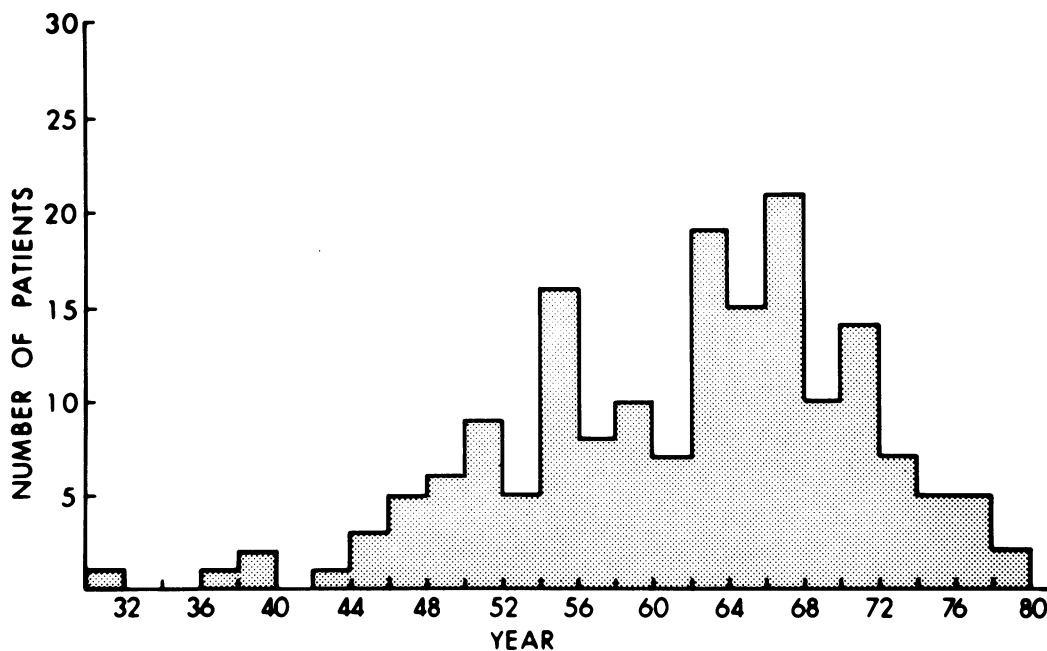


FIG. 1. Year of original operation for peptic ulcer.

All patients in this series developed at least one marginal or recurrent ulcer, but 27 had a second occurrence, seven a third, and one each a fourth and fifth episode. Table 5 reflects these data, with patients grouped according to initial ulcer operation. The highest frequency (25%) of second marginal ulcers was found in patients originally undergoing vagotomy and resection, while the lowest frequency occurred in the vagotomy and drainage group (8.2%).

Symptoms and Location

The symptoms of recurrent ulcer include pain, hemorrhage, obstruction, and perforation (Table 6). The 41% incidence of hemorrhage as a primary symptom is about twice that seen in patients initially presenting with peptic ulcer disease, while the perforation rate of 1% is much lower than that for the original disease.^{9,10} It should be noted that 10% of patients had multiple ulcers at the time of first recurrence.

The majority of recurrent ulcers occurred at either the margins of gastroenterostomy anastomoses, in the efferent loop of jejunum, or in the duodenum, with some in the intact antrum, as shown in Table 7. The 20 ulcers listed as "stomach just proximal to anastomosis" occurred within 1 cm of the anastomosis, but jejunal ulcers with an edge on the gastric side less than 1 cm from the suture line were classified under the "at anastomosis" category.

Diagnosis

Although almost all recurrent ulcers were confirmed by either surgical findings or endoscopy, the initial diagnosis was often made by upper GI series. Records revealed that GI series achieved a 71% sensitivity (106 positive of 150 tested) in diagnosing marginal or recurrent ulcer, while endoscopy had an 85% sensitivity (67 of 79 tested).

Many patients with recurrent ulcer, particularly those in the later years of this study, were evaluated for Zollinger-Ellison syndrome. Table 8 shows represen-

TABLE 2. Concomitant Disease

Disease	
Alcoholism	29
Arteriosclerosis	19
Urinary tract disease	17
Hypertension	11
Psychiatric problems	10
Emphysema	9
Gallbladder disease	9
	104

TABLE 3. Operations for Peptic Ulcer

Operation	Number of Patients
Resection	
Billroth II	79
Billroth I	11
Vagotomy and drainage	
Gastroenterostomy	34
Pyloroplasty	15
Vagotomy and resection	
Billroth II	11
Billroth I	9
Drainage only	7
	166

tative data for 25 such patients prior to surgery for recurrent ulcer. The average serum gastrin level in patients having undergone vagotomy and drainage is significantly higher than that in patients with gastrectomy, as expected. Stimulation tests (secretin or calcium infusion) on all patients tested were negative for gastrinoma, however.

Treatment

The variety of operations performed for recurrent ulcer was greater than the number of standard procedures for initial peptic ulcer. The procedures were intended to reduce acid formation or to correct other abnormality *e.g.*, anastomotic stricture.

Table 9 gives the distribution of surgical procedures for recurrent ulcer, grouped according to initial operation. The operations grouped under "other" included simple revisions of gastroenterostomy for obstructing ulcer, closure of perforation, oversewing of bleeding sites, creation of Roux-en-Y loops, and conversion of

TABLE 4. Symptom-Free Interval after Ulcer Operation

Operation	Years
Resection	
Billroth II	4.1
Billroth I	2.6
Vagotomy and drainage	
Gastroenterostomy	2.9
Pyloroplasty	3.0
Vagotomy and resection	
Billroth II	3.5
Billroth I	1.8*
Drainage only	8.7*
All patients	3.7

* $p < 0.05$.

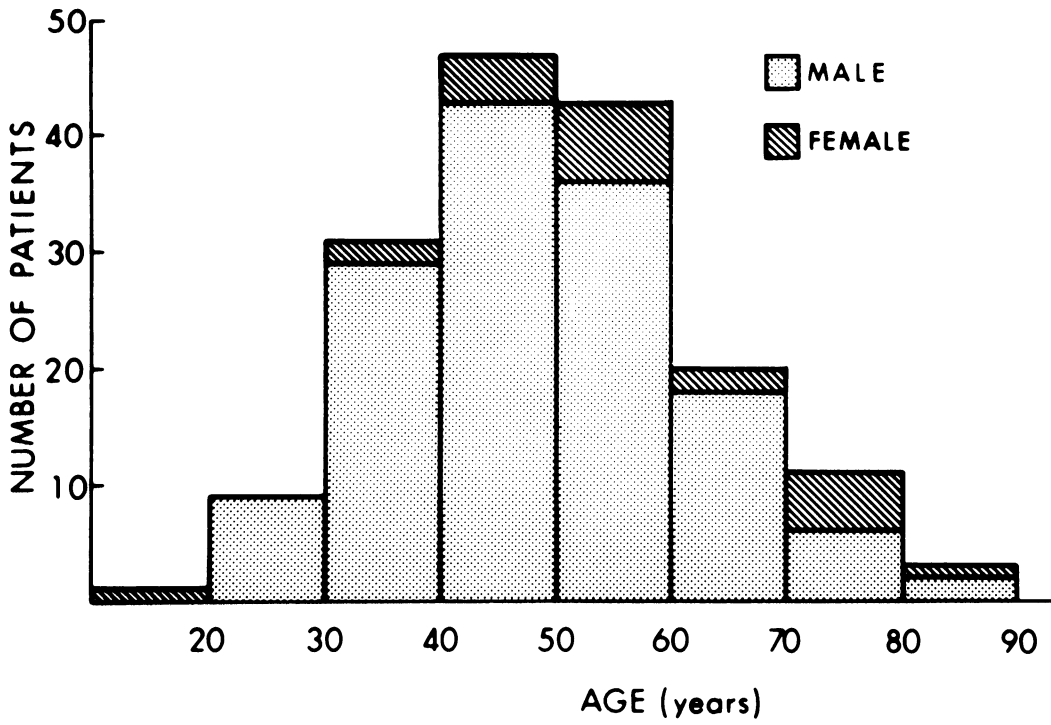


FIG. 2. Patient age at the time of first marginal ulcer.

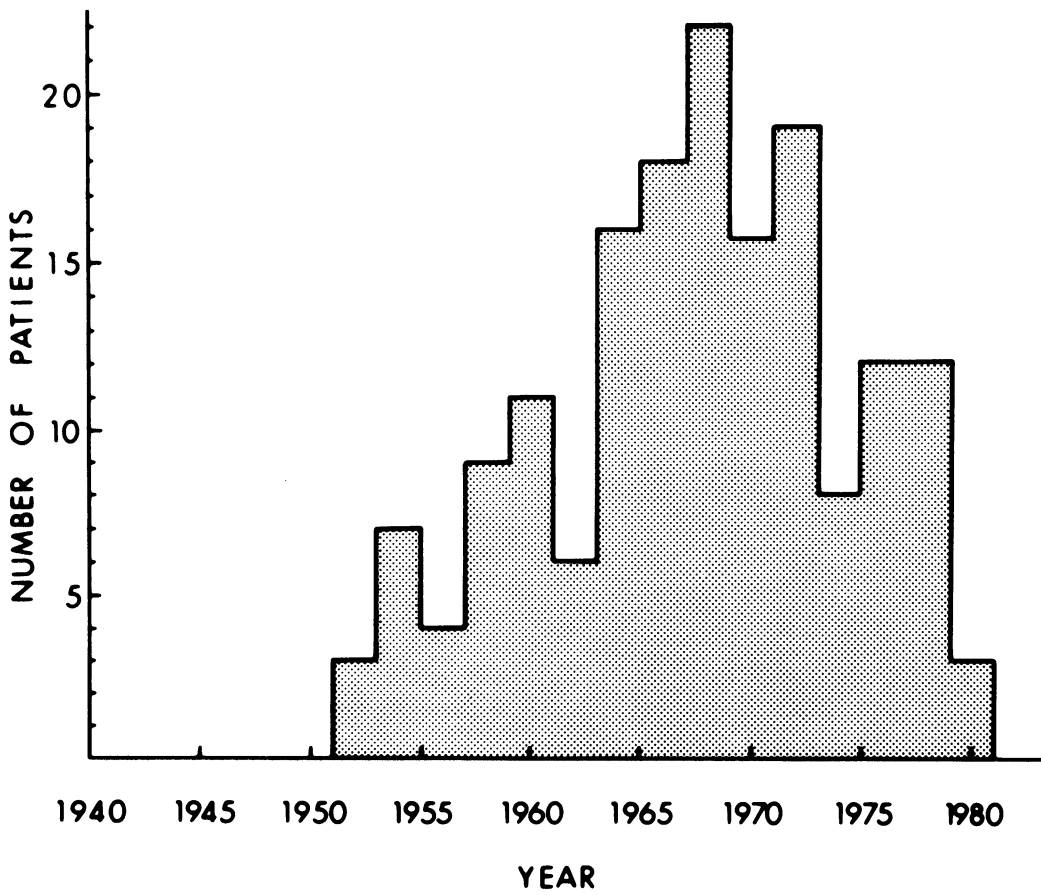


FIG. 3. Year of occurrence of first marginal ulcer.

TABLE 5. Number of Recurrent Ulcers

Operation	1	2	3	4	5	Total
Resection	73	14	3	0	0	90
Vagotomy and drainage	45	2	1	1	0	49
Vagotomy and resection	15	3	1	0	1	20
Drainage only	6	1	0	0	0	7
						166

Billroth I to Billroth II procedures. Thirty-four (20.5%) of the patients were treated medically, a group that included patients who refused further surgical treatment. This group of patients developed seven second episodes of marginal ulcer, for a second-recurrence rate of 20.6%. Sixty-six per cent of patients without previous vagotomy underwent this procedure during the second operation. Over half of those who did not were medically treated (18 of 33). Over 90% of patients receiving two operations underwent some form of resection.

Operative mortality for the 132 operations for recurrent ulcer was 2.3% (Table 10). The three deaths were attributed to renal failure, sepsis, and respiratory failure. Two followed simple closure for suture of a bleeding site and perforation in acutely ill high-risk patients, and a third followed resection and vagotomy. There were 14 significant complications that prolonged hospitalization for at least one week. Three complications required reoperation. The group of patients who received vagotomy as their treatment had the lowest complication rate, 5.1%. Patients undergoing resection or re-resection, and those receiving "other" procedures had significantly increased complication rates.

Second Recurrence

Twenty-seven patients suffered a second episode of marginal or recurrent ulcer, for a second-recurrence rate of 20.4% (Table 11). Twenty-four of those were subsequently treated surgically. Recurrent marginal ulcers developed from one month to nine years later, and the average time from first to second recurrence

TABLE 6. Primary Symptoms of Recurrent Ulcer

Symptom	Number (Percent)
Pain	75 (45%)
Bleeding	68 (41%)
Obstruction	20 (12%)
Perforation	2 (1%)
Other (diarrhea)	1 (less than 1%)
	166

TABLE 7. Site of Recurrent Ulcer

Site	Resection	Vagotomy and Drainage	Vagotomy and Resection	Drainage
Antrum of intact stomach		16		0
Body or stump of stomach	5		3	
Stomach just proximal to anastomosis	13	5	2	0
At anastomosis	30	9	8	1
Afferent loop	6	0	0	0
Efferent loop	28	11	6	3
Bulbar and postbulbar	8	8	1	3

was $1.47 \pm .36$ years. There were no operative deaths from the surgical treatment of second recurrent ulcer. The morbidity rate for the 24 procedures was 12.5% (Table 12).

When second-recurrence rates were analyzed according to prior operation for marginal ulcer, as shown in Table 11, no operation showed particularly good efficacy in preventing a second recurrence. The high frequency of second-recurrence following resection and vagotomy was surprising. More predictable was the very high rate of recurrence following non-acid-reducing procedures of drainage revision only.

The incidence of second recurrent ulcer was analyzed according to decade during which the operation for the first episode of recurrent ulcer was performed (Table 13). There was a significant ($p < 0.05$) decrease in the percentage recurrence rate for second marginal ulcer from the 1960s to the 1970s.

Ultimate Outcome of Treatment

Follow-up of five years or more from the time of original surgery was available for 136 patients (81.9%), while 97 patients had ten or more years follow-up (58.4%). The average length of follow-up was 12.3 years.

Table 14 summarizes the data available on the final condition of the patients three or more years either after their last surgical procedure or, in the case of medically treated patients, from the date of their first recurrent ulcer. Patients who died or were lost to follow-up prior

TABLE 8. Postoperative Serum Gastrin Levels

Operation	Mean \pm SD	Negative Stimulation Tests
Resection (9)	69.6 \pm 60.3	0
Vagotomy and drainage (8)	136.2 \pm 87.6	4/4
Vagotomy and resection (8)	45.5 \pm 36.5	5/5

TABLE 9. Treatment of First Marginal Ulcer

Treatment	Resection	Vagotomy and Drainage	Vagotomy and Resection	Drainage	Total
Vagotomy	45	7	4	3	59
Resection or re-resection	4	18	0	3	25
Vagotomy and resection	15	12	3	1	31
Other	8	3	6	0	17
Medical	18	9	7	0	34
					166

to three years composed 12% of the total population. Most unrelated deaths were due to cancer, cardiovascular disease, or hepatic failure. The four related deaths include the three operative deaths, as well as one additional patient who developed unexplained massive hepatic failure six weeks following radiation treatments for recurrent gastric ulcers.

Of the patients available for adequate follow-up, those with definite recurrent marginal ulcer composed 11.5% of the population. Possible recurrence is defined as symptoms of recurrent ulcer requiring hospitalization or recurrent outpatient treatment, but without documentation of recurrent ulcer. Assessment of significant symptoms was based on medical records or patient answers to questionnaires. Patients qualifying for inclusion in the significant symptoms category had at least one of the following: occasional episodes of epigastric pain, mild occasional diarrhea, mild dumping symptoms controlled by diet, occasional vomiting, or moderate to severe dietary restriction. Based on available follow-up data, our series shows that 58.2% (71 of 122) of patients would achieve an overall satisfactory to excellent evaluation of their surgical (or medical) treatment for recurrent ulcer.

Discussion

While many of the findings in this retrospective study are comparable with those of other series of recurrent or marginal ulcer patients,^{2,3,5,8,11-17} some results did

differ and deserve comment. In terms of the patient population characteristics, there are significantly more original gastric ulcers (15%) than expected (3-5%).^{2,11,12} However, further analysis of this category reveals a very high incidence of gastric ulcer in the female segment of the population (64%). In addition, the male veteran population, composing 90 of the 166 cases in this series, had a gastric ulcer rate of 14.5% in the original pool of patients with ulcer disease.⁹ This adult veteran population, with its high incidence of alcoholism, predisposes to the risk of ulceration being confused with alcoholic gastritis. However, our reliance on firm diagnostic criteria was intended to avoid any such confusion.

Although the 71% sensitivity rate of upper GI series is low, such x-ray examinations may still serve as an important tool in the diagnosis of recurrent ulcer, despite previous claims to the contrary.¹⁵ In addition to revealing some ulcers, GI series helps to evaluate other important issues, such as gastric emptying. Advancements in endoscopic techniques undoubtedly account for the increased sensitivity of this examination in diagnosing lesions, compared with figures given in previous series.^{2,12,18} One of the important diagnoses to rule out in the patient with recurrent ulcer is gastrinoma. Serum gastrin assays have been performed on most of the patients with recurrent ulcer at either hospital since that test became available. Patients with positive results for gastrinoma were excluded from our study. Occult gastrinoma and recurrent ulcer formation may occur with hyperparathyroidism as part of MEN-I syndrome, but no patients in this series had known parathyroid disease. Since some patients in this study were treated before the Zollinger-Ellison syndrome was recognized and before that disease could be diagnosed accurately, it is possible that some unrecognized gastrinoma patients may have been included earlier. In addition to the substantial frequency of known alcoholism in this patient population, the other associated diseases that were found are typical for this population. The one unexpected interesting finding is the high number of patients with associated urinary tract disease.

TABLE 10. Morbidity and Mortality Rates of Surgical Treatment of Initial Marginal Ulcer

Operation	Complications	Mortality Rate
Vagotomy (59)	3 (5.1%)	0
Resection or re-resection (25)	5 (20%)	0
Resection and vagotomy (31)	3 (9.7%)	1 (3.2%)
Other (17)	3 (17.6%)	2 (11.8%)
Total (132)	14 (10.6%)	3 (2.3%)

TABLE 11. Proven Second Marginal Ulcer

Previous Operation	Number	Percent Recurrence
Vagotomy (59)	10	16.9
Resection or re-resection (25)	3	12.0
Resection and vagotomy (31)	6	19.4
Revision drainage (9)	5	55.5
Other (8)	3	37.5
Total (132)	27	20.4

The use of highly selective vagotomy (HSV) as treatment for duodenal ulcer occurred later chronologically,¹⁹ and our methods of case detection disclosed no patients treated initially with HSV.

The frequency distribution of the site of marginal ulceration was different in this series from that of previous series, with the number of ulcers within 1 cm distal to the anastomosis being nearly equal to the number in the efferent loop, while the number in the afferent loop was only one seventh that in the efferent loop.² One group⁸ suggested that perianastomotic or suture line ulceration is less severe than jejunal ulceration. Our data would support the hypothesis that perianastomotic lesions have as great a potential for recurrence as more distally located jejunal ulcer.

The large number of patients with marginal ulcer following resection and vagotomy (as first operation) was interesting. Because vagotomy and antrectomy have the lowest recurrent ulcer rate among operations for peptic ulcer,^{9,20-22} this probably reflects the large number of patients treated with vagotomy and antrectomy. Review of this group of patients revealed incomplete initial vagotomy or inadequate second operation (*i.e.*, gastroenterostomy revision only) as the main contributing factors to recurrence. Other examples of inadequate initial surgical procedures leading to recurrent ulcer formation were well represented in this study. In reviewing the records of patients who received resection alone as their initial operation and developed a second recurrent ulcer, 11 of 15 had less than a two-thirds gastrectomy. Inadequate vagotomy was also quite common, with a second vagotomy procedure being performed in one third (23 of 69) of patients with recurrent ulcer who had had a vagotomy as part of their first definitive operation. There was only one known case of retained antrum as a cause of recurrent ulcer following Billroth II procedure in this series, however. Antral G cell hyperplasia was not recognized in any patient in this study.

The choice of gastroenterostomy as original operative procedure for duodenal ulcer disease is less frequent in

TABLE 13. *Recurrence Rate for Second Marginal Ulcer by Decade*

Decade	Number of Marginal Ulcers	Number of Second Recurrences	Percent
1950s	23	4	17.4
1960s	73	16	21.9
1970s	67	7	10.4*

* $p < 0.05$.

this series than in others.^{2,6,7,13,23,24} Consequently, only one gastrojejunal fistula was present in our series, occurring 29 years after gastrojejunostomy.

A few patients in this series underwent simple "drainage revision" operations for marginal ulcer. These procedures do not reduce acid secretion further and were predictably followed by a high incidence of recurrent disease. These are inappropriate procedures for such a potentially chronic problem.

The group of patients who received only medical treatment for recurrent ulcer had a second recurrent ulcer rate comparable with that of surgically treated patients. However, it should be noted that six patients who were included in the group of 24 patients undergoing a second operation for recurrent ulcer had undergone more than six months of medical treatment and were essentially failures of medical treatment. The advent of cimetidine therapy in 1975 made medical treatment of recurrent ulcer a more attractive alternative²⁵ than previously.^{23,26} Some of the patients in this series did receive cimetidine therapy. The overlap of our study period with the availability of this medication was relatively small, however, and there were insufficient data to evaluate this medication as an alternative to surgical therapy.

Stabile and Passaro¹¹ summarized the results of 3,352 surgically treated cases of recurrent ulcer in which acid-reducing operations were performed, with the overall operative mortality being 3.8%. Combining procedures for first, second, and subsequent marginal ulcers in the present series shows an overall operative mortality of 3/163, or 1.8%. However, it should be noted that two of the operative deaths followed "non-acid-reducing" types of operations, leaving a 0.76% mortality rate for

TABLE 12. *Morbidity, Mortality and Recurrence Following Reoperation for Second Marginal Ulcer*

Procedure	Number	Morbidity	Mortality	Recurrence
Vagotomy	9	1	0	4
Resection or re-resection	2	0	0	0
Resection and vagotomy	2	0	0	0
Revision drainage	9	2	0	3
Other	2	0	0	0
	24	3 (12.5%)	0	7 (29.2%)

TABLE 14. *Long-Term Follow-up after Last Operation*

Definite recurrence	14
Possible recurrence	19
Significant symptoms (no recurrence known)	28
Related deaths	4
Unrelated early death (less than 3 years)	16
Lost to follow-up	28
No significant symptoms	57

definitive ulcer operations only. The mortality rate in the present series for non-acid-reducing procedures was 6.25% (2/32), compared with the 12.1% figure quoted in the literature.¹¹ The recurrence rate of the latter type of operation was 48.4%,¹¹ and the present series shows a rate of 52.4%. The overall recurrence rate for the series of acid-reducing operations was 18.3% (24/131), higher than the average of 12.6% from previous studies.¹¹ The only death following an acid-reducing operation came after a vagotomy and resection, the procedure that, according to others, has the highest mortality rate in the literature (7.9%).¹¹

Previous studies^{2,8,11,12,14-16,26} conclude that ulcer following gastroenterostomy is best treated by adequate gastric resection and vagotomy. Vagotomy is probably the best choice for recurrence following gastric resection. Antrectomy and revagotomy probably should be employed for recurrence following vagotomy and drainage, with revagotomy alone or combined with re-resection giving best results after initial vagotomy and resection.

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DISCUSSION

DR. JAMES C. THOMPSON (Galveston, Texas): Dr. Jones, you say that patients with the Zollinger-Ellison syndrome and with alkaline reflux gastritis were excluded. How many patients were in each group?

One of the things I was surprised at is that if you take your pure duodenal ulcer patients and gastric ulcer patients and add them together, you have 152 patients, of whom 25, or 16%, recurred after gastric ulcer. If you look at most series of recurrent ulcers, that's an extraordinarily high percentage, because, first, ordinarily people with gastric ulcer don't make a whole lot of acid, and, second, patients with gastric ulcer have a fairly normal duodenum, so that the incidence of marginal ulceration after gastric ulcer, which in most hands, I think, is treated by a Billroth I resection, is really quite small.

You don't know, of course, how many DU or GU patients were originally at risk, because you're seeing only those people whose ulcer recurred; but 16% seems high. And the problem is much greater in women. It's double, or triple, the expected recurrence.

I was also surprised at the low percentage of perforation as an indication for operation, since we always consider perforation as a

signal of a virulent ulcer diathesis, and it is from this group that one might expect recurrences.

I'm sure that you and Dr. Schirmer and your colleagues have wondered why marginal ulcer after simple gastroenterostomy takes so long to develop, compared with patients who have vagotomy or patients who have resection. The classic paper on this was by Lewisohn, and he followed patients up to 30 years, at which time recurrences were still developing. On the other hand, patients who at more than two or three years after a vagotomy and drainage, or a vagotomy and antrectomy operation, are probably out of the woods.

This is particularly strange to me, since by many tenets, simple gastroenterostomy should be viewed as an ulcerogenic operation, as it causes a rise in the pH of the antrum, and, thereby, must interfere with the acid inhibition of gastric release. I wondered what your current thoughts are on this, since you've probably thought more about it than anybody else.

Last, I'd just like to say that we subscribe to your program for treatment of recurrent ulceration, which is, in turn, similar to that outlined by Stabile and Passaro. We feel strongly that every patient with a marginal ulcer should have a vagotomy and resection, primary