Akademisk avhandling som med vederbörligt tillstånd av Medicinska fakulteten vid Umeå Universitet för avläggande av medicine doktorsexamen kommer att offentligen försvaras i Samhällsvetarhuset, sal D, Umeå Universitet, måndagen den 20 mars 1978, kl 09.15.

Sammanfattningen baseras på följande rapporter, till vilka kommer att refereras med siffrorna I-V.

I: The development of mucosal changes after gastric surgery for ulcer disease.
   K-G Janunger, L Domellöf & S Eriksson.

II: Lipid islands in the gastric mucosa after resection for benign ulcer disease.
    L Domellöf, S Eriksson, H F Helander & K-G Janunger.

III: Gastric polyps and precancerous mucosal changes after partial gastrectomy.
    K-G Janunger & L Domellöf.

IV: CEA reactivity in the gastric mucosa after partial gastrectomy.
    K-G Janunger, L Domellöf, J Lindgren & P Sipponen.
    Sänd för publicering.

V: The risk for gastric carcinoma after partial gastrectomy.
   L Domellöf & K-G Janunger.
ABSTRACT


The development of benign and malignant mucosal changes in the gastric remnant were studied early (1-3 years) postoperatively in 55 patients and late (10-24 years) postoperatively in 336 of 676 patients subjected to partial gastrectomy for ulcer disease.

Chronic gastritis with atrophy, intestinal metaplasia and cystic dilatation of the gastric glands was found early postoperatively with the same prevalence in gastric and duodenal ulcer patients. Whereas the prevalence of atrophy, and of acute and chronic gastritis was the same both early and late postoperatively, the prevalence of intestinal metaplasia, cystic dilatation and lipid islands increased with time. The prevalence of inflammatory changes late postoperatively was not correlated to sex, age or type of anastomotic procedure.

A significantly increased risk for stump carcinoma was found in male patients more than 12 years postoperatively. No difference correlated to type of ulcer disease or anastomotic procedure could be demonstrated. In duodenal ulcer patients the time interval between operation and diagnosis of carcinoma was independent of age at operation, while in gastric ulcer patients the interval was shorter with increasing age at operation.

Gastric stump carcinomas were found in 12 of the 336 (3.6%) patients examined gastroscopically; four of these were early carcinomas. In four patients with stump carcinoma the correct diagnosis could not be established at the first examination.

Gastric polyps and precancerous mucosal changes were the only macro- or microscopical findings in some cases with already existing non-visible carcinoma.

The CEA immunohistochemical study of the gastric mucosa showed a positive reaction in 10 of 49 patients; 6 of the 10 had carcinoma, precancerous changes or adenomatous polyp. Three patients with diagnosed or later discovered carcinoma had CEA negative reactions. However, the results indicate that there is a correlation between demonstrated CEA content and increased risk for development of stump carcinoma. To evaluate whether this method can be used to identify patients at special risk for development of gastric carcinoma requires further study.

Because of increased risk for stump carcinoma, gastric ulcer patients ought to be examined with gastroscopy from about 10 years after partial gastrectomy, and duodenal ulcer patients from about 15 years, irrespective of the type of anastomotic procedure. Re-examinations ought to be performed every two to four years. In patients with gastric polyps or precancerous mucosal changes re-examinations should be performed earlier, within 6-12 months.
INTRODUCTION

Surgery for ulcer disease - a historical review

A successful resection of the distal part of the stomach and pylorus with gastroduodenal anastomosis was first performed by Theodor Billroth in Vienna in 1881. Billroth’s patient had a carcinoma, but in the same year the Polish surgeon Rydygier successfully performed the same operation for gastric ulcer. Partial gastrectomy with gastro-jejunal anastomosis was used by Billroth in 1884. These basic surgical procedures are usually called Billroth I and Billroth II resections respectively.

Partial gastrectomy first became an accepted method in the treatment of chronic gastric ulcer. Duodenal ulcers, on the other hand, were at the beginning of the twentieth century usually treated by gastroenteroanastomosis. Partial gastrectomy for duodenal ulcer first came into use after the First World War. However, the status of surgical procedures in the treatment of ulcer disease was a matter of discussion during the 1920’s and the 1930’s. Many physicians regarded an ulcer as always curable by conservative measures, and therefore the mortality associated with gastric surgery was deemed unacceptable. This opinion was further supported by the first reports on gastroscopic examination of the gastric remnant after surgery. Using rigid tubes, Schindler studied in 1940 the gastric mucosa and reported severe inflammatory changes in most of the operated patients (65). However, no biopsies were taken and the evaluation was based on inspection alone.

However, in spite of reservations, on the part of some physicians, the clinical results of surgery regarding ulcer recurrence and ulcer symptoms were encouraging, and the surgical treatment of ulcer disease became a widespread and frequently used clinical routine, as illustrated by the large number of operations performed at the Surgical Clinic, Umeå Hospital (Fig 1).
Chronic inflammatory changes of the gastric mucosa are found in increasing prevalence with increasing age in the normal population (38,72,80). The features of the inflammation (chronic gastritis) are infiltration of inflammatory cells between the gastric glands, reduction of the glandular epithelium (mucosal atrophy), fibrosis, metaplasia of the epithelial cells with occurrence of intestinal-like epithelium (intestinal metaplasia) and cyst-like dilatations of the gastric glands (38). The etiology of chronic gastritis is supposed to be of immunological character in patients with pernicious anemia (gastritis type A according to Strickland) (76). Chronic gastritis in non-operated patients without anemia has a more complex nature. Factors such as heredity, diet, alcohol intake, smoking habits, reflux of intestinal contents etc. have been found to be of importance (38).

Already in 1938 Konjetzny stated that gastric carcinoma never occurred in a healthy gastric mucosa (34). Follow-up studies in patients with chronic atrophic gastritis have demonstrated a higher incidence of gastric carcinoma than expected (71,81). Morson (1955) reported intestinal metaplasia to be a frequent finding in the mucosa surrounding gastric
carcinomas (51). A possible correlation between intestinal metaplasia and carcinoma has been discussed by several authors (7,30,35,37,47), and some have regarded it as a precancerous condition (62). However, intestinal metaplasia is also quite often found in the pyloric mucosa of patients with duodenal ulcer (51), a disease that very rarely occurs together with gastric carcinoma (15,64).

Gastric mucosal polyps are considered to be rare in non-operated patients (48), and their occurrence in the gastric remnant after partial gastrectomy has only been described in a few case-reports (8,21,42). Opinions differ as to whether there is a risk for malignant transformation in gastric polyps (4,20,46,50,78). This can be at least partly explained by the lack of a generally accepted classification of such polyps. Several authors have reported malignant transformation within so-called adenomatous polyps in a fairly high frequency (for review see Ming) (48).

Carcinoembryonic antigen (CEA) is by definition an antigen whose occurrence is limited to normal embryonic tissue and, in adult organisms, to malignant tumours. In 1965 Gold and Freedman (18) described a method for preparation of anti-CEA antiserum. CEA was initially supposed to be a tumour-specific antigen (19), but later the occurrence of CEA in both malignant and non-malignant tissue has been described by several authors (for review see Martin et al) (45). In the gastric mucosa CEA has been demonstrated by immunohistochemical and immunofluorescence methods in carcinomas and in the mucosa with intestinal metaplasia (12). However, recently it has been demonstrated that the CEA reactivity found in the non-cancerous mucosa mainly was attributable to a normal cross-reacting antigen (NCA2) (6). The occurrence of CEA reactivity has not been studied with highly specific antisera (absorbed with NCA2) in patients regarded to have increased risk for gastric carcinoma; e.g. patients with pernicious anemia, chronic atrophic gastritis or after partial gastrectomy.

Postoperative mucosal changes

The first studies on postoperative mucosal changes were performed by in-
spection through a rigid tube. Histological examination of the gastric mucosa became possible after the construction of biopsy capsules, developed by the end of the nineteen-forties by, among others, the Swedish gastroenterologist Tomenius. Several studies on the postoperative histological changes have been performed (23,37,40,68,83), but the biopsy capsule method permits only one biopsy to be taken blindly from the gastric remnant, and McDonald (1967) claimed that the mucosal changes caused by gastric surgery were not completely elucidated (44). Using fibre optic instruments with forceps biopsy equipment, it is now possible to take multiple biopsies under visual control. The studies performed with this new technique have either included only duodenal ulcer patients (17,54,67,70) or have disregarded the ulcer disease (56,74). Further, the mean observation times have been relatively short. Thus, our present knowledge about the development of mucosal changes after partial gastrectomy is still incomplete.

**Gastric resection and carcinoma**

Partial gastrectomy was long considered to be a prophylaxis against gastric carcinoma simply because it removes the most frequent site for carcinoma, the antrum. Although Balfour in 1922 reported four cases of carcinoma occurring after partial gastrectomy (2), a possible connection between the surgical procedure and the later carcinoma was not systematically studied until the 1950’s. To exclude carcinomas present at the time of operation, most authors agree that only carcinomas discovered more than 5 years after the operation for ulcer disease are considered as so-called stump carcinomas (9).

Numerous clinical reports of stump carcinoma have been published (for review see Dahm & Rehner, 1975) (9). However, comparing the frequencies of carcinomas found after gastric surgery with those of carcinomas found in non-operated patients provides no information about a possible increased risk for stump carcinoma. The frequency of stump carcinoma in autopsy series, however, suggests that there is an increased risk (26, 75), but because of bias in the selection of patients subjected to autopsy, this hypothesis must be verified by other methods. Long-term
follow-up studies, that are published, also suggest an increased risk for carcinoma long after operation (25,36). However, in only a fraction of patients were the diagnoses definitely verified, and an overestimation of the risk for carcinoma can, therefore, not be excluded. This criticism also applies to later studies, in addition to the fact that carcinomas discovered within 5 years after operation have been included (24,53). Thus, a conclusive answer to the important question whether partial gastrectomy implies an increased risk for carcinoma demands further study.

The prognosis of stump carcinoma is regarded as poor (9), mainly because of late diagnosis, as the gastric stump is an unrewarding field for X-ray examination (1). However, fibre optic gastroscopy has improved the diagnostic possibilities, and cases of early gastric stump carcinomas have been described and the value of gastroscopic examination emphasized (13,57,61). The clinical value of a systematic gastroscopic follow-up of operated patients, however, has not been estimated. Furthermore, the diagnostic accuracy in gastroscopy with multiple forceps biopsies has not been controlled by systematically repeated examinations in the operated patients.

AIMS OF THE PRESENT STUDIES

As outlined above, our present knowledge about the development of benign mucosal changes and the frequency of carcinoma found after partial gastrectomy is still incomplete or inconsistent. Further, the diagnostic accuracy in gastroscopy with forceps biopsies in the gastric remnant, and the clinical value of a systematic follow-up of operated patients, have not been evaluated.

The aims of the present studies, therefore, were:

1: to study the occurrence of macro- and microscopical mucosal changes in the gastric remnant early and late after gastric resection, with special regard to initial ulcer disease and anastomotic procedure
2: to study the prevalence of carcinoma of the gastric remnant and the
time interval between operation and diagnosis of carcinoma with respect to ulcer disease and age at operation
3: to evaluate the possibilities of an early diagnosis of stump carcinoma through systematic gastroscopic follow-up of operated patients and to evaluate the diagnostic accuracy
4: to investigate whether any macro- or microscopical findings can be used as early indicators of increased risk for carcinoma
5: to investigate whether the presence of carcinoembryonic antigen (CEA), as demonstrated by immunohistochemical methods, is correlated to an increased risk for development of stump carcinoma
6: to define a possible risk group and to develop a schedule for the clinical follow-up of operated patients.

MATERIAL

Patients operated for benign ulcer disease at the Surgical Clinic, Umeå Hospital, have been studied early (1-3 years) and late (10-24 years) postoperatively after Billroth I and Billroth II resections. The gastroscopic follow-up was started in 1973 and is still in progress; therefore the number of patients included in the first papers (I and II) is less than in the later (III, V).

Patients examined early postoperatively (I,II): See Table I.
43 patients (18 gastric ulcer (GU), 23 duodenal ulcer (DU), 2 pyloric ulcer) operated according to Billroth I and 14 (4 GU and 10 DU) operated according to Billroth II have been gastroscopically examined 1-3 years postoperatively. Only patients with GU type I according to Johnson (28) were included.

Table I. Patients available for examination early (1-3 years) postoperatively

<table>
<thead>
<tr>
<th></th>
<th>GU</th>
<th>Mean age ± SD</th>
<th>DU</th>
<th>Mean age ± SD</th>
<th>Pyloric ulcer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billroth I</td>
<td>18</td>
<td>59.1 ± 7.5</td>
<td>23</td>
<td>55.0 ± 14.3</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>Billroth II</td>
<td>14</td>
<td>68.5 ± 9.5</td>
<td>10</td>
<td>59.1 ± 16.9</td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>
Table II. The initial series and patients examined late postoperatively. The examinations were performed in the Billroth I group 10-23 years (mean 13.1) and in the Billroth II group 15, 20, and 24 years (mean 20.6) postoperatively. Mean age is calculated for age at operation in the initial series and age at examination in the examined series for the patients with gastric ulcer (type 1 according to Johnson) (28) and duodenal ulcer.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>GU</th>
<th>Mean age ± SD</th>
<th>DU</th>
<th>Mean age ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billroth I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial series</td>
<td>188</td>
<td>111</td>
<td>77</td>
<td>99</td>
<td>54.3 ± 11.9</td>
<td>70</td>
<td>46.2 ± 13.8</td>
</tr>
<tr>
<td>Examined series</td>
<td>108</td>
<td>61</td>
<td>47</td>
<td>58</td>
<td>63.5 ± 9.8</td>
<td>39</td>
<td>58.6 ± 12.1</td>
</tr>
<tr>
<td>Billroth II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial series</td>
<td>488</td>
<td>370</td>
<td>118</td>
<td>126</td>
<td>50.4 ± 11.8</td>
<td>311</td>
<td>44.0 ± 13.1</td>
</tr>
<tr>
<td>Examined series</td>
<td>228</td>
<td>175</td>
<td>53</td>
<td>44</td>
<td>65.0 ± 9.4</td>
<td>147</td>
<td>60.0 ± 10.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial series</td>
<td>676</td>
<td>484</td>
<td>193</td>
<td>225</td>
<td>52.3 ± 11.9</td>
<td>381</td>
<td>44.5 ± 13.1</td>
</tr>
<tr>
<td>Examined series</td>
<td>336</td>
<td>236</td>
<td>100</td>
<td>102</td>
<td>64.2 ± 9.6</td>
<td>186</td>
<td>59.8 ± 10.7</td>
</tr>
</tbody>
</table>
Patients examined late postoperatively (I, II, III, IV, and V): See Table II.

The initial series of patients operated according to Billroth I (1952-1956) consisted of 188 patients (111 male, 77 female) of which 108 (61 male, 47 female) have been examined. The initial Billroth II series consisted of 488 patients (370 male, 118 female) and of these 228 (175 male, 53 female) have been examined. Prior to the examination late postoperatively, 198 patients had died. Information about time and cause of death in these patients was received from the local official registrar.

6 patients operated for gastric stump carcinoma at the Surgical Clinic, Umeå Hospital, have in paper V been included together with the patients with stump carcinoma found during this follow-up to study the influence of initial ulcer disease on the time interval between operation and diagnosis of carcinoma.

Non-operated patients:

In order to study the prevalence of lipid islands in a clinical series of non-operated patients, the findings in 286 consecutively examined patients over 40 years of age were used (II).

To compare the prevalence of gastric polyps in operated and non-operated patients, 407 consecutively examined non-operated patients over 40 years of age have been studied (III).

methods

Gastroscopic examination: The operated patients living in the county of Västerbotten were offered the gastroscopic examination. The patients were examined physically and gastroscopically by either of two endoscopists with special interest in these patients. The gastroscopies were performed with Olympus GIF-D2 or GIF-K instruments. Routinely, 6 forceps biopsies were taken from the stoma and 6 from the fundus. From mucosa with macroscopically different appearance, when present, multiple biopsies were taken separately. Polypectomy with cautery was done in a few suitable cases. The patients were called for re-examination every two
years, earlier when macro- or microscopical findings suggestive of malignancy were present.

**Histological methods:** The biopsy specimens were fixed in a 10% buffered formalin solution and embedded in paraffin. Adjacent sections 4 μ thick were stained with hematoxylin-eosin and with periodic acid-Schiff stain, as mucus stain according to McManus. All histological specimens were examined on two occasions by a single examiner (Dr Sune Eriksson).

The histological criteria for moderate and severe atrophy and the criteria for mild, moderate and severe chronic gastritis are demonstrated in Fig 2.

**Ultrastructural studies** of gastric biopsy specimens were performed in 5 patients with lipid islands after gastric surgery and in 5 normal controls. The fixation and staining procedures are described in detail in paper II.

**Immunohistochemical methods:** CEA was purified from liver metastases of colon carcinoma according to Thomson (77). The antiserum to CEA was prepared in rabbits. The staining of CEA in the histological sections was accomplished with a three-layer bridge immunoperoxidase method described by Primus et al (59). The methods are detailed in paper IV.

**Statistical methods:** As 70.7% of the patients are still living, the frequency of carcinomas found cannot be compared with the figures in official death rate statistics. Therefore we have calculated the expected number of gastric carcinomas in a non-operated population of the same age and sex distribution, using the normal probabilities obtained from "Cancer Incidence in Sweden". Because of the higher incidence of carcinoma in the county of Västerbotten, a regional adjustment was made with a factor of 1.37 for males and 1.33 for females. A bias in the comparison between the normal population and the operated patients was also compensated for by the assumption that the stump carcinomas were diagnosed 5 years earlier than carcinomas in the general population, because of the gastrosopic follow-up.
Fig 2: a) Body mucosa with mild chronic gastritis (slightly increased number of lymphocytes and plasma cells superficially). b) Body mucosa with moderate chronic gastritis and moderate atrophy. Moderately increased number of inflammatory cells and reduced amount of body glands. c) Body mucosa with severe chronic and acute gastritis. Lymphocytes, plasma cells and granulocytes abundant in superficial as well as deep layers of the mucosa. d) Body mucosa with severe atrophy - only solitary body glands preserved. The glands are cystically dilated (H-E x 115).
Stalsberg and Taksdal (75) presented a hypothesis that an increased risk for carcinoma in operated patients is found only more than 15 years postoperatively. We analysed our material and found an identical risk in the period 9-11 years postoperatively. Thus we have studied 3 sub-periods, namely 0-8, 9-11, and 12 years and more postoperatively. The probability that an operated male patient will develop a stump carcinoma during one year of the last sub-period was estimated as a function of age. A maximum likelihood estimation was performed under the restriction of non-decreasing probability with increasing age (3).

RESULTS AND COMMENTS

The development of benign mucosal changes after partial gastrectomy (I and II)

The patchy distribution of the mucosal changes in the stomal region was demonstrated by individual evaluation of the 6 biopsies taken in 24 Billroth II operated patients. In 50% of the patients more than one degree of atrophy was found and in 37% two or even three different degrees of chronic gastritis. This patchy distribution has been described (44) but not previously considered when comparing postoperative mucosal changes. Because of the variation among individual biopsies, the different degrees of atrophy and chronic gastritis were not compared separately in this study.

In DU patients, examination of the proximal border of the resected specimen revealed almost normal body mucosa. In contrast, more pronounced inflammatory changes were found in the GU patients. However, after periods of up to 3 years the biopsy findings revealed no statistically significant difference between DU and GU patients. This is contrary to the findings recently reported by Pulimood et al (59). However, their shorter mean observation time may explain the different result. If chronic inflammatory mucosal changes are of importance for the development of gastric carcinoma, our findings may explain why several investigators have found stump carcinoma with the same prevalence after resection for either gastric or duodenal ulcer (16,36,41,65,75). This is remarkable, as gastric carcinoma very rarely occurs together with duodenal ulcer (15,64).
Cystic dilatation of the gastric glands and intestinal metaplasia were found in a higher prevalence late postoperatively than early (the data regarding intestinal metaplasia in DU patients were not fully significant). This progress of degenerative mucosal changes after partial gastrectomy has not been reported earlier, and invalidates the opinion that patients with intestinal metaplasia should be subjected to partial gastrectomy (62).

Influence of the type of anastomotic procedure on the mucosal changes was found only with regard to the prevalence of cystic dilatation of the gastric glands late postoperatively. The Billroth II-operated patients showed a significantly higher prevalence, which may reflect the longer mean observation time in these patients. There was no relationship between sex or age factors and the mucosal changes seen late postoperatively. In the non-operated patients chronic gastritis was found with higher prevalence in older patients, without sex difference (38,72,80). Our findings indicate that operation per se causes the more severe long-term alterations, masking the effects attributable to age.

Lipid islands, visible as small (seldom more than 5 mm) white to yellow-white patches in the gastric mucosa, were studied in operated and non-operated patients (II). Histologically these patches consisted of foam cells beneath the surface epithelium; in frozen sections they stained intensely with scarlet red, indicating the presence of lipid. No mitotic figures or polymorphism were found. In serial sections, the mucosa surrounding lipid islands showed chronic gastritis and intestinal metaplasia, but there were few inflammatory cells within the lipid islands. Ultrastructural study of the islands revealed numerous electron-lucid spheres mainly in the cytoplasm of macrophages and in a few endothelial cells. Within 3 years postoperatively, lipid islands were rare findings (1.8% in Billroth I-operated patients, 6.2% in Billroth II-operated). Their prevalence increased with time after operation, and they were found in 59.5% 23 years after Billroth II resection. No differences dependent on sex, age, original ulcer disease or anastomotic procedure could be found. In the non-operated controls, with comparable age, lipid islands were found in 6.3%. All of these patients had varying de-
degrees of chronic gastritis, and at gastroscopy there was visible reflux of intestinal content.

The etiology of lipid islands is unknown, but their occurrence only in diseased mucosa has been pointed out (14), and is in accordance with our findings. Hyperlipidemia has been suspected as an etiologic factor (43), a relationship we have not been able to verify. Absorption of micellar lipid has been demonstrated in human gastric mucosa with intestinal metaplasia (63,73), and this seems to be the most likely explanation for the lipid accumulations beneath the mucosal cells that constitute the lipid islands. In the gastric remnant the absence of pyloric function permits intestinal micellar fat to come into contact with the gastric mucosa.

The occurrence of lipid islands after gastric surgery has not been previously reported. The high prevalence (about 60%) found late after partial gastrectomy may, in fact, be even higher, as small lipid islands are easily overlooked at gastroscopy. It is important to be aware of their occurrence in the gastric mucosa, as they can both macro- and microscopically be misinterpreted as small carcinomas (22,29). A high prevalence of lipid islands in non-operated persons has been reported from Japan (32), a country with an extremely high incidence of gastric carcinoma. We have also found lipid islands in several cases of carcinoma, but whether these islands are of any etiological importance for the development of carcinoma remains to be determined.

Gastric polyps and precancerous mucosal changes after partial gastrectomy (III)

Gastric polyps were found in 8.9% (30 of 336) of the operated patients, which is about twice the prevalence found in the non-operated control group (4.9% of 407) with comparable mean age. A similar prevalence of gastric polyps in a clinical series has recently been reported (55). The two materials, however, are not completely comparable, as duodenal polyps have been included, and the age distributions are different.
The polyps in our material were classified macroscopically as sessile or pedunculated (Table III). The sessile polyps correspond to type I-III according to Yamada (84) and the pedunculated to type IV. Our classification proved clinically useful, as some of the polyps changed in appearance with regard to the Yamada types over a course of several examinations.

Morphologically the polyps were classified as hyperplastic or adenomatous, in accordance with several authors (27, 46, 48, 50, 78). In addition polyps from which biopsies revealed only granulation tissue were classified as granulation polyps. This type of polyp was only found in operated patients, and in one patient after previous gastroscopic examination with biopsies. Polyps which on biopsy showed the same changes as the surrounding mucosa were classified as hyperplastic. Adenomatous polyps could only be definitively diagnosed after complete removal by cautery or at operation.

Of the operated patients, 30 revealed polyps; in 28 the polyps were sessile and in 2, pedunculated (Table III). Two patients had sessile polyps of granulation type, and 26 of hyperplastic type. However, in five of the patients with hyperplastic polyps, further controls changed the diagnoses (vide infra Diagnostic accuracy).

Table III. The diagnostic findings in the 30 operated patients with gastric polyps. In brackets subgroups according to Yamada (84)

<table>
<thead>
<tr>
<th>Macroscopic appearance</th>
<th>Primary diagnoses</th>
<th>&quot;Final&quot; diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 sessile (I-III)</td>
<td>28 hyperplastic polyps</td>
<td>2 granulation polyps, 1 adenomatous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 precancerous mucosal changes, 3 carcinomas, 21 hyperplastic polyps</td>
</tr>
<tr>
<td>2 pedunculated (IV)</td>
<td>2 adenomatous polyps</td>
<td>2 adenomatous polyps</td>
</tr>
</tbody>
</table>
The two pedunculated polyps were removed by cautery, and histological examination showed both to be adenomatous polyps.

The frequency of polyps in the gastric stump has not been reported before, but our findings indicate that polyps are more frequently found in operated patients than in non-operated persons of comparable age. Health control studies in Japan (79) have yielded a considerably lower prevalence of polyps than we have found in non-operated patients, but the series are not comparable. Hyperplastic polyps are reported to be the most common type in the stomach, comprising 75-90% (46), which is in accordance with our findings in both operated and non-operated patients. However, the frequency of adenomatous polyps found in our series may be an underestimation, as the diagnosis can only be made after complete removal (69), which was done only in a few cases.

Precancerous mucosal changes (See Fig 3) were found in the biopsy specimens of four patients (2 males and 2 females) at examination late after operation, but in none of the non-operated controls. The two male patients were subjected to gastric re-resection after about one year during which repeated biopsies showed persistent precancerous changes. In one patient a macroscopically invisible early carcinoma 8 mm in diameter was found. In the other patient multifocal precancerous changes were found, but no obvious carcinoma. The two female patients have not yet been operated, but are being regularly followed by gastroscopy.

There is no report on the clinical significance of precancerous mucosal changes in biopsies from operated patients. Japanese experience with regular gastric biopsy in what they call "border-line lesions" in non-operated persons indicates that such lesions progress into invasive carcinoma slowly or not at all (52). Our experience with precancerous mucosal changes in biopsies from operated patients is limited, but the finding at operation of an already existing carcinoma prompts us to recommend a careful follow-up if these patients are not operated.
Diagnostic accuracy regarding gastric polyps and carcinoma (III)

In the series of 336 patients examined late postoperatively, 12 carcinomas have been diagnosed, 11 at elective examinations. In 7 patients the diagnoses were correctly made at the first examination. In three patients re-examinations were performed due to the presence of hyperplastic polyps, and after one to two years carcinomas were found. In the fourth patient, gastric re-resection was performed because of precancerous mucosal changes in the biopsies at repeated examinations (vide supra). Further, among the 26 patients with a primary diagnosis of hyperplastic polyp, one patient had an adenomatous polyp and another later revealed precancerous mucosal changes in the biopsies. The latter patient has not yet been subjected to gastric re-resection.

In the non-operated stomach the diagnostic accuracy attained with gastroscopy and biopsy is reported to be 92-99% with respect to carcinoma (11,31). Also in reports on early carcinoma in the gastric remnant the diagnostic accuracy has been regarded as good (57,61). These statements, however, have not been confirmed by systematic re-examination. It has been emphasized that several biopsies should be taken to improve the
diagnostic accuracy (11). In the operated patients, however, we have found that the risk for bleeding is not negligible, and we have therefore limited the number of biopsies from the stoma to six. Our experience with repeated gastroscopies in 193 operated patients is that the diagnostic accuracy is not fully satisfactory: four of eleven carcinomas were not correctly diagnosed at the first examination. Biopsies should always be taken irrespective of macroscopical findings, as stump carcinomas often are not visible, an experience recently reported by other authors (57).

Opinions differ as to the relationship between gastric polyps and carcinoma (48), although many authors agree that adenomatous polyps often undergo malignant transformation and occur together with carcinoma in a high frequency (46.78,82). This opinion is supported by our finding of an adenomatous polyp adjacent to a stump carcinoma. Hyperplastic polyps are not regarded as associated with increased risk for carcinoma. However, Tomasulo (78) reported these polyps to be present in almost 30% of cases of carcinoma. We would emphasize this observation, and call attention to the fact that these polyps may be the only visible evidence of an existing carcinoma.

CEA immunohistochemical study of the gastric mucosa after partial gastrectomy (IV)

For this study 49 patients gastroscopically examined about 20 years after partial gastrectomy were selected: three had gastric stump carcinoma, two precancerous mucosal changes, one an adenomatous polyp and 21 patients had hyperplastic polyps. 22 patients had no macro- or microscopical evidence of malignant or premalignant changes. Biopsies from 5 normal non-operated patients were used as controls.

A positive CEA reaction was found in 10 patients: 6 had carcinoma, precancerous changes or adenomatous polyp. Biopsies from two of these patients showed positive CEA reactions in non-cancerous mucosa 1-2 years before the carcinomas were diagnosed. However, positive CEA reactions were also found in 3 patients without any macro- or microscopical evi-
dence of malignant or premalignant changes. To date, no signs of carci-
noma or precancerous changes have been found in these patients, but the
observation period is short. Three patients with known or later disco-

vered carcinoma had CEA negative biopsies from non-cancerous mucosa.

In biopsies from carcinomas (of the diffuse type according to Laurén)(39)
the CEA reaction was found in the cytoplasm of the malignant cells, but
seemed to vary in intensity from cell to cell. In non-cancerous mucosa,
CEA reactivity was found in the luminal border of the foveolar epithe-

lial cells, while cells deeper in the gastric glands were negative.
Intracellular CEA was not seen, and no correlation to intestinal meta-
plasia was demonstrated, which is in accordance with a recent report (6).

We have used a highly specific anti-CEA antiserum absorbed according to
Burtin et al (6), in order to eliminate normal cross-reacting antigens
(NCA, NCA2). At present, there seems to have been a "false positive" re-
action in four of 49 patients (8%); however, only further follow-up can
disclose true false positive reactions. A false negative reaction was
found in three patients (6%). The anti-CEA titre of our antiserum was
low due to repeated absorption, which may explain the false negative
cases. Our results, however, indicate a correlation between the CEA con-
tent of the gastric mucosa as demonstrated with CEA immunohistochemical
methods and the risk for malignant transformation.

Statistical evaluation of the risk for stump carcinoma (V)

The initial series consisted of 676 patients operated according to Bill-
roth I or Billroth II more than 10 years earlier (Table II). 198 patients
had died prior to the follow-up examination, three because of stump car-
cinoma verified at autopsy. In the group of 336 examined patients, 11
with stump carcinoma have been found (one additional after paper V was
completed). 142 patients still alive (27%) were not examined because
they had left the county, were too old, or declined the examination.

In the Billroth I group, 4 carcinomas were found, compared to 1.6 ex-
pected, and in the Billroth II group the corresponding figures were 10
and 6.6 respectively. This implies no statistically significant difference in the risk for carcinoma with respect to operation procedure.

The comparison of observed and expected numbers of carcinomas has been carried out in three different postoperative subperiods as described under Statistical methods (Fig 4). In male patients the expected number of carcinomas during the first 3 years postoperatively was 2.5, the observed was 0 (zero). 9-11 years after the operation the expected number was 1.7 and the observed 2. 12 years and more postoperatively the expected number was 4.0, or 5.7 with the assumption that the stump carcinomas were diagnosed 5 years earlier due to gastroscopic follow-up. The observed number is 11, and compared to 4 the difference is statistically significant (p=0.006), but is not fully significant compared to 5.7 (p=0.063). In the female patients the observed number in the last subperiod is 1, which is the number expected.

![Fig 4. Expected and observed number of patients with carcinoma.](image)

Note: In the group ≥12 years postoperatively two numbers of expected carcinomas are given because of bias, caused by earlier diagnosis due to gastroscopy. The lower number corresponds to normal conditions and the higher to the condition that the carcinomas are discovered 5 years earlier than normal. ns = not significant.
The question whether gastric resection implies a greater risk for later carcinoma is still a matter of dispute (33,58), and can only be definitely answered by long-term studies of complete operation series. Stalsberg and Taksdal (75) found an increased risk for stump carcinoma only more than 15 years postoperatively, and possibly a decreased risk before that time. An increased risk long time after the operation can be masked by a decreased risk during the first postoperative period if a comparison of expected and observed number of carcinomas is performed for the entire postoperative period. Therefore we analysed our material to find a period with normal risk. This appeared to be 9-11 years postoperatively. The increased prevalence later is illustrated by Fig 5.

With the assumption that the stump carcinomas were diagnosed 5 years earlier than carcinomas in the general population, due to gastroscopic follow-up, the difference between expected and observed numbers is not fully significant. A 5-year interval is selected for statistical reasons: this assumption, however, is much exaggerated, as three patients had died prior to the follow-up, seven had advanced carcinomas and only three male patients had stump carcinomas not causing symptoms at the time of diagnosis. Therefore the influence of the follow-up is much less and the increased risk is regarded as real. In addition, one more patient with stump carcinoma has been found after the statistical calculations were completed.
Stump carcinoma is reported to be rare in female patients (9), but most authors have not related this observation to the sex ratio in the initial operation series. Possible sex difference cannot, therefore, be evaluated. Krause (36), however, compared the expected and observed number of carcinomas in female patients and found five verified (and another four not verified) compared to the expected 4.7. These differences are not statistically significant. Thus, neither his study nor ours indicates that operation increases the risk of carcinoma in female patients, but neither do the data at present exclude the possibility of increased risk.

Studying the influence of type of ulcer disease and age at operation on the time interval between the operation and the diagnosis of carcinoma, we found that the interval was shorter in older patients operated for gastric ulcer. In duodenal ulcer patients, however, the age at operation had no influence on the time interval. This finding may explain why several authors have reported a higher frequency of stump carcinoma in gastric ulcer patients than in duodenal ulcer patients in series with a short mean observation time (5,10,25,49,53). If chronic gastritis is of etiological importance for the development of carcinoma, this difference in time interval may be explained by the finding in paper I that gastric ulcer patients already at operation have advanced, probably long-standing, inflammatory changes in the body mucosa. In duodenal ulcer patients the operation initiates the inflammatory reaction, and therefore the development of carcinoma will be later in these patients. If this assumption is true, a higher prevalence of stump carcinoma is to be expected in gastric ulcer patients than in duodenal ulcer patients. However, since the former are operated at an older age (see Table II), a larger fraction will die from other diseases before the development of carcinoma.

The mean age of the patients with stump carcinoma was 63.4 years (9.3 SD) which is not different from the mean age of all examined patients (63.2 years). The mean age at diagnosis of carcinoma in non-operated patients in the county of Västerbotten is somewhat higher, 67.3 years (12.3 SD). Comparison of the estimated annual incidences of gastric carcinoma among operated and non-operated men living in Västerbotten shows the greatest
difference for operated patients in the younger age groups; the estimates were in the ratio 12:1 for the age group 50-55 years (V). Other authors have found patients with stump carcinoma to be older than non-operated patients with gastric carcinoma (16,24). This difference from our data, however, can probably be explained by the liberal attitude towards gastric resection even in younger persons prevailing during the period at which our patients were operated.

Clinical implications

Our results show that male patients subjected to partial gastrectomy more than 12 years earlier have an increased risk for gastric stump carcinoma. Therefore, these patients ought to be examined by gastroscopy, as no other method offers a reasonable diagnostic accuracy. The carcinoma seems to appear earlier in gastric ulcer patients, and we therefore recommend examination from about 10 years postoperatively. In duodenal ulcer patients it is probably sufficient that the examination is performed at about 15 years postoperatively. The diagnostic accuracy regarding early gastric stump carcinoma is not fully satisfactory (III), and therefore the examinations must be repeated. In patients with gastric polyps or precancerous mucosal changes, we recommend re-examination within 6-12 months, as these findings have proved to be the only visible evidence of an existing carcinoma in a number of patients. In patients without macro- or microscopical findings suggestive of malignancy, examination every two to four years is probably sufficient. Although no study has yet shown an increased risk for carcinoma in female patients, we recommend that these patients also be included until further evidence is collected.

During the last 10 years, partial gastrectomy for ulcer disease has been performed in 40 to 35 (mean 65) patients each year at our clinic. Since the introduction of selective proximal vagotomy (SPV) in duodenal ulcer patients, the number has decreased to about 40 per year. In our experience only about 60% of the patients are available for examination 10 years or more postoperatively. Although 10% of the patients will require re-examination within one year, the total number of gastroscopies in
operated patients probably will not exceed 100 per year at a clinic of comparable size. 1100-1300 gastroscopies are performed each year at our clinic; thus, these patients will account for less than 10% of all gastroscopies.

GENERAL SUMMARY AND CONCLUSIONS

1: Chronic gastritis with atrophy, intestinal metaplasia and cystic dilatation of the gastric glands was found early postoperatively (1-3 years) after partial gastrectomy with the same prevalence in gastric and duodenal ulcer patients. Whereas the prevalence of atrophy, and of acute and chronic gastritis was the same both early and late postoperatively (10-24 years), the prevalence of intestinal metaplasia, cystic dilatation and lipid islands increased with time. The prevalence of inflammatory changes late postoperatively was not correlated to sex, age or type of anastomotic procedure (I, II).

2: A significantly increased risk for stump carcinoma was found in male patients more than 12 years postoperatively. No difference correlated to type of ulcer disease or anastomotic procedure could be demonstrated. In duodenal ulcer patients the time interval between operation and diagnosis of carcinoma was independent of age at operation, while in gastric ulcer patients the interval was shorter with increasing age at operation (V).

3: Gastric stump carcinomas were found in 12 of the 336 (3.6%) patients examined gastroscopically; four of these were early carcinomas. In four patients with stump carcinoma the correct diagnosis could not be established at the first examination.

4: Gastric polyps and precancerous mucosal changes were the only macro- or microscopical findings in some cases with already existing non-visible carcinoma.

5: The CEA immunohistochemical study of the gastric mucosa showed a positive reaction in 10 of 49 patients; 6 of the 10 had carcinoma, precancerous changes or adenomatous polyp. Three patients with diagnosed or later discovered carcinoma had CEA negative reactions. However, the results indicate that there is a correlation between demonstrated CEA content and increased risk for development of stump carcinoma. To evaluate
whether this method can be used to identify patients at special risk for
development of gastric carcinoma requires further study.

6: Because of increased risk for stump carcinoma, gastric ulcer patients
ought to be examined with gastroscopy from about 10 years after partial
gastrectomy, and duodenal ulcer patients from about 15 years, irrespec­
tive of the type of anastomotic procedure. Re-examinations ought to be
performed every two to four years. In patients with gastric polyps or
precancerous mucosal changes re-examinations should be performed earlier,
within 6-12 months.

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