Pancreatic function and the absorption of fat, iron, vitamin B₁₂, and calcium after total gastrectomy for gastric cancer

K. FISCHERMANN, S. HARLY, H. WORNING, AND A. ZACHO

From the Finsen Institute, Department of Surgery, the Finsen Laboratory and the Central Laboratory, Blegdamshospitalet, Copenhagen

EDITORIAL COMMENT Twelve patients who had had a total gastrectomy have been carefully studied. No difference was found in those patients who had had either a Roux or an interposition type of operation.

In the surgical treatment of gastric cancer total gastrectomy may be required. Such an extensive surgical procedure is only justified if the operative mortality is sufficiently low and the patient's general condition after the operation tolerable.

The first patient who survived total gastrectomy was operated upon by Schlatter in 1897. A few months later Hofmann (1898) demonstrated that the patient could be kept in a positive nitrogen balance; he could even obtain retention of nitrogen by administering a high-protein diet.

In recent decades total gastrectomy has been used to an increasing extent in the treatment of gastric cancer. The primary mortality has fallen to acceptable levels: Nakayama (1958) 3.2%; ReMine, Priestley, and Berkson (1964) 16%; Efskind, Bugge-Asperheim, and Helsing (1965) 9.4%. The five-year survival rate has remained constant, between 10 and 12%, but in a few series (Allison, 1963) it is 20%.

Several Scandinavian authors have published studies on total gastrectomy in the treatment of gastric cancer (Holst, 1937; Mikkelsen and Wandall, 1949; Fretheim, 1953; Zacho and Fischermann, 1959, 1961, and 1966; Lewin, 1960; and Efskind *et al.*, 1965). Holst, in particular, must be emphasized as the Scandinavian pioneer of total gastrectomy in gastric carcinoma.

In the Surgical Department of the Finsen Institute 561 patients with cancer of the stomach were treated during the period 1948 to 1963 (Zacho and Fischermann, 1966). In 248 of these cases the tumour was removed, in 102 by total gastrectomy. Total gastrectomy was carried out in cases where the oesophagus as well as duodenum had to be resected

to obtain a minimum distance of 5 cm. from the tumour. Thus, total gastrectomy was only performed on patients having large, widespread tumours in the stomach. The primary mortality of the radical total gastrectomies was 8% in the last five-year period from 1959 to 1963 inclusive and the five-year survival rate is shown in Figure 1.

The primary mortality is so low and the five-year survival rate so high that total gastrectomy must be considered fully justified in treating cancer of the

FIG. 1. Five-year survival among 52 patients who had survived total gastrectomy (Zacho and Fischermann, 1966).

stomach. The general condition and the results of a number of function tests on patients who have had total gastrectomy form the substance of our report.

MATERIALS AND METHODS

Twelve patients who had undergone total gastrectomy for cancer of the stomach were selected at random (Table I). None of these patients had signs of recurrence at the time of the follow-up examination; the follow-up period ranged from six months to 15 years.

TABLE I
SURVIVAL TIME AND TYPE OF OPERATION IN
12 PATIENTS WITH TOTAL GASTRECTOMY

No.	Sex	Age at Operation (yr.)	Type of Operation	Follow-up Time (yr.)
1	♀	70	Roux-Y	15
2	♂	45	Roux-Y	13
3	♂	62	Roux-Y	13
4	♂	67	Roux-Y	12
5	♀	53	Interposition	8
6	♂	49	Interposition	6
7	♂	65	Interposition	4
8	♀	68	Interposition	1
9	♀	73	Interposition	1
10	♂	63	Interposition	1
11	♀	67	Interposition	1
12	♂	56	Interposition	½

In addition to removal of the entire stomach, all had had high vagotomy, and half of them, in addition, partial resection of the pancreas. In four gastrointestinal continuity was re-established by a Roux-Y anastomosis. In the remaining eight an intestinal segment had been interposed isoperistaltically between the oesophagus and duodenum. This segment was taken either from the jejunum as advocated by Longmire and Beal (1952) and Henley (1952) or from the transverse colon as suggested by State, Barclay, and Kelly (1951).

From the time of the operation the patients had been on a high-protein, low-fat diet, which was otherwise composed according to each individual patient's habits and taste. During the same period all the patients had received a permanent supplement of vitamins A, B, and C by mouth and vitamin B₁₂ in the form of Cycobemin intramuscularly 60 µg. every third week, and iron in the form of ferroamine acetic acid (Glycifer).

All the patients were admitted to hospital for the follow-up examination which included thorough questioning regarding symptoms and signs as well as a physical examination.

BLOOD STUDIES Haemoglobin, serum iron, transferrin, calcium, phosphorus, and protein were estimated, and paper electrophoretic separation of the plasma proteins was done.

RADIOGRAPHS The skeletal bones were examined to detect osteoporosis.

ABSORPTION TESTS These were performed for vitamin

B₁₂, fat, iron, and calcium. Moreover, external pancreatic function was investigated.

Vitamin B₁₂ absorption was studied by the Schilling test shortly after the operation in all subjects. As might be expected, it was very low (0.1 %).

Absorption of fat was investigated by determining the average faecal excretion of fat on a diet having a daily fat content of 70g.

Iron absorption was studied in a whole-body counter, the counts being made before and after oral administration of ferrosulphate containing 0.6 µC ⁵⁹Fe as described by Faber and Leroy (1965).

Calcium absorption was studied by daily counting in a whole-body counter following oral administration of 1.9-2.7 µC ⁴⁷Ca in the form of chloride dissolved in water or milk. The seven-day retention was used as a measure of the calcium retention.

Pancreatic function was investigated by the method of Thaysen, Müllertz, Worning, and Bang (1964). A thin tube of polyvinyl was passed down to the ligament of Treitz, in cases with Roux-Y anastomoses to a site just distal to the entero-anastomosis. The situation of the tube was checked radiologically. After the fasting intestinal contents had been collected, the patients were given a standardized liquid meal by mouth, and during the subsequent 80 minutes, fractionated into four 20-minute portions, the intestinal contents were collected. The pH as well as the concentration of the enzymes α-amylase, lipase, trypsin, and chymotrypsin in the aspirates were determined (Worning and Müllertz, 1967).

RESULTS

The patients were subjectively feeling well. They had no postprandial complaints such as nausea, vomiting, or regurgitation. None had dumping. All were able to eat normal portions.

The stools were of normal appearance with no macroscopically visible fat.

We do not aim at the pre-morbid weight, as most of the patients had been overweight before developing gastric cancer (Zacho, Larsen, and Christiansen, 1965), but we aim at an ideal weight.

Table II lists the haemoglobin concentration as well as the serum levels of iron, transferrin, and protein. Two patients had moderate anaemia and a reduced serum level of iron. The serum protein was normal in all cases, and paper electrophoresis showed a normal distribution of protein in all cases.

The absorption of fat was investigated in three of the patients with Roux-Y anastomoses. The average daily faecal excretion ranged from 18 to 55 g. (Table III).

Iron absorption was studied in six patients. All six had a normal haemoglobin concentration at the time of the investigation. In the three patients with a short follow-up period (less than one year) there was an iron absorption of 0.2, 0.7, and 0.8 % which must be considered reduced. In the other three,

TABLE II

SERUM CONCENTRATIONS OF HAEMOGLOBIN, IRON, TRANSFERRIN, AND PROTEIN								
No.	Sex	Age at Operation (yr.)	Type of Operation	Follow-up Time (yr.)	Haemoglobin (g./100 ml.)	Serum Iron (mg./100 ml.)	Transferrin (mg./100 ml.)	Serum Protein (g./100 ml.)
1	♀	70	Roux-Y	15	12.3	0.101	0.258	6.6
2	♂	45	Roux-Y	13	16.3	0.097	0.460	7.0
3	♂	62	Roux-Y	13	11.2	0.035	0.416	6.5
4	♂	67	Roux-Y	12	13.6	0.130		6.6
5	♀	53	Interposition	8	11.1	0.043	0.538	7.3
6	♂	49	Interposition	6	14.9	0.086	0.324	7.3
7	♂	65	Interposition	4	14.2	0.107	0.439	7.0
8	♀	68	Interposition	1	14.4	0.074	0.420	7.2
9	♀	73	Interposition	1	14.7	0.080	0.412	6.4
10	♂	63	Interposition	1	12.9	0.090	0.318	7.6
11	♀	67	Interposition	1	14.1	0.136	0.358	7.1
12	♀	56	Interposition	½	13.0	0.088	0.292	7.1

TABLE III

FAT ABSORPTION IN THREE PATIENTS WITH ROUX-Y ANASTOMOSES			
Patient No.	Anastomosis	Follow-up Time (yr.)	Fat Excretion in Faeces (average g./day)
2	Roux-Y	7	41.8
3	Roux-Y	5	54.8
		7	20.2
4	Roux-Y	4	32.3
		7	17.5

with follow-up periods of from one and a half to 12 years, the absorption was normal (1.5-3 %).

Calcium absorption was studied in all 12 patients. The results are given in Figs. 2, 3, and 4 and in Table IV. The retention of calcium depends to some extent upon the form in which the calcium salt is administered. Retention appears to be at a maximum when it is administered in aqueous solution; the addition of a carrier, or solution in milk reduces the

retention. Figure 5 illustrates the retention in five normal subjects; the seven-day retention is between 12 and 24 %. The retention in patients with Roux-Y anastomoses and with interposition operations is shown in Figures 2, 3, and 4. It is apparent that only two had a seven-day retention below 12 %. In both the follow-up period was less than one year. In Table IV these values are compared with serum calcium, serum phosphorus, Nordin's product (1960), and the result of the x-ray examination of the bones.

One patient had a reduced serum calcium level, a low serum phosphorus level, reduced Nordin's product (1960), and radiologically confirmed osteoporosis, but a normal absorption of calcium. Of the two patients with a low calcium absorption, one had questionable osteoporosis, but both had normal serum levels.

Pancreatic function was studied in nine patients,

FIG. 2. Calcium retention in four patients who received ⁴⁷Ca in water. The dotted lines represent patients with Roux-Y anastomoses and the solid line the retention in one patient who had had an interposition operation.

FIG. 3. Calcium retention in three patients with Roux-Y anastomoses. In these cases ⁴⁷Ca was administered in water to which had been added calcium chloride.

FIG. 4.

FIG. 4. Calcium retention in eight patients in whom total gastrectomy had been followed by interposition of a segment of the small bowel between the oesophagus and duodenum. In these cases ⁴⁷Ca was administered in milk.

FIG. 5.

FIG. 5. Calcium retention in five normals. ⁴⁷Ca was administered in milk.

and the results are given in Table V and Figure 6. The pH in the small intestine, except for the first portion, is significantly higher than in healthy persons with achlorhydria. The concentrations of enzymes are also illustrated in Figure 6. As the enzyme concentrations in a normal population show a positive skew distribution, normalized by logarithmetization (Thaysen *et al.*, 1964), the negative standard deviations in a linear system (Fig. 6) are consequently smaller than the positive ones. This explains the skew position of the mean values in the figure.

TABLE V

pH IN THE INTESTINAL LUMEN DURING DIGESTION OF A FLUID MEAL IN NORMALS WITH ACHLORHYDRIA AND IN PATIENTS WITH TOTAL GASTRECTOMY

Portion of Lumen		N	Mean	S.D.	P
I	Normals	8	6.498	0.404	N.S.
	Total gastrectomy	8	6.250	0.247	
II	Normals	11	6.610	0.375	<0.05
	Total gastrectomy	8	7.110	0.547	
III	Normals	11	6.596	0.479	<0.005
	Total gastrectomy	7	7.517	0.522	
IV	Normals	10	6.560	0.512	<0.005
	Total gastrectomy	7	7.416	0.434	

TABLE IV

SERUM LEVELS OF CALCIUM AND PHOSPHORUS, NORDIN'S PRODUCT, AND RESULTS OF X-RAY EXAMINATION OF SKELETAL BONES

Roux-Y Anastomosis	Serum Ca (mg./100 ml.)	Serum P (mg./100 ml.)	Nordin's Product [Ca] ^a [× P] ^a (4,600–20,000)	Absorbed ⁴⁷ Ca (7-day %)	Osteoporosis
1	8.3	1.4	1,120	37	+
	6.8	1.8	1,019		
2	9.6	2.8	6,936	19	○
3	9.2	3.2	7,974	20	○
4	9.1	3.4	8,711	21	○
Interposition					
5	9.6	4.2	15,606	30	○
6	9.8	3.3	10,249	25	○
7	9.5	3.1	8,239	21	○
8	9.8	3.9	14,315	7–10	○
9	9.7	3.4	10,550	10	○
10	9.7	3.4	10,550	43	○
11	10.3	3.7	14,959	34	○
12	10.0	3.0	9,000	27	○

FIG. 6a, b, c, and d. The concentration of (a) amylase, (b) trypsin, (c) chymotrypsin, and (d) lipase in the four intestinal aspirates in patients with total gastrectomy. The columns indicate the normal concentration (mean $\pm$ 2 standard deviations).

+ Roux-Y anastomosis.

○ Intestinal interposition.

In the normal organism the concentration of enzymes is highest in the portion first collected, while in the subsequent three portions it is stationary. In the patients the concentration of enzymes was lowest in the first portion, increasing in

the subsequent portions. This was least marked with lipase, which was, on an average, significantly reduced in all portions, while the concentrations of amylase, trypsin, and chymotrypsin were reduced only in the first portion and normal in the others.

DISCUSSION

The patients' condition following total gastrectomy depends upon the method of re-establishing the continuity, the composition of the diet, and the prophylactic administration of vitamins, iron, etc.

The previously employed end-to-side anastomoses between the oesophagus and the jejunum, in some cases combined with a Braun anastomosis, cause severe trouble in the form of regurgitation, post-gastrectomy complaints, and weight loss (Bugge-Asperheim and Helsing, Jr., 1965). This method should therefore not be used. Incidentally, Hedenstedt and Heijkenskjöld (1965) have demonstrated that these complaints may be relieved by interposing a jejunal segment between the oesophagus and the duodenum.

In the present study no difference was found between the results in patients with Roux-Y anastomoses and those who had had interposition operations. However, the latter should probably be preferred, as they re-create normal continuity in the gastrointestinal tract, and it is our impression that these patients make a more rapid recovery.

It is well known that total gastrectomy invariably entails steatorrhoea, which may be due to one or more of the following factors: reduced pancreatic function, an unfortunate mixture of food and digestive juices, a rapid passage through the intestine, and an altered bacterial flora in the small intestine.

The enzyme concentration in the intestine is low during the early stage of digestion, just as following subtotal gastrectomy by the Billroth II method (Lundh, 1958). This is presumably due to the rapid emptying of the stomach and the consequently greater dilution of the pancreatic juice, not to a reduced secretion of enzymes, as the concentration of enzymes in the subsequent portions collected was normal. An exception is the lipase concentration which was reduced in all portions in a number of the patients. It is impossible to tell whether this phenomenon represents adaptation to the low-fat diet that the patients have taken since the operation. There is no experimental proof that lipase secretion should adapt itself to the diet (Grossman, Greengard, and Ivy, 1943; Abdeljlil and Desnuelle, 1964), but it is possible that the experimental period has been too short in these studies.

The bacterial flora in the small bowel was not investigated in the present material, but the altered environment during digestion (Table V) must entail altered conditions for growth.

The iron absorption findings are rather difficult to assess, as all the subjects had normal haemoglobin levels at the time of the tests. However, the values for

absorption were strikingly low in the three patients whose follow-up periods were less than one year. Whether the iron absorption improves in time cannot be answered on the basis of the present findings, but it is worth noting that only a few of the patients showed signs of slight iron deficiency, even after a long follow-up period (Table II).

In 15 totally gastrectomized patients Nicolaysen and Rågård (1955) found loss of calcium, but Ekblom and Hed (1965) explained this as a reduced calcium intake, rather than reduced absorption. This assumption is supported by the present results which showed a reduction of calcium absorption in only a very few patients. The osteoporosis found in the patient with a normal calcium absorption is presumably due to reduced intake of calcium.

SUMMARY

In the Surgical Department of the Finsen Institute in Copenhagen we have treated 561 patients with cancer of the stomach from 1948 to 1963 inclusive. In 248 of these cases the tumour was removed, in 102 by total gastrectomy. The primary mortality for radical total gastrectomy was 8% during the last five-year period from 1959 to 1963, and the five-year survival rate (1948-1959) 26% for patients having radical surgery and 7% for those having palliative operations.

The general condition and the results of a number of function tests in 12 patients subjected to total gastrectomy are described. The investigations revealed that the patients were in a good general condition.

It is concluded that total gastrectomy for cancer of the stomach, when the anastomosis is established by a satisfactory technique, is not a disabling procedure.

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