Suid-Afrikaanse Tydskrif vir Geneeskunde : South African Medical Journal

Kaapstad 6 Februarie 1960 Deel 34 No. 6 Volume 34 Cape Town, 6 February 1960

SOME ASPECTS OF THE PATHOGENESIS AND SURGICAL MANAGEMENT OF PEPTIC ULCERS*

D. J. DU PLESSIS, CH.M., F.R.C.S., *Department of Surgery, University of the Witwatersrand, and Johannesburg General Hospital*

Surgical management depends on pathology, and in discussing the surgical approach to peptic ulcers we must base it on what is known of the pathogenesis of this condition. Peptic ulceration is not a single entity, but the common result of many disturbances, and successful management demands that we differentiate between the different types of peptic ulcers on the basis of the antecedent disorder.

The purpose of this paper is to discuss the different types of peptic ulcers with particular reference to their pathogenesis and to speculate about the value of the various methods of surgical treatment available for each one, with the emphasis on the risks of recurrent ulceration after the operation.

Peptic ulcers are produced by the corroding effect of acid and pepsin on the mucous membranes of different parts of the gastro-intestinal tract to which the acid and pepsin have access, and it is obvious that ulceration will occur as a result of either an excessive secretion of acid and pepsin, as occurs in duodenal ulceration, or a decrease in the resistance of the mucous membrane to an otherwise normal secretion of acid and pepsin, as is seen in gastric ulcers. In view of this, the logical form of surgical treatment for duodenal ulcers is a removal of the acid-producing area of the stomach[4] and operations for gastric ulcers should remove all the mucous membrane with a decreased resistance to acid and pepsin. In both types of operations care should be taken not to disturb the balance between acid secretion and mucosal resistance, because this will inevitably result in a recurrence of ulceration.

GASTRIC ULCERS

It is well known that the mucosal lining of the stomach can be divided into 3 different types—cardiac, fundic and pyloric. The fundic mucosa is encountered in the fundus and body of the stomach, whereas the cardiac region is found around the oesophageal opening and the pyloric region in the pyloric antrum. The pyloric and cardiac mucosae very closely resemble each other and for practical purposes can be described together.[5]

The fundic mucosa occupies the vast central area of the stomach, whereas the pyloric type of mucosa occupies on the average only 13·8% of the area of the adult stomach.[1] An interesting feature is that the pyloric mucosa extends further along the lesser curvature than along the greater curvature, and we thus find that in the adult the pyloric mucous membrane extends on the average 39·6% of the length of the lesser curvature, as opposed to only 13·2% of the length of the greater curvature[1] (Fig. 4). In absolute measures the pyloric area in the adult covers on an average 7·2 cm. of the lesser curvature and 5·2 cm. of the greater curvature.[1] It is possible, of course, that the pyloric mucous membrane might actually join up with the cardiac mucous membrane in some individuals, although I have not personally encountered such a case in human beings. Such a distribution of gastric mucous membrane is normal in certain animals like the horse and the pig, and consequently it is conceivable that it does occur in human beings in certain cases.

My interest in the aetiology of peptic ulcer commenced early in 1953, when during routine histological examination of gastric ulcers I was struck by the fact that none of these gastric ulcers occurred in an area with fundic mucous membrane and it thus seemed as if gastric ulceration was a disease of the pyloric mucous membrane only. This observation led me to examine 66 gastric ulcers microscopically and I found that in none of these cases was the mucous membrane adjoining the ulcers of the fundic variety. In all the cases there was a marked gastritis in the neighbourhood of the gastric ulcer, which frequently obscured the histological appearance to a certain degree. In 13 of these cases fundic mucosa was found very close to the ulcer, varying between 2 and 18 low-power fields away from the ulcer edge itself.

Fig. 1. A photomicrograph to illustrate chronic atrophic gastritis in pyloric mucosa.

* This article is based on papers presented at the 42nd South African Medical Congress (M.A.S.A.), East London, C.P., September-October 1959.

The reason for this susceptibility on the part of the pyloric mucosa to develop gastric ulceration seemed to be of fundamental importance, and I proceeded to investigate the matter further. Histological examination was made of 28 stomachs, resected for duodenal or gastric ulcers, by serial sections taken along the lesser and greater curves and the anterior and posterior walls. In each one chronic gastritis was encountered. The distribution of this gastritis was carefully plotted and the severity of the chronic gastritis was subdivided into chronic superficial gastritis and chronic atrophic gastritis.

Chronic superficial gastritis consists of an abnormal cellular infiltration with the formation of lymphoid follicles in the deeper layers of the mucosa. It may affect fundic and pyloric mucous membrane.

Chronic atrophic gastritis is a more advanced stage of gastritis[8] and results in flattening of the rugae and a granular mucosa which on microscopy, in addition to the features of superficial gastritis, shows varying grades of atrophy of the mucous membrane.

In the pyloric mucosa this atrophy results in extreme thinning of the mucous membrane to a stage where it is surprising that it can still resist ulceration (Fig. 1). In the fundic mucosa there is destruction of the chief and parietal cells, and the response to this irritation appears to be replacement of the damaged fundic glands by non-specific mucus-secreting cells arranged in coils to resemble the pyloric glands. These are called pseudo-pyloric glands.[2] This post-inflammatory metaplasia was clearly responsible for the original mistaken belief that gastric ulcers appeared only in the pyloric mucosa, because many gastric ulcers were found in fundic mucous membrane transformed by this pseudo-pyloric metaplasia (Fig. 2).

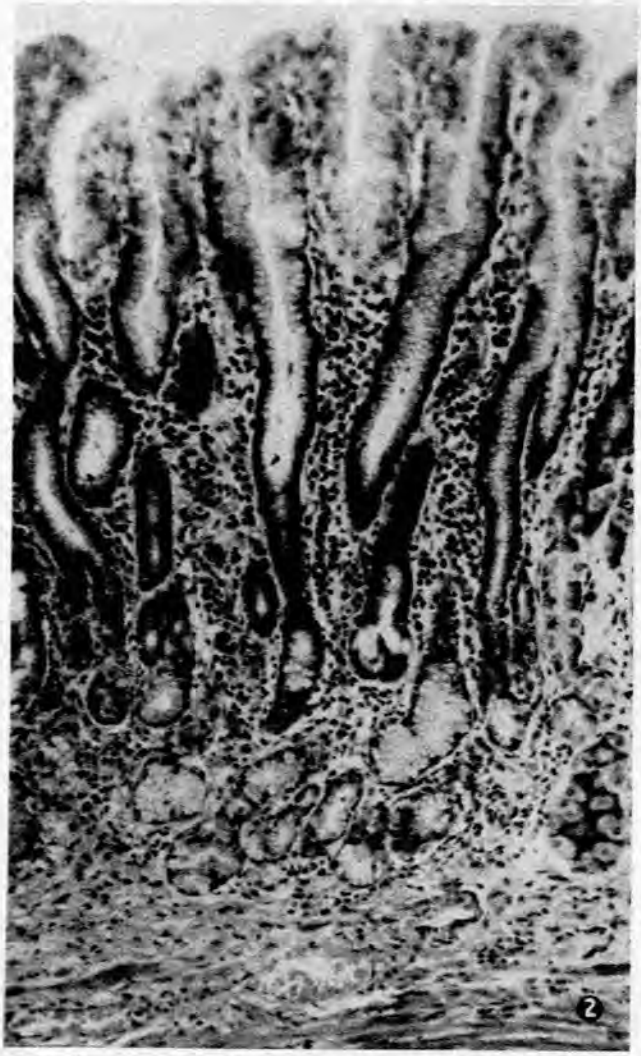


Fig. 2. A photomicrograph to illustrate pseudo-pyloric glands in fundic mucosa affected by chronic atrophic gastritis.

Another form of reaction is the formation of an intestinal type of mucosa[8,14]—intestinal metaplasia.

Sometimes the glands become distended to form small cysts. This may be due to destruction and subsequent repair with fibrosis and obstruction at the neck of the glands,[12] but at other times it is a result of gland regeneration following injury[31] (Fig. 3).

It was now obvious that the original concept was incorrect and that gastric ulcers may occur not only in pyloric mucosa but also in fundic mucosa which is the seat of chronic gastritis, and that the metaplasia described above disguises the fact that it is truly fundic mucosa. It is not surprising that such a mistake can be made if only a small portion of mucosa is available, because sometimes in severe atrophic gastritis it is impossible to decide whether one is dealing with pyloric or fundic mucous membrane.

Chronic gastritis is a very common if not invariable finding in stomachs resected for gastric ulceration[14] and the problem is to decide whether the gastritis is the primary event which leads to the development of gastric ulcer or whether it is the gastric ulcer which in turn produces the chronic gastritis in the surrounding gastric mucous membrane. Although it is impossible to give a dogmatic answer to this problem, there is nevertheless very suggestive evidence that the chronic gastritis is the primary event.[30,35] On many occasions I have encountered severe chronic gastritis of the superficial or the atrophic variety without any gastric ulcer present, whereas I have never encountered a gastric ulcer without severe surrounding chronic gastritis. The concept is thus that a chronic gastritis is the primary event and that a gastric ulcer may develop in this region.

It is now necessary to explain the cause of this chronic gastritis which is considered to be the precursor of the chronic ulcer. There is every indication that in many cases a chronic irritation of the surface of the gastric mucous membrane is certainly a very important factor. Such a chronic irritation can, of course, be caused by food taken by mouth, and a classical example of such a condition is chronic alcoholism,[6] where the recurrent irritation of strong liquor produces severe chronic gastritis. In this type of chronic gastritis the whole stomach is usually affected and often the fundic mucosa is more severely affected than the pyloric mucosa. Because of this extensive destruction of acid-producing cells, so little acid is secreted in the stomach that the formation of a chronic gastric ulcer is unlikely, and one thus not infrequently finds that these people do not present with a chronic gastric ulcer, but rather with diffuse atrophic gastritis and sometimes a superimposed acute gastritis (following a drinking bout) with resultant acute erosions and haemorrhage (Fig. 5).

Another known cause of chronic gastritis is gastric stasis, and this is the explanation for the fairly high incidence of

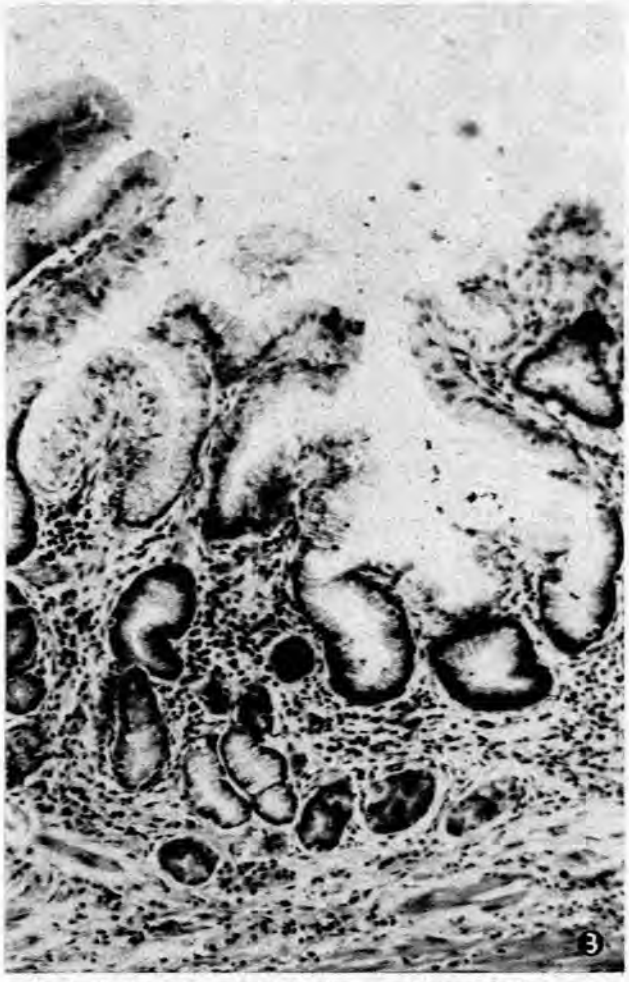


Fig. 3. A photomicrograph to show a microcyst in the gastric mucosa without any obstruction in the neck of the gland.

gastric ulcers after vagotomy without adequate drainage of the stomach.[9,10]

Another cause of chronic irritation to the mucous lining of the stomach occurs after gastrojejunostomy where there is repeated reflux of bile and pancreatic juice into the stomach.[12,13] This persistent irritation produces a chronic gastritis which sometimes goes on to produce a chronic gastric ulcer or haematemesis from multiple superficial erosions. The gastritis produced by a gastrojejunostomy is centred around the stoma, and there seems very little doubt that it has been produced by the reflux of bile and pancreatic secretion through the stoma (Fig. 6).

In other cases of gastric ulcer one finds that the chronic gastritis extends from the pylorus proximally for a variable distance into the stomach, usually confined to the pyloric antrum and lowermost portion of the fundus[14,30] and mostly along the lesser curvature[2,3] (Fig. 7). It is a common condition, increasing in extent and severity with increasing age.[30] The remainder of the gastric mucous membrane appears normal. It is thus suggestive that the factor producing the chronic irritation arises in the region of the pylorus and extends for a variable distance proximally. It seems thus highly unlikely that this form of irritation has been produced by food or fluid taken by mouth and, in view of the fact that it seems likely that reflux of bile and pancreatic secretion through a gastrojejunostomy stoma can produce surrounding chronic gastritis, it is suggested that this type of chronic gastritis, extending from the pylorus proximally, has arisen as a result of the reflux of bile and pancreatic secretion through an incompetent pylorus.

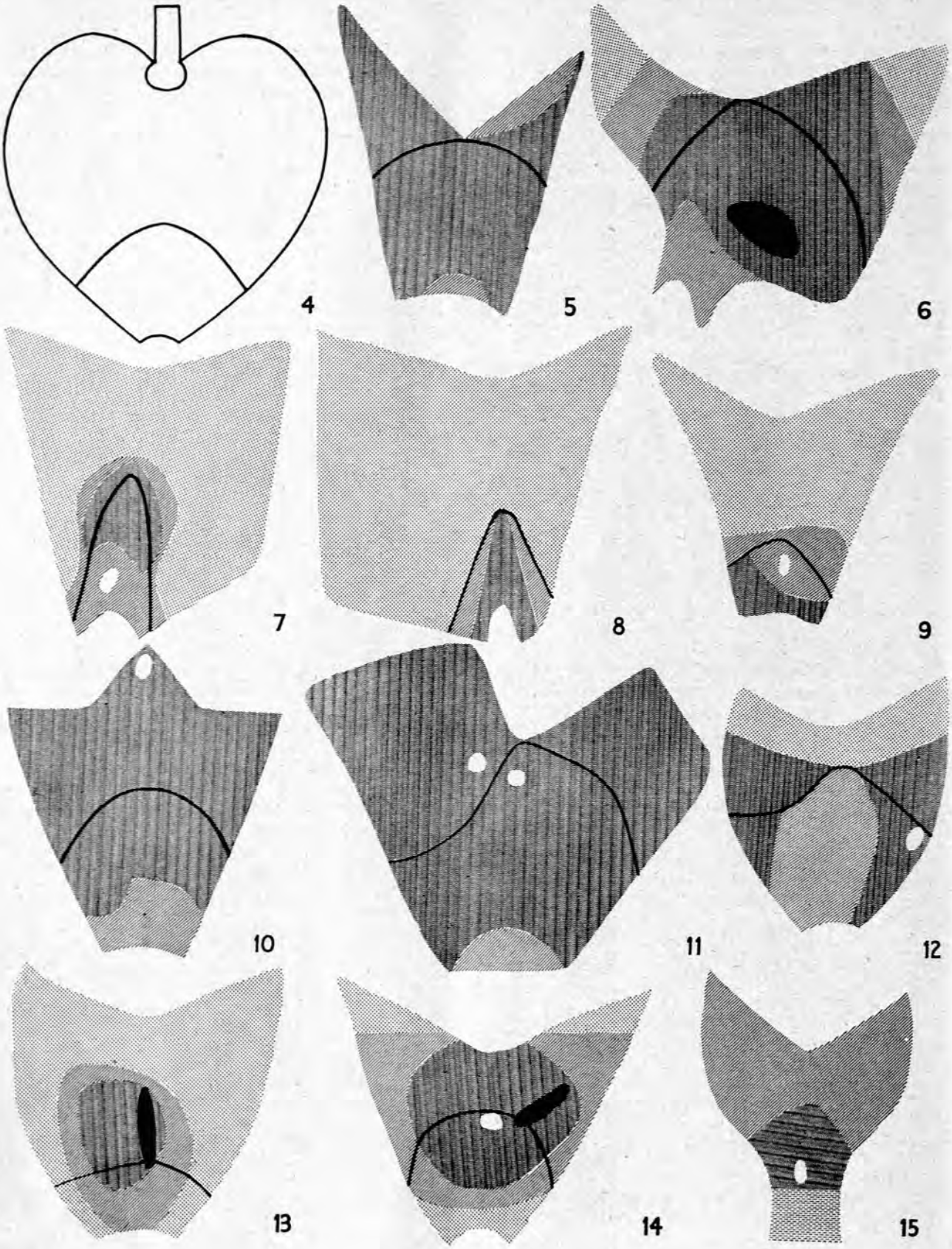
It has previously been pointed out that the pylorus is not a sphincter which prevents gastric emptying, but that its purpose is to prevent the reflux of bile and pancreatic secretion back into the stomach when duodenal contraction takes place.[7] If this function is inadequate then bile and pancreatic secretion can reflux into the stomach during duodenal contraction, in which case the distal portion of the stomach will be constantly irritated by this fluid. It is thus suggested that this type of gastric ulcer is the result of an incompetent pyloric sphincter which allows duodenal reflux and in that way produces a chronic gastritis in the distal portion of the stomach, which is the precursor of the chronic gastric ulcer in that region.

That such a condition probably exists in many people is shown in a review of a large number of cases in which it was found that only 27·8% of stomachs of normal people showed absence of gastritis,[3] and one has found it in the presence of duodenal ulcers[8] (Fig. 8). This gastritis always extends from the pylorus proximally and it is maximal along the lesser curvature, presumably because the tone of the stomach opposes the anterior and posterior stomach walls, leaving only a small region along the lesser curvature for fluid to reflux, in exactly the same way as liquid taken by mouth runs down along the lesser curvature. The presence of such a chronic gastritis in the pyloric region of the stomach largely centred on the lesser curvature is a common finding, and is not an indication of a diffuse gastritis of the stomach.[8]

If it is accepted that this type of irritation is a common feature then, of course, it is easy to understand how in selected cases a chronic gastric ulcer will occur in the pyloric region of the stomach, particularly along the lesser curvature. It is also easy to understand that in some cases a duodenal ulcer occurs in the presence of a gastric ulcer[11] because there is nothing to prevent a hypersecreting stomach from also having an incompetent pyloric sphincter, thus allowing sufficient reflux to produce a chronic gastritis along the lesser curvature with the resultant formation of a chronic gastric ulcer. In these cases the extent of the chronic gastritis is limited; otherwise there would not be enough secretory cell mass to produce sufficient gastric secretion to cause a duodenal ulcer (Fig. 9).

An interesting speculation now is to decide why gastric ulcers particularly occur in the region of the pyloric mucosa. Is it merely because the pyloric mucosa is closer to the pylorus and that it is thus likely to be most severely affected by the refluxing duodenal contents, or is the pyloric mucosa in fact less resistant to this refluxing fluid so that a gastric ulcer is produced in this area in preference to the fundic mucosa? There has been some suggestion that the pyloric mucosa close to its junction with the fundic mucosa is especially susceptible to ulceration,[32,34] and this will explain the classical location of gastric ulcers, but it is by no means invariable, and we know that a gastric ulcer may be found more proximally in fundic mucosa[30,32,33] (Fig. 10).

In 3 cases studied with severe atrophic gastritis affecting the pyloric and fundic mucosa, a gastric ulcer was found in


4
5
6
7
8
9
10
11
12
13
14
15

the pyloric region in 2 cases and in the fundic mucosa in 1. On the other hand, I have found a person with two gastric ulcers, one in the pyloric and one in the fundic region (Fig. 11).

One interesting finding has been to see the junction between fundic and pyloric mucous membranes and to find that the body mucosa shows superficial gastritis only and the pyloric mucosa immediately adjoining it shows severe atrophic gastritis, suggesting that the latter area is more susceptible to irritation (Fig. 17). When performing a gastric resection for a gastric ulcer, therefore, it is important that the surgeon should remove an extensive area of the lesser curvature so as to remove the pyloric mucous membrane and the area which has been subjected to gastritis quite irrespective of the situation of the gastric ulcer. For this reason I recommend that in all gastrectomies performed for gastric ulceration a Pauchet manœuvre should be performed to ensure that all the susceptible and damaged mucous membrane is removed at the time of the operation to prevent the recurrence of another gastric ulcer. If this is not done then damaged mucosa is left behind which may produce another gastric ulcer.

In these cases the duodenum is normal and therefore there is no increased chance of a duodenal ulcer occurring later. There is thus no particular need to perform a Polya type of operation and I consequently prefer a Billroth I operation because it eliminates the afferent loop, which is the source of potential trouble at a later stage.[7] There is of course the possibility of duodenal reflux into the gastric remnant with the formation of a new gastric ulcer, and for that reason I wonder whether a Roux-Y type of operation is not preferable in this type of lesion.

During this investigation an interesting observation was encountered in connection with the effect of cortisone on the development of peptic ulcers. It is known that cortisone increases the gastric secretion and in such an event will be likely to produce a duodenal ulcer if the gastric mucosa is normal.[4,15] If, however, cortisone is administered to a person with an incompetent pyloric sphincter which allows free reflux and the development of chronic gastritis, the anti-inflammatory effect of cortisone will result in severe gastric mucosal atrophy with very little inflammatory reaction; one such case was encountered where a marked feature was the gross chronic atrophy of the gastric mucosa with virtually no inflammatory reaction (Fig. 16). This patient actually developed a spontaneous gastrocolic fistula and no doubt this extension of gastric ulcer into the colon was also the result of this lack of inflammatory reaction to the irritation produced by the duodenal reflux (Fig. 12). It thus seems that the administration of cortisone may be responsible for the development of either a duodenal ulcer or a gastric ulcer, depending on the function and efficiency of the stomach and the pyloric sphincter.

Figs. 4-15.

Stippled area	=normal gastric mucous membrane
Interrupted transverse lines	=normal duodenal mucous membrane
Diagonal lines	=chronic superficial gastritis
Wavy lines	=chronic atrophic gastritis
Black areas	=gastro-enterostomy stoma
White areas	=gastric ulcers

Thick black line outlines the junction between pyloric and fundic mucosa. These diagrams illustrate the following:

Fig. 4. The average distribution of cardiac, fundic and pyloric mucosa in an adult stomach.
Fig. 5. The distribution of gastritis in a stomach resected for haematemesis in a European male aged 39 who was a chronic alcoholic. (No chronic ulcer was present.)
Fig. 6. The distribution of gastritis in a stomach resected for haematemesis in a Coloured male aged 43 who had had a previous gastro-jejunostomy. (No chronic ulcer was present.)
Fig. 7. The distribution of gastritis in a stomach resected for a chronic gastric ulcer. (Coloured male aged 49.)
Fig. 8. The distribution of gastritis in a stomach resected for a chronic duodenal ulcer. (European male aged 43.)
Fig. 9. The distribution of gastritis in a stomach resected for active chronic gastric and duodenal ulcers. (Coloured female aged 46.)
Fig. 10. The distribution of gastritis in a stomach resected for a chronic gastric ulcer high up on the lesser curvature. (European male aged 68.)
Fig. 11. The distribution of gastritis in a stomach resected for two chronic gastric ulcers. (European male aged 42.)
Fig. 12. The distribution of gastritis in a stomach resected for a chronic gastric ulcer and gastrocolic fistula in a European female aged 41 who had received large doses of cortisone for the previous 7 years.
Fig. 13. The distribution of gastritis in a stomach resected for a jejunal ulcer following a previous gastro-enterostomy in a European male aged 69.
Fig. 14. The distribution of gastritis in a stomach resected for a gastric ulcer following a previous gastro-enterostomy in a European male aged 62.
Fig. 15. The distribution of gastritis in a stomach resected for a gastric ulcer following a previous Billroth I gastrectomy for a duodenal ulcer in a European male aged 51.

DUODENAL ULCER

This condition is now usually considered to be due to excessive secretion of acid and pepsin by a stomach which contains an abnormally large number of acid-secreting cells.[16,17]

The increased volume of acid and pepsin produced by this increased parietal-cell mass will, of course, pass over the pyloric mucous membrane of the stomach and then down the bowel, and the fact that it produces an ulcer only in the first part of the duodenum indicates a relatively poor resistance in that area.

The defence of the fundic mucous membrane of the stomach against this high acid secretion is inherent in the mucosa and it is clearly very high because ulceration never occurs in fundic mucosa which is still intact. The pyloric mucosa is protected by the mucus and alkali secreted by the pyloric glands, and this too is a very efficient protective mechanism, for it is unusual to find a gastric ulcer in the presence of an abnormally high acid secretion. Sometimes this does happen if there is a localized gastritis which lowers the resistance of that area without interfering with the acid-secreting mechanism. Under these circumstances we then find the comparatively rare combination of an active duodenal ulcer and an active gastric ulcer present at the same time.

Beyond the ampulla of Vater there are virtually no Brunner's glands, and the protection of the bowel beyond that point against acid and pepsin depends entirely on the neutralizing and buffering effect of the bile and pancreatic secretion.

The first portion of the duodenum up to the ampulla of Vater depends for its protection on the secretion of mucus and alkali by the Brunner's glands, which closely resemble the pyloric glands histologically,[5] and duodenal ulceration may thus be considered to be due to an imbalance between the acid-secreting cells of the stomach and the Brunner's glands. It is known that a congenital inadequacy of the Brunner's glands may occur[5] and this may explain those cases of duodenal ulceration without an abnormally high

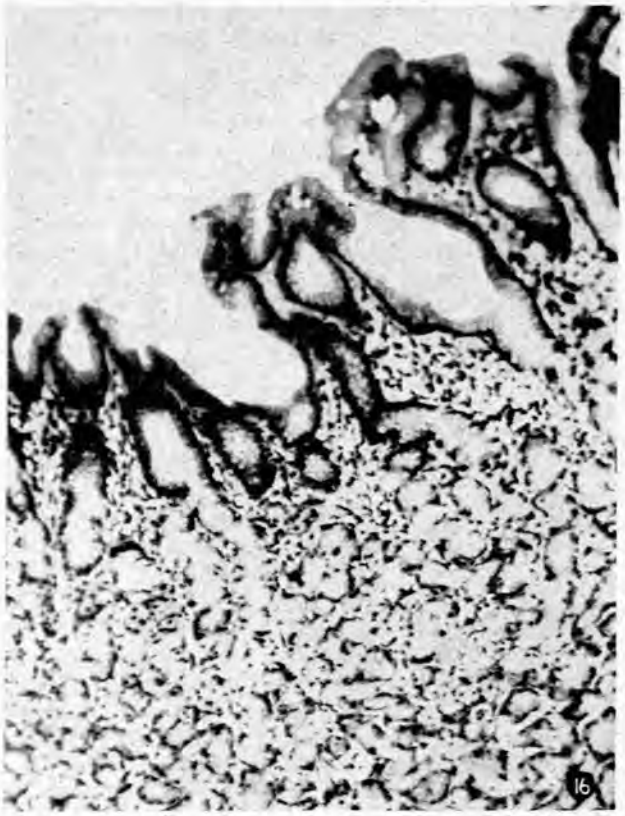


Fig. 16. A photomicrograph showing atrophy of the fundic mucosa without significant cellular infiltration in a European female aged 41 with a gastrocolic fistula. She had been on large doses of cortisone for 7 years.

acid secretion.[34] In addition, it should be kept in mind that there is a severe duodenitis present in cases with duodenal ulceration, and mucosal thinning and atrophy of the Brunner's glands[35] (Fig. 18). Whether this is the cause or the effect of the duodenal ulcer is uncertain, but the end result in any event would be a lowering of the mucosal resistance, and consequently any operation which does not divert acid and pepsin away from the duodenum will be liable to be followed by a recurrence of a duodenal ulcer. This is probably the explanation for the comparatively high incidence of duodenal ulceration after a Billroth I operation performed for duodenal ulceration[18] and for the disappointing results with sleeve resections, which at first glance would appear to be the most logical operation for a duodenal ulcer.[19-29] For the present it thus seems as if the Polya type of gastrectomy is the most reliable operation for duodenal ulceration, although this type of operation results in the reflux of bile and pancreatic secretion into the gastric remnant, which may develop a gastritis and in time a gastric ulcer. It seems likely that a Hoffmeister valve will assist in directing the bile away from the gastric remnant into the efferent loop and consequently I feel that this refinement should be used when performing a Polya type gastrectomy.

STOMAL ULCER

Just as a duodenal ulcer is produced by a hypersecreting stomach which overcomes the resistance of the duodenal mucosa, and many gastric ulcers by reflux of bile and pancreatic juice which produces chronic gastritis, so we can also subdivide stomal ulceration after gastrojejunostomy or gastrectomy into two varieties. The one variety will be produced by a hypersecreting stomach which produces irritation of the jejunum leading to a jejunal ulcer (Fig. 13). On the other hand the stoma allows free reflux of pancreatic secretion into the stomach, producing the surrounding chronic gastritis which will be the precursor of a stomal ulcer on the gastric side of the suture line (Fig. 14). This, of course, may occur after a Billroth I operation too (Fig. 15).

The differentiation between these two types of stomal ulcers is important because the management is naturally quite different.

If the stomal ulcer is in the jejunum then it is obvious that an excessively high volume of acid and pepsin is being secreted by the stomach, and treatment should be directed at removing this high volume of acid from the susceptible jejunum. If the stomal ulcer is on the gastric side of the suture line, then clearly the treatment should not be directed at decreasing acid secretion but at the removal of the affected gastric mucous membrane and a prevention of a repetition of the same occurrence by diverting bile and pancreatic secretion away from the stomach, as with a Roux-Y type of anastomosis.

What has been said is obviously highly theoretical and dependent on certain experimental data which are as yet unproved. More proof is obviously necessary before these factors can be established as fact, and therefore I hope that this paper will be looked upon as a preliminary and provisional report. We are still in the stage of observation as far as the correct surgical treatment of peptic ulcers is concerned and we are not yet in a position to formulate a definite hypothesis. We must thus be careful when attempting to do so, because a misconception may impede the progress of knowledge. Any hypothesis must be subjected to repeated and stringent criticism and it is in that spirit that I present this paper.

SUMMARY

1. Gastric ulcers occur in mucous membrane damaged by chronic gastritis.

2. There are many causes of chronic gastritis, but a striking type is seen around the stoma of a gastro-enterostomy, presumably caused by the irritation of refluxing bile and pancreatic secretion.

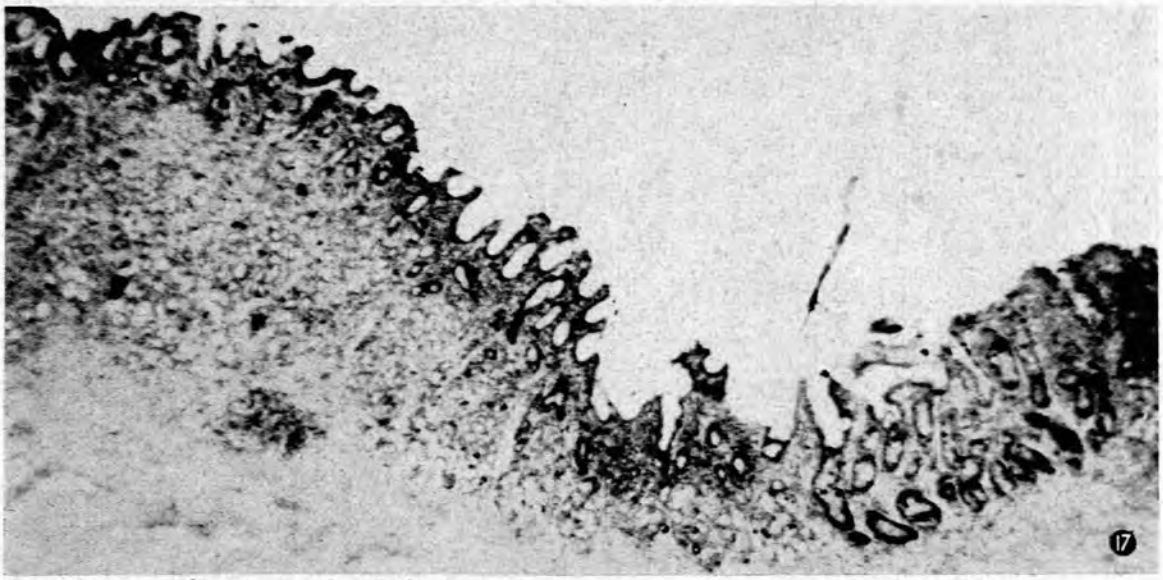
3. Many cases have been found with chronic gastritis in the distal part of the stomach extending from the pylorus for a variable distance proximally. It is suggested that this may be due to reflux of bile and pancreatic secretion through an incompetent pyloric sphincter.

4. The majority of gastric ulcers are found in pyloric mucosa. This may be due to the distal situation of this type of mucosa, but there is some evidence that pyloric mucosa is less resistant to irritation than fundic mucosa.

5. Not all gastric ulcers occur in pyloric mucosa. Some are obviously in fundic mucosa, whereas others are in fact in fundic mucosa but the pyloric metaplasia of chronic gastritis disguises this fact.

6. Surgical treatment of gastric ulcers must include removal of all affected mucous membrane.

7. In cases with duodenal ulceration there is a congenital or acquired defect in the duodenum and for that reason a



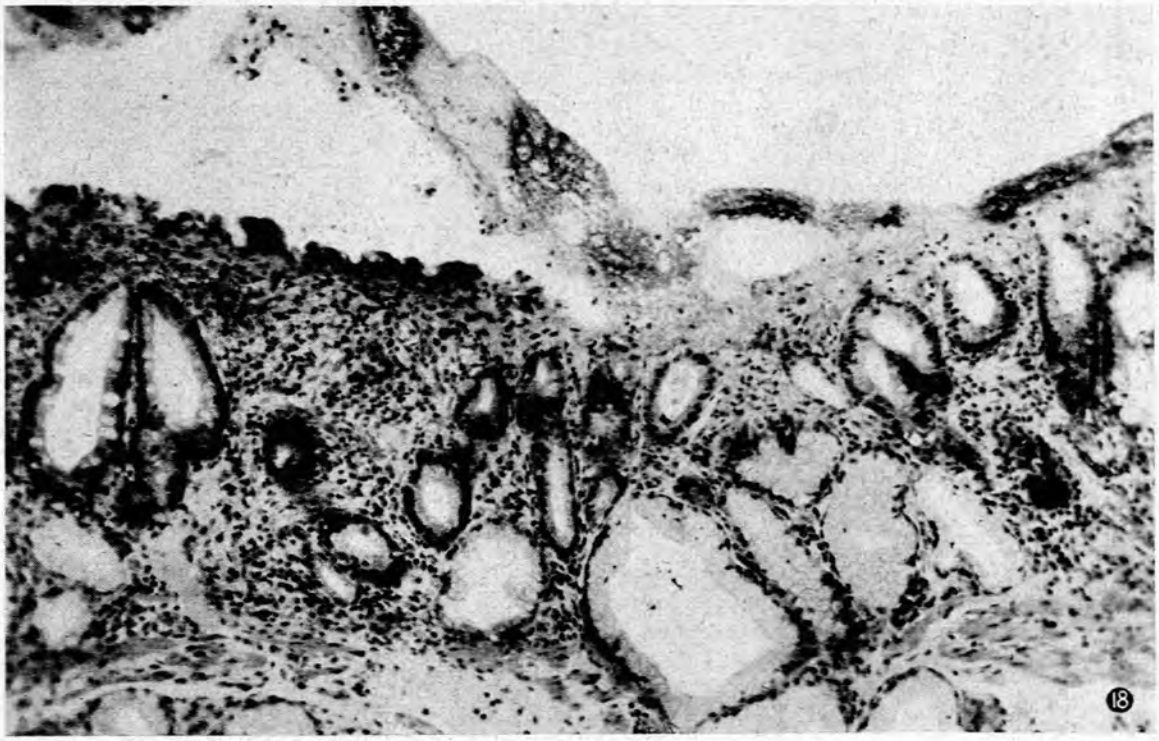


Fig. 17. A photomicrograph to illustrate an apparent increased susceptibility of the pyloric mucosa to gastritis. The pyloric mucosa is very thin and atrophic whereas the adjoining fundic mucosa shows only superficial gastritis.
Fig. 18. A photomicrograph showing severe duodenitis in a patient with a chronic duodenal ulcer.

Billroth I gastrectomy or a tubular resection will result in a recurrence of a duodenal ulcer in many cases.

8. A stomal ulcer may be in the jejunum, due to excessive acid secretion, or on the gastric side of the stoma following on the chronic gastritis produced by the refluxing bile and pancreatic secretion. The surgical treatment will vary according to the site of the stomal ulcer.

REFERENCES

1. Landboe-Christensen, E. (1944): Acta path. microbiol. scand., suppl. **54**, 671.
2. Wood, I. J. and Taft, L. I. (1958): *Diffuse Lesions of the Stomach.* London: Arnold.
3. Hebbel, R. (1949): Amer. J. Path., **25**, 125.
4. Bruce, J., Card, W. I., Marks, I. N. and Sircus, W. (1959): J. Roy. Coll. Surg. Edin., **4**, 85.
5. Landboe-Christensen, E. (1944): Acta path. microbiol. scand., suppl. **52**.
6. Doig, R. K. and Wood, I. J. (1952): Med. J. Austral., **1**, 593.
7. du Plessis, D. J. (1956): Med. Proc., **2**, 29 and 77.

8. Morson, B. C. (1955): Lancet, **2**, 1068.
9. Dragstedt, L. R. *et al.* (1955): Arch. Surg., **71**, 136.
10. Oberhelman, H. A. and Dragstedt, L. R. (1955): Surg. Gynec. Obstet., **101**, 194.
11. Johnson, H. D. (1955): Lancet, **1**, 266.
12. Palmer, E. D. (1954): Medicine, **33**, 199.
13. *Idem* (1948): Gastroenterology, **10**, 671.
14. Magnus, H. A. (1937): J. Path. Bact., **44**, 389.
15. Dragstedt, L. R. (1956): Gastroenterology, **30**, 208.
16. Hunt, J. N. and Kay, A. W. (1954): Brit. Med. J., **2**, 1444.
17. Cox, A. J. (1952): Arch. Path., **54**, 407.
18. Walters, W. (1957): Arch. Surg., **74**, 615.
19. Tanner, N. C. (1954): Postgrad. Med. J., **30**, 523.
20. Kay, D. W. (1956): J. Roy. Coll. Surg. Edin., **2**, 54.
21. Woodward, E. R. *et al.* (1956): Arch. Surg., **72**, 1003.
22. Connell, F. G. (1929): Surg. Gynec. Obstet., **49**, 696.
23. Kaplan, R. S. and State, D. (1956): Amer. J. Gastroent., **26**, 29.
24. Wangensteen, O. H. (1956): *Ibid.*, **26**, 37.
25. Berne, C. J. (1954): *Ibid.*, **22**, 126.
26. Thal, A. P., Perry, J. F. and Wangensteen, O. H. (1957): Surgery, **41**, 576.
27. Wangensteen, O. H. (1957): *Ibid.*, **41**, 686.
28. Zollinger, R. M. and Ellison, E. H. (1955): Ann. Surg., **142**, 709.
29. Gray, S. J., Ramsey, C. G. and Reifenstein, R. W. (1954): New Engl. J. Med., **251**, 835.
30. Stout, A. P. (1947): Bull. N.Y. Acad. Med., **23**, 101.
31. *Idem* (1945): N.Y. St. J. Med., **45**, 973.
32. Oi, M., Oshida, K. and Sugimura, S. (1959): Gastroenterology, **36**, 45.
33. Karsner, H. T. (1949): *Human Pathology*. Philadelphia: J. B. Lippincott.
34. Marks, I. N. and Shay, H. (1959): Lancet, **1**, 1107.
35. Collins, V. P. (1943): Ann. Surg., **118**, 1005.