Current Practice

Gastric Ulcer

A. MORTON GILL,* M.D., F.R.C.P.

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In every case of chronic benign gastric ulceration two factors are present: hydrochloric acid, and progressive erosion of an area of mucosa by the digestive action of the gastric juices. Our understanding of this process makes a fascinating story, linked with the names of two famous patients, Alexis and Tom.

Two hundred years ago five processes were said to occur in the stomach during the digestion of a meal. These were concoction, putrefaction, trituration, fermentation, and maceration. So vague were these terms that William Hunter remarked somewhat irritably, "Some physiologists will have it that the stomach is a mill, others that it is a fermenting vat, others again that it is a stew-pan; but in my view of the matter, it is neither a mill, a fermenting vat nor a stew-pan, but a stomach gentlemen, a stomach."

The first person to undertake research in this field was de Réaumur[1] who trained his pet buzzard to swallow and then eject a perforated metal tube containing pieces of sponge, which on squeezing produced a fluid found to be acid in reaction and capable of digesting food *in vitro*. Unhappily the bird perished, buzzards proved to be in short supply, and ducks, which were then used, did not appreciate their role as research workers and refused to co-operate. Spallanzani,[2] not without certain misgivings, repeated these experiments, using himself as subject. As a result he was able to postulate that gastric digestion was a chemical process exerted by a fluid secreted by the stomach and which he called the gastric juice. About 40 years later Prout[3] and Tiedemann and Gmelin[4] proved, independently of each other, that the acidity of gastric juice is due to the presence of muriatic acid, later renamed hydrochloric.

Alexis and Tom

The names of many patients have become famous in our long medical saga, but surely none so unlikely as that of the tough, young, hard-drinking French Canadian trapper Alexis St. Martin, who owed his life and his subsequent fame to the United States Army surgeon William Beaumont. Beaumont was summoned after an accidental discharge from a shotgun had torn a great hole in the young man's side. On finding that his patient would be left with a permanent gastric fistula Beaumont had the wit and the patience to use this for a long series of experiments and observations lasting over a period of eight years.[5] Thus for the first time—though under the most primitive conditions—the physiology and morbid anatomy of the living human stomach was studied in detail. Beaumont confirmed the earlier observations that hydrochloric acid is responsible for digestion, and, by noting that it is distinct from mucus and secreted by different cells, suspected the presence of another agent of digestion. This suspicion was confirmed when pepsin was isolated some years later. During the course of his studies Beaumont recorded the time taken for the digestion of many articles of food, and remarked the depression or abolition of secretion by fevers and by the emotions of fear and anger and the flow engendered by food entering the stomach or by the introduction of a tube. He anticipated the radiologist by noting the normal emptying time of the stomach, the waves of peristalsis producing mixing of the stomach contents, and the way in which emptying is achieved by small jets of chyme being shot at intervals through the pylorus. He observed the injurious effects of excess tea, coffee, and alcohol and anticipated the gastroscopist by observing gastritis—the first man to do so in a living subject. The nervous factor in gastric secretion observed by Beaumont was confirmed in the human subject by a practical, though somewhat macabre, experiment conducted by Regnard and Loye[6] when they stimulated the vagus of a decapitated criminal and saw drops of juice forming on the gastric mucosa 45 minutes after execution.

More than a century after Alexis—and again in North America—another patient, whom we know of as Tom, made a further vital contribution to our knowledge of the genesis of gastric ulceration. Tom had been given a gastric fistula because of an acquired oesophageal stricture and collaborated with Wolf and Wolff[7] to produce a series of unique observations. The reaction of the gastric mucosa to various emotions was studied, and in particular the effect of anxiety and resentment. Of special significance in relation to the ulcer problem was the finding that an increased secretion of mucus by the stomach occurs both while eating an ordinary meal and after mechanical irritation of the gastric mucosa. Furthermore, ulceration having all the characteristic appearances of the chronic type could be induced if the mucus was persistently wiped off a given area of mucosa, thus allowing the gastric juice to exert its powerful erosive action on an unprotected spot. This type of experimental ulcer healed rapidly and spontaneously once the mucus was allowed to return. Thus it was apparent that in time an area of gastric mucosa would ulcerate if its resistance was lowered and if it was constantly bathed in acid gastric juice of sufficient concentration.

The role of mucus has recently been emphasized by Malhotra,[8] who considers that the two most important protective barriers against ulceration are the surface epithelial cells themselves with their astounding capacity for regeneration, and the film of mucus which covers them. He produced evidence suggesting that the consistency of food affects the quality of gastric mucus derived from swallowed saliva; foods needing much mastication stimulate a high salivary output. He argues that by augmenting gastric mucus salivary mucus may help to protect against peptic ulceration.

Pathological Changes

Viewed through a gastroscope it will be found that in most instances gastric ulceration is a single lesion, the commonest site being the lesser curve of the pars media, proximal to the incisura angularis. The general shape is rounded or oval, punched-out in appearance if acute, and ragged or irregular if chronic. The edge is sometimes oedematous, and not infrequently there is a surrounding zone of erythema with the

* Physician, West London Hospital, Hammersmith, W.6.

whole often based on an area of atrophic mucosa, puckered to produce a starfish effect if there has been much scarring as a result of previous ulceration.

When viewed through a microscope the chronic ulcer is seen to be a defect of the mucosa, submucosa, and muscle. Repair is by the formation of granulation tissue, which then becomes fibrous, and it is the presence of fibrosis that distinguishes the acute from the chronic ulcer. The fibrotic tissue retracts, and by overgrowth of epithelium from the margin the defect is closed. Thus the chronic ulcer when healed always leaves a telltale scar, marking for all time its former presence.

Presentation and Diagnosis

The popular conception of the "ulcer type," largely fostered by advertising beamed from a particular source, is that of the high-powered, chain-smoking business tycoon with enormous drive. From time to time this gentleman assumes an anguished expression, swallows one of the magic tablets, and gains instant relief. This picture, though exaggerated, is not entirely untrue, and could be as good a description of the man with a pyloric ulcer as the one with a duodenal. Both tend to affect men in their third and fourth decades, and give rise to epigastric pain, often referred to the back, aggravated by skipping meals and waking the patient in the small hours, relieved by eating and by alkalis, and associated with bouts of vomiting several hours after a meal with a consequent relief of pain. Clinical examination usually reveals localized deep tenderness and guarding in the epigastrium but little else.

On the other hand, the lesser curve ulcer becomes more common as age advances, the incidence in women rising after the menopause, and is relatively high in the aged of both sexes. Here the clinical picture is often blurred and may lead to the suspicion of carcinoma, with left hypochondriac pain brought on by meals, causing the patient to become afraid to eat, with a consequent loss of weight and later appetite. Sleep is not usually disturbed, but vomiting may lead to dehydration and later cachexia.

Though not common, particular mention must be made of the ulcer high in the fundus, near the cardia, because in this case there may be central chest pain with radiation into the arms, no clear relationship to meals, and sometimes even aggravation by exertion. Since these patients are usually elderly and may well have electrocardiographic changes suggestive of ischaemic heart disease, such ulcers can easily be missed.

The clinical diagnosis of gastric ulceration in the first instance depends almost entirely on the interpretation of a detailed and accurate history, with an attempt at separation into three main syndromes; the juxtapyloric, the lesser curve, and the ulcer proximal to the cardia. Even so radiology is essential for localization,[9] and should never be omitted. Furthermore, even with expert radiology not all gastric ulcers are visualized —sometimes there may be uncertainty about whether or not an ulcer is present—and it is not always possible to interpret radiologically between the benign and the malignant lesion. It can also be very difficult to decide on the presence or absence of a concomitant gastritis, and it may not be easy to decide whether or not an ulcer has healed under treatment. In such cases the next step is to call in the gastroscopist.

Gastroscopy

Gastroscopy with the modern flexible fibrescope instrument is both painless and safe. Ariga[10] has recorded a complication rate of only 0.003% in a series of 829,000 examinations collected from several centres. Such was not always the case, and it is said that when the first rigid instrument was shown to a professional sword-swallower he declined the honour, remarking that swords and not trumpets were his métier. Indeed, because of the risk involved these early rigid instruments were rarely used in this country, but the later semi-rigid Schindler and Hermon Taylor gastroscopes gave excellent vision and allowed confirmation of a clinical diagnosis in a number of *x*-ray negative cases. In my own series of over 5,000 examinations with the Hermon Taylor instrument 17% of all gastric ulcers had not been visualized radiologically. Since the fibrescope gastrocamera can safely be used at all ages, and since gastric ulceration becomes more common with advancing years, one would expect that as clinicians become more adept with the new instruments so the percentage of lesions found will rise. My present registrar, using the Olympus model GTF fibrescope gastrocamera, has to date found a gastric ulcer in 11 patients out of 46 with negative *x*-rays. These include people of both sexes in their seventh and eighth decades. Gwyn Williams and his colleagues,[11] using Olympus model GF.B., found chronic ulceration in 3 out of 16 patients whose barium meal did not show a crater.

Apart from radiology and gastroscopy there are at present no other diagnostic procedures capable of demonstrating gastric ulceration, but other investigations may be necessary in certain cases. These include full blood count, examination of blood film, determination of haematocrit, estimation of serum iron, calcium, phosphorus, electrolytes, and urea, examination of stools for occult blood, determination of the patient's blood group and salivary secretor status, determination of volume and acid concentration of night secretion, and secretory response to histamine acid phosphate. It seems likely that pentagastrin will replace histamine as a tool for the study of gastric secretion.[12]

Other Causes

We have so far considered the patient whose gastric ulcer manifests itself by producing a chronic dyspepsia, and this is certainly the most common mode of presentation. There are, however, others which should be remembered.

Acute ulceration may occur in association with severe and extensive burns, chronic hypoxia, head injuries, encephalitis, intracranial tumours, cerebrovascular lesions, and following operations on the brain.

Acute or chronic ulceration may result from the use of a wide range of drugs, including, for example, acetylsalicylic acid, phenylbutazone, indomethacin, or corticosteroids, and so appear to complicate the original disease.

Chronic ulceration may occur in association with endocrine disorders, as in the case of the Zollinger–Ellison syndrome, in which a pancreatic tumour produces gastrin so that the stomach, under a constant powerful stimulus, pours out juice of a high acid concentration. Night secretion in this condition may amount to as much as two litres, and a profuse watery diarrhoea may add to the patient's misery and confuse the diagnosis. Again, in the polyglandular syndrome, with multiple adenomata, involvement of the parathyroids, and a high serum calcium level, the patient may present with bilateral renal calculi or renal failure. In this connexion it is of interest that Smallwood[13] has recently shown that the intravenous administration of calcium to human subjects produces an increase in the gastric secretion of acid and pepsin. Vagotomy permanently abolishes this response, indicating that it is the result of vagal stimulation.

Acute or chronic ulcers may present with any one of their complications. Of these the one most frequently seen by a physician is chronic iron-deficiency anaemia, the result of oozing from a chronic ulcer over a period of months. In such cases the dyspepsia may seem quite trivial to the patient and may not even be mentioned.

A massive haemorrhage can occur from both acute and chronic ulcers, and since the bleeding originates in the stomach there is in most cases haematemesis followed by melaena. This

is from the outset a medical emergency, to be treated as such, and so long as bleeding continues the threat to life remains. It is of paramount importance for physician and surgeon to consult together at an early stage, so that if the bleeding does not cease, or ceases and then recurs, the surgeon is not asked to undertake the impossible task of operating on a dying patient.

Daily copious vomiting with dehydration and weight-loss, the result of chronic ulceration producing organic pyloric stenosis or hourglass deformity (now rarely seen), seldom present any difficulty in diagnosis and require surgical relief.

Should the long-standing chronic dyspeptic with a history of ulcer develop anorexia, and specially a distaste for meat, then his gastric ulcer may have become malignant. The true incidence of this complication is very difficult to assess, but is not usually considered to be higher than 5% in Britain, though a figure five times as great is often quoted in the United States. Clearly so much depends upon the interpretation given by the histopathologist of biopsy, resection, and autopsy specimens.

Presentation by perforation has been discussed in an earlier article in this series.[14]

Treatment and Prognosis

Ulcer treatments come and ulcer treatments go, and the latest in a long line is carbenoxolone sodium, which has been shown statistically by Doll and colleagues[15] to promote the healing of gastric ulcers. The same can be said for bed rest and a total ban on smoking. Carbenoxolone sodium is capable of producing unfortunate side-effects, including oedema, hypertension, and hypokalaemia. A reduction in dosage will decrease the incidence and severity of side-effects, but will also decrease the rate of healing of the ulcer. It has now been found that the dosage need not be lowered if given in combination with thiazide diuretics, in which case the rate of healing is not affected.[16] Carbenoxolone sodium is believed to exert its healing effect by causing an increased secretion of mucus by the gastric epithelium and particularly by regenerating epithelial cells in the vicinity of the ulcer.[17]

That the patient's peace of mind, induced by faith in his physician's treatment, affects healing was shown[18] when an unselected and consecutive series of ambulant patients received no other treatment except a daily subcutaneous injection of 1 ml. of distilled water. Healing was confirmed by gastroscopic observation.

In my view the ulcer problem lies not in how to achieve healing but in how to prevent recurrence, and here the physician has precious little to offer. A review of those patients who had received medical treatment for peptic ulcer under my care between 1946 and 1956 showed that, out of a total number of 882, 187 had had gastric ulceration, and in all healing had been confirmed by gastroscopy. Of these 187 cases 60% had recurred within two years and no less than 85% at the end of five years.

Indications for Surgery

Ferriman[19] has put the position clearly. Surgery is necessary for persistent or repeated haemorrhage, for pyloric stenosis, for hour-glass deformity, if there is concomitant ulcer deformity of the duodenum, when a large hiatus hernia is also present, or where malignant change is proved or suspected. It is also advisable for those patients with a long history, a large ulcer, or both. A trial of medical treatment is justifiable in most other cases, surgery being reserved for its failures. Since the long-term results of medical treatment are so poor it follows that the majority of patients with a chronic gastric ulcer will eventually come to surgery. A discussion on the various types of operation available would be out of place here, but it should be said that, having agreed with the surgeon that the patient would benefit from a certain operation, it is then for the physician to assess him as an operative risk, and for the surgeon to estimate the technical problems; both together can explain to the patient the operation envisaged. The value to the patient of a friendly medico-surgical team cannot be overstressed.

Gastritis and Gastric Ulcer

Out of the vast literature on this subject it is possible to select only a few of those contributions considered to be particularly relevant to this section.

The chronic gastric ulcer develops only in a stomach capable of secreting hydrochloric acid, and it cannot develop so long as a normal mucosa lies snugly under its protective mucus barrier. Under what circumstances then may the gastric mucosa become exposed to digestion by its own juices? Dragstedt and his colleagues[20 21] consider that lesser curve ulcers develop when there is antral stasis promoting an augmented hormonal phase of secretion sufficient to overwhelm the mucus barrier. Certainly giant lesser curve ulcers appeared rapidly after vagotomy when this operation was first introduced. Gross stasis was present, and the addition of a drainage procedure led to the disappearance of these ulcers. Burge[22] holds the same opinion as Dragstedt, and has pointed out how frequently lesser curve ulcers are found in association with juxtapyloric lesions causing intermittent obstruction at the distal end of the stomach. He and his colleagues[23] have shown that in such cases the operation of bilateral selective vagotomy with pyloroplasty is curative, and a recent five-year follow-up indicates that the long-term results are excellent. Further evidence in support of Dragstedt's views has come from Lai,[24] who reported that the highest concentration of gastrin occurs in the antral mucosa, that gastrin-like activity is at a high level when stenosis is present and is as high or even higher in benign gastric ulcers as in uncomplicated duodenal ulceration. On the other hand, Schrager and his colleagues[25] found marked inflammatory changes in the antral mucosa in cases of gastric ulceration, together with degeneration with metaplasia, and concluded that an abnormal production of hormone would be unlikely to be responsible for the development of a gastric ulcer.

du Plessis,[26] while not denying the views of Dragstedt and Burge, considers that only a small proportion of gastric ulcers develop in this way, and that the majority develop in an area of atrophic gastritis, the end stage of a widespread inflammatory lesion of the gastric mucosa, which is in turn the result of persistent reflux of duodenal contents through an abnormally functioning pylorus.

Vesely and colleagues[27] also accept Dragstedt's views concerning the significance of gastric stasis, but only in those cases where a gastric ulcer develops after a duodenal ulcer has been present for some years. They hold that the majority of gastric ulcers form on an atrophic mucosa, immunological processes being of aetiological importance. In this connexion Doniach and Roitt[28] have reported a raised incidence of parietal cell antibodies in patients with gastric ulcer, while Freisinger[29] found a high antiurease titre when a gastric ulcer was present. He considers that the likely physiological role of urease is that of protection against acid digestion, and suggested the possibility of an antigen-antibody mechanism in the genesis of chronic gastric ulceration. Mackay and Hislop[30] also believe that atrophic gastritis, patchy at first, is the precursor of gastric ulceration, and list the possible causes of such a gastritis as dietary irritants, malnutrition, alcohol, drugs, chronic infection with enteric bacteria, and autoimmune reactivity.

A possible clarification of these opposing views has come from Johnson and his colleagues,[31] who have produced evidence that chronic gastric ulcers are of two main kinds, one being associated with hypersecretion and very marked blood group O predominance, the other with hyposecretion, no evidence of

group O predominance, and strong evidence for an excess of group A. Hypersecretion ulcers are either prepyloric or in association with duodenal ulceration. Commenting on this important paper, Davenport[32] accepts that there are indeed two types of gastric ulcer with profound physiological and genetic differences. He suggests that in those with apparent hyposecretion of acid this occurs because the normal high barrier opposing diffusion of hydrogen ions into it has been broken, and mentions that aspirin is one of the substances capable of causing a transitory change in this barrier.

Conclusions

Chronic benign gastric ulceration develops only in a stomach capable of secreting hydrochloric acid, and it cannot develop if there is a normal mucosa which remains protected by its mucus barrier.

Chronic gastric ulcers can be divided into two types:

(1) Those which are juxtapyloric, or combined with duodenal ulceration, are associated with gastric hypersecretion. In this type the operative factor may be antral stasis with augmentation of the hormonal phase of gastric secretion. If the output of gastrin reaches a sufficiently high level the resulting hypersecretion might be sufficient to overwhelm the mucous barrier.

(2) Those associated with hyposecretion perhaps develop on an area of atrophic mucosa, a patch of mucosa whose resistance has been lowered, the surface cells then losing their capacity for regeneration. Such a patchy atrophic gastritis might result from faulty diet, malnutrition, local irritants, alcohol, smoking, drugs, infection, ischaemia, autoimmune processes, or even degeneration associated with ageing.

Though the majority of gastric ulcers can be persuaded to heal by medical means the recurrence rate remains extremely high, and medicine has to date no answer to this problem. It is the surgeons who have so far produced lasting results.

REFERENCES

1 De Réaumur, *Hist. acad. roy. d. Sci. Paris*, 1752, **66**, 266.
2 Spallanzani, L., *Fisica Animale*, 1780, **1**, 1. Modena.
3 Prout, W., *Phil. Trans. B*, 1824, **114**, 45.
4 Tiedemann, F., and Gmelin, L., *Die Verdauung nach Versuchen*, 1826, Leipzig.
5 Beaumont, W., *Experiments and Observations on the Gastric Juice, and the Physiology of Digestion*, 1833. Plattsburgh.
6 Regnard, and Loye, *Expériences sur un supplicié. Progres. Med.*, 1885.
7 Wolf, S., and Wolff, H. G., *Human Gastric Function*, 1943. New York.
8 Malhotra, S. L., *Gut*, 1967, **8**, 548.
9 Edwards, F. C., and Coghill, N. F., *Quart. J. Med.*, 1968, **37**, 337.
10 Ariga, K., *Gastroent. Endosc.*, 1966, **8**, 7.
11 Gwyn Williams, D., Truelove, S. C., Gear, M. W. L., Massarella, G. R., and Fitzgerald, N. W., *Brit. med. J.*, 1968, **1**, 535.
12 *Lancet*, 1967, **1**, 291.
13 Smallwood, R. A., *Gut*, 1967, **8**, 592.
14 Shepherd, J. A., *Brit. med. J.*, 1968, **1**, 625.
15 Doll, R., Hill, I. D., Hutton, C., and Underwood, D. J., *Lancet*, 1962, **2**, 793.
16 Doll, R., Langman, M. J. S., and Shawdon, H. H., *Gut*, 1968, **9**, 42.
17 Goodier, T. E. W., Horwick, L., and Galloway, R. W., *Gut*, 1967, **8**, 544.
18 Gill, A. M., *Lancet*, 1947, **1**, 291.
19 Ferriman, D., *Gut*, 1962, **3**, 38.
20 Dragstedt, L. R., Oberhelman, H. A., jun., Evans, S. O., and Rigler, S. P., *Ann. Surg.*, 1954, **140**, 396.
21 Dragstedt, L. R., *Gastroenterology*, 1956, **30**, 208.
22 Burge, H., *Vagotomy*, 1964. London.
23 Burge, H., Gill, A. M., and Lewis, R. H., *Lancet*, 1963, **1**, 73.
24 Lai, K. S., *Gut*, 1964, **5**, 327.
25 Schrager, J., Spink, R., and Mitra, S., *Gut*, 1967, **8**, 497.
26 du Plessis, D. J., *Lancet*, 1965, **1**, 974.
27 Veselý, K. T., Kubíčková, Z., and Dvořáková, M., *Gut*, 1968, **9**, 57.
28 Doniach, D., and Roitt, I. M., *Semin. Haemat.*, 1964, **1**, 313.
29 Freisinger, F. S., *Gut*, 1963, **4**, 339.
30 Mackay, I. R., and Hislop, I. G., *Gut*, 1966, **7**, 228.
31 Johnson, H. D., Love, A. H. G., Rogers, N. C., and Wyatt, A. P., *Gut*, 1964, **5**, 402.
32 Davenport, H. W., *Gut*, 1965, **6**, 513.

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Antibiotics in Acute Respiratory Infections

Acute infection of the respiratory tract is the most common cause of ill-health in temperate climates. The U.S. National Health Survey showed that three out of every five acute illnesses were respiratory affections, mostly minor infections of the upper respiratory tract; in Western Europe it has been estimated that acute respiratory disease is responsible for one-fifth of all time lost by adults from work by reason of illness, and three-fifths of all time lost from school by children. Although much useful symptomatic treatment may be given to patients suffering from these infections, the most important policy decision is whether or not a patient should receive an antimicrobial drug and, if so, which one. But there is great confusion and much conflicting advice about the criteria which should govern these decisions. Clinicians are constantly exhorted to avoid the indiscriminate use of antimicrobial drugs, but it is difficult to understand the value of these general dicta, since few doctors could be accused of using antibiotics in a deliberately careless fashion. The problem is rather to delineate the situations in which such drugs are indicated and in which they are not. On the one hand, all would agree that severe bacterial pneumonia deserves immediate antibiotic treatment, and most doctors would deny such drugs to a previously healthy person suffering a mild cold. The difficulties lie in the very large middle ground of respiratory infections of intermediate severity and of uncertain cause.

Only some of these infections are bacterial in origin, and it is often difficult to decide on clinical grounds which they are. Clinicians are often unsure when a viral infection is complicated by a bacterial one. Even if the infection is bacterial the nature of the infecting organism is almost always unknown, and so, therefore, is its drug sensitivity pattern, at the start of treatment. Suitable specimens for culture often cannot be obtained, especially in children, and when they are obtained the organisms found may represent the true respiratory pathogen poorly. It is to be hoped that some of these difficulties will be lessened by advances in laboratory technique, and fluorescent antibody methods have already given promising results in the early diagnosis of infections caused by respiratory syncytial virus and certain other agents.

Prescribing Policy

Since a rational antimicrobial drug policy is so difficult to formulate for these common illnesses, can one make any kind of balance sheet of the pros and cons of antimicrobial drug treatment? On the one hand it would be improper to withhold antibiotics from a patient with a possible bacterial infection, so the diagnostic uncertainties favour widespread use of these drugs. On the other hand, antimicrobial drugs carry with them a risk of unwanted side-effects, usually minor, but