MEDICAL ASPECTS OF CHRONIC PEPTIC ULCER

By R. Sleigh Johnson, M.D., M.R.C.P.

Physician, London Chest Hospital, Southend General Hospital, Royal Waterloo Hospital

General Considerations

Few diseases, whether from their frequency of incidence or their difficulties in treatment, can claim a more rightful place in medical attention than peptic ulcer, a comment applying with equal force to physician and to surgeon, and to hospital as well as to general practice. Figures of hospital emergency admissions show few conditions more demanding on the medical side than acute gastric haemorrhage, while surgical complications of peptic ulcer demand a like proportion of beds. In such an ever-present disease, it is a disturbing thought that despite unceasing clinical study and experimental work, the aetiology should defeat exact investigation and remain largely obscure, and perhaps no less disturbing that so little uniformity of agreement should have been reached on policies of treatment, particularly in circumstances where medical and surgical aspects overlap. In consequence, the results of treatment of peptic ulcer cannot yet be claimed to be wholly satisfactory, whether the path chosen be that of medical zeal or of no less enthusiastic surgery. An attempt to review and co-ordinate these varying trends of opinion may not, therefore, be out of place.

Incidence

In distribution peptic ulcer is world-wide and without respect of race, occupation or class, occurring within a wide range of ages. In incidence it is without doubt one of the commonest afflictions of mankind. From autopsy findings it is estimated that at some period in his life one person in ten is so affected, though not always is the lesion revealed by symptoms. The age group most commonly involved lies between 20 and 40 years, but acute ulcers revealed by haemorrhage or even perforation are met with in infancy or early childhood. A familial factor is often easily traced, and is found in about a quarter of all cases. It is probable that many more gastric ulcers than duodenal are relatively symptomless and therefore undiagnosed, autopsy findings of healed ulcers confirming a higher incidence in the stomach, but from the clinical standpoint duodenal ulcer is much the commoner disease, in a proportion of at least three to one, and correspondingly more resistant to treatment. With regard to sex incidence, duodenal ulcer shows a marked preponderance for the male subject, being between three and four times commoner in men, whereas gastric ulcer is relatively more frequent in women. In two respects, those of physique and of psychological make-up, an 'ulcer-type' may be readily recognized in the spare, lean build and anxious over-active manner, predominantly seen when the site is duodenal.

It occasions no surprise that the incidence of peptic ulcer appears to have risen considerably during the past 30 years, and even more during the past decade, in response to strain and stress of living and the increased pace of life; part of this apparent rise is no doubt due to improved facilities for diagnosis, and part to a failure to distinguish recrudescence from primary disease, but after allowance has been made for these factors there is certainly a real increase, particularly in duodenal ulcer. The greater incidence of this lesion in men is reflected anatomically in the hypertonic type of stomach known to predominate in the male, with its hypersecretion and rapid rate of emptying, whereas simple gastric ulcer is less constantly linked with hyperacidity and excess of tone, and is therefore by no means rare in the asthenic, anaemic type of woman with low-lying or hypotonic stomach. This distinction of type is further emphasized in the different psychological and emotional background of the two groups.

Aetiology

The problem of causation of peptic ulcer is still unsolved. Occupational factors in aetiology are unconvincing. Whereas a type of employment demanding physical rush and mental strain, with inconstant hours, hasty and irregular meals, no doubt contributes to break-down in those predisposed, peptic ulcer is common enough among all classes of occupation and society, humble or well-to-do. Of greater influence and importance are psychological factors. It is common knowledge how frequently ulcer symptoms, including perforation or haemorrhage, may immediately follow a period of nervous stress, anxiety or emotional
upset; the engorging effect upon the mucosa, the oversecretion and muscular spasm of the stomach which follow such disturbances can be seen with the eye and are sufficient explanation of events. Yet in most cases these are probably contributory rather than causative factors, responsible more often for the breakdown and recrudescence which may so readily be mistaken for the start of the disease, for onset is insidious and few patients can accurately define it.

Habits

The relation of tobacco and alcohol to peptic ulcer is similar; while there is no proof that smoking, even in excess, is a direct causative factor, it is generally agreed that the swallowing of nicotine excites free secretion of gastric juice, which can only be undesirable and harmful to an empty stomach. The renewal of pain which follows a lapse into the cigarette habit or an alcoholic indulgence is sufficient reminder. Of greater importance are habits of eating, though given less attention and emphasis than details of diet. Rushed and irregular meals, eaten against time, perhaps in un congenial surroundings, with an unsuitable choice of food, may initiate symptoms or lead to breakdown in the predisposed. Inadequate preparation of food for gastric digestion may ensue from defective or carious teeth, and a contributory gastritis be set up. Acute infections of any kind may act in a similar way to nervous worry, fatigue, or faulty habits, in precipitating the acute exacerbations so characteristic of the disease. In some patients a seasonal incidence of breakdown is noted, mainly at the change to colder weather.

Pathology and Pathogenesis

Chronic peptic ulcer is usually a single lesion, but separate ulcers are not uncommon in stomach and duodenum, or more than one ulcer may be present in the stomach. Similarly, active and healed lesions may co-exist, or a single ulcer may show extension and healing in different directions at the same time, although one of these processes is usually predominant. The region liable to peptic ulceration corresponds accurately with the extent of exposure to the acid gastric secretion. The great majority of ulcers are included in a site within the lesser curvature of the stomach, particularly in its central third, or within the first two inches of the duodenum, the duodenal cap or bulb; the pylorus is frequently involved and its function affected by a pre- or post-pyloric ulcer. For the same reason a characteristic lesion is common in the area of jejunum directly opposed to a patent gastro-enterostomy, while rarely a typical peptic ulcer may develop in ectopic gastric mucosa at the lower end of the oesophagus or in a Meckel’s diverticulum. The greater curvature of the stomach is a rare site for benign ulceration, and this situation of itself should arouse suspicion of malignancy.

Opportunities for direct study of peptic ulceration in its varying stages were formerly confined to operative or post-mortem inspection. Within the last few years, however, our knowledge of its life history and pathology has been greatly extended and clarified by the direct inspection in the living subject afforded by gastroscopy.

An acute stage necessarily precedes the development of every chronic peptic ulcer, and is revealed as a sharply circumscribed loss of tissue beginning in the mucosa. This forms a shallow erosion, often small in size, with clean cut, punched out edges and smooth floor, sometimes covered by white or yellowish slough, and tending to become terraced as it reaches the subacute stage. Signs of inflammation of the surrounding mucosa may or may not be present, but at this stage there is no protective thickening of the peritoneal surface. Such an ulcer, if destruction of tissue is rapid and progressive, may quickly penetrate all layers of the gut, unresisted by any barrier of fibrosis, and terminate in perforation with its dramatic consequences.

Healing, on the contrary, frequently takes place at this early stage by growth of a thin layer of mucosal cells across the defect, leaving either a normal looking surface or little more than a stellate puckering of the mucosa to mark the site. Many such acute ulcers are wholly unproductive of symptoms. Should the healing process fail or be incomplete, however, the ulcer slowly extends both in surface area and in depth, with a progressive penetration into the submucous and muscular layers of the viscus or beyond. Such a process may extend over a period of years, surface healing failing to keep pace with the rate of ulceration. The chronic ulcer resulting commonly becomes thickened and indurated by inflammatory connective tissue formation at its base, with deep or terraced margins, in some cases undermined. The floor of such an ulcer may appear clean and covered with granulation tissue, or be concealed beneath a fibrinous exudate or slough, in which thromosed vessels of considerable size may be situated. Adhesions to adjacent organs are usual. An ulcer of long duration, and the liver, pancreas or omentum may form part of its base. This process of scarring in ulcers of marked chronicity may also promote a gross deformity and obstruction within the organ, seen in pyloric stenosis or hour-glass stomach, while organic occlusion may be closely simulated by muscular spasm and oedema.
This fluctuating life-cycle of a chronic peptic ulcer, reflected clinically in periodic remissions and exacerbations of symptoms, is found pathologically to correspond with phases of fresh ulceration and partial healing. Periods of quiescence or complete absence of symptoms tempt both patient and clinician to assume that the ulcer has healed, an error often supported by pathological and X-ray tests. Direct inspection, however, in these cases will frequently show that the lesion is not healed, but merely inactive and dormant. What is often thought to be a fresh ulceration is but the reactivity or breakdown of an old-standing lesion. For like reason, a sudden unexpected haemorrhage or perforation may sometimes be the first indication that all is not as well as was thought.

A further pathological aspect of a benign but indolent gastric ulcer is the possibility of malignant change, a question which has been the subject of prolonged and intensive study. Widely differing views are held by experienced observers as to the frequency of such change, and even as to its occurrence, opinion of its incidence varying from nil up to ten or more per cent. The feasibility of possible malignant transformation of an inflammatory lesion which is constantly subjected to external irritation is paralleled in the case of other body surfaces, notably the skin. Yet there are many difficulties in accepting this view of so-called 'ulcer-cancer' production. The common site of carcinoma in the stomach, with its predilection for the pyloric zone or greater curvature, differs radically from that of simple ulcer; carcinoma is practically unknown in the first part of the duodenum, where as a sequel to long-standing irritation of chronic ulcer it would be frequently anticipated, even more commonly than in the stomach. Similarly unmet is malignant disease at a gastro-jejunal stoma. In the great majority of cases of carcinoma of the stomach, moreover, the age incidence affects an older period, and the history of digestive disorder is relatively short, the disease appearing clinically to start de novo rather than as a sequel to long-standing dyspepsia. From serial inspection of very large numbers of benign ulcers over a period of years, gastroscopists of wide experience have stated that they have yet to be convinced of malignant change occurring, and surgeons in this country of the experience of Ogilvie hold the view that these are diseases of completely differing aetiology. With this view the present writer concurs. The contrary view of a frequent malignant change has received its main support from evidence based upon the naked eye and histological features of ulcers removed at operation, and has been favoured in particular by American surgeons, including MacCarty and Broders and Allen and Welch. It is well recognized, however, that owing to digestive changes the histological features of benign and malignant ulcers may be closely similar, while secondary inflammatory reaction at the margins of a gastric carcinoma is of common occurrence and a further source of confusion. Naked eye differentiation is accepted as being of little or no value, and size is of no significance—a carcinoma may be small, a simple ulcer enormous.

The importance of this differentiation is stressed in its bearing upon policies of treatment, notably in the forming of a right judgment between the respective claims of medicine and surgery. If the danger of malignant change is great, every chronic ulcer should be removed forthwith; if remote, then decisions of surgery are to be based upon other grounds, and each case assessed upon its merits.

Theories of Causation of Peptic Ulcer

In the development of a peptic ulcer, the lining membrane of the stomach or duodenum at the affected site, normally impervious to the action of the gastric juice, is by some means made susceptible to digestive action, and consequent ulceration, by predisposing factors still not wholly understood. Many differing theories of causation have been advanced, and attempts, mostly unsuccessful, made to reproduce their effects experimentally. Brief mention may be made of some of these hypotheses. Firstly, the view has been put forward of a common specific infective causation. In this regard it is clear that the lesions of peptic ulcer are unrelated to any specific bacteriology; the occasional association of acute ulcer with severe generalized infection, revealed for the most part post-mortem, shows no common identity of organisms, and, as in its rare sequel to burns, the ulcer here is probably a reactor to the absorption of tissue-breakdown or histamine products. Moreover, no similarity of bacteriology has been demonstrated as affecting the ulcer lesions and oral infection when this is present. Ulcers produced experimentally in animals by injection of organisms into the gastric mucosa show rapid healing and no tendency to progress to a chronic stage; traumatic ulcers of the stomach, both in the animal and the human subject, caused by the swallowing of a foreign body show a similar prompt resolution.

Vascular anomalies have been similarly credited, by interfering with the nutrition of the affected zone of digestive mucosa. The frequent demonstration of thrombosed vessels in the base of a chronic ulcer has suggested that a local vascular spasm of the mucosal arterioles from excessive stimulation of sympathetic nerve supply may be the primary factor, bringing about a loss of blood
supply to the area with necrosis of mucous membrane by infarction. Alternatively, a spastic contraction of the muscularis mucosae has been adduced, with supposed compression of small vessels producing anaemia of the mucosa and subsequent digestion. Such theories are at once disproved by the free anastomosis of vessels found in the stomach, wide ligature of which fails experimentally to produce ulceration; the thrombosis so often seen is the result and not the cause of the lesion. Similarly, an attempt to explain the production of peptic ulcer by a neurogenic disturbance carries little weight; the sole neurological association which can be demonstrated in ulcer subjects is a vagal overaction, a reasonable explanation of the hypersecretion and hypermobility of the stomach which is so often present. A further theory of causation pronounced is the lack of a supposed specific protective substance (named 'anti-pepsin' or 'defendin' by its advocates) and regarded as normally inhibiting auto-digestion by the gastric secretion. Such a view is of theoretical interest only, and unsupported by any demonstrable evidence, in common with a number of other suppositions of aetiology.

While the responsible factors for initiation of tissue loss remain obscure, the failure of healing of the breach of surface, when once begun, is less difficult to understand. There is present in these subjects with considerable constancy an inability of the mucous membrane to resist the digestive action of the acid gastric juice, a defect roughly proportionate to the degree of hyperacidity present. Thus, broadly speaking, the healing of a duodenal ulcer, with its higher level and more constant association of gastric acidity, is a more prolonged and difficult task than the healing of a benign gastric ulcer. Hyperacidity is, moreover, not a necessary requirement, for mucosal resistance so impaired may still be inadequate to allow of healing, even in the presence of normal gastric acidity, as is found in the chronic gastric ulcers of many patients of asthenic build. Similarly, a general state of diminished tissue resistance throughout the body associated with undernutrition, or with toxic or infective processes in other systems, will from its inclusion of the gastric function readily be understood as contributory to ulcer breakdown; an inadequate secretion of protective mucus locally by the stomach in these states may have similar result.

Whether the ultimate cause is then the excess of hydrochloric acid itself or some other abnormal condition of the gastric secretion is a moot point, for acidity by no means represents the sum total of peptic activity. Again, whether the weak spot in defence is a lack of cellular resistance to digestion or, as noted, a lack of cellular protection by mucus-secreting cells (a secretion lessened in ulcer subjects) is equally unknown. The important point is that the presence of hydrochloric acid in excess is the main certain factor in maintaining the activity of peptic ulcer.

Time factors are of no less significance. Where, as in ulcer subjects, the duration of exposure of the mucosa is prolonged, for example during the night or for long fasting hours between badly-spaced meals, times during which the normal stomach would produce little or no acid, this abnormal digestive process is intensified.

This general relation of hyperchlorhydria or the 'acid-pepsin' factor to peptic ulcer is confirmed in a number of ways. The site of ulceration, for example, is confined strictly to those portions of the digestive tract coming into direct contact with the acid gastric secretion, a generalization true even in the case of unusual sites of ulceration, such as the oesophagus. Simple ulcer, in corollary, is never found among the 10 per cent. or so of the population with a congenital histamine-achlorhydria. Confirmation of the significance of acid exposure is given by the varying results of surgical resection in treatment. Where this is adequate and achlorhydria is produced, recurrent ulceration does not occur. Where, however, the removal of acid-producing gastric mucosa is of insufficient extent, this liability to recurrence remains. The legacy of stomal or jejunal ulceration after an ill-chosen gastro-jejunostomy in a patient with high acidity is a further example of the inadequacy of any treatment which fails to eliminate acid production.

Experimental work in animals gives similar conclusions. Gastric ulcers produced artificially in animals fail to heal if the normal neutralization of acidity by duodenal contents is prevented, or if an abnormally high level of acidity is maintained in the stomach, either by direct administration of acid or by maintaining a hypersecretion by histamine injections.

Despite this evidence from various sources, the question of acidity is clearly not the whole story and the problem of causation remains a complex one. Although a great hypersecretion of acid (up to 0.4 per cent. HCl) is the common finding in peptic ulcer, especially of the duodenum, other patients will show normal levels of acidity or less, and it has to be admitted, therefore, that the problem is still incompletely solved.

Of scarcely less importance in the aetiology of peptic ulcer is the question of muscle tone and contractility. Duodenal ulcer subjects in particular commonly have a hypertonic stomach undergoing violent peristalsis, with rapid emptying of acid secretions into the duodenum. In other cases, pylorospasm will be the cause of a persistently high acidity of gastric contents from delay in
emptying of the stomach. Much stress has been laid by gastroscopists upon the even closer anatomical relationship of ulcer incidence to hyperrugosity of the stomach mucosa, the more so in duodenal cases.

**Symptoms of Peptic Ulcer**

In the establishment of diagnosis of peptic ulcer, symptoms far outweigh physical signs in importance, and a detailed study of the patient’s complaints and of factors affecting them should lead far along the road. Detailed history-taking in a suspected case of peptic ulcer is of such outstanding value that it should never be omitted or curtailed; in itself it may be almost conclusive, and place the realm of physical examination and laboratory tests into that of confirmatory measures.

The outstanding symptom of peptic ulcer is pain related to the taking of food. Its special features may be so characteristic as to be practically diagnostic and will include the following considerations:——

(a) **Duration and periodicity.**
(b) **Relation to the taking of food.**
(c) **Situation and paths of spread.**
(d) **Character and severity.**
(e) **Aggravating and relieving factors.**

These may be considered in detail.

**a) Duration and periodicity**

In time-relations two special features are commonly revealed in history-taking. The first relates to the total duration of pain, which in most cases of ulcer extends over a period of months or years. The second feature is the nearly constant occurrence during this time of periods of freedom from symptoms, partial or complete, for spells of a few days, weeks or even months, during which the ulcer is quiescent but not healed. Such free intervals often bear a seasonal relationship, though not constantly so; frequently, however, no reason can be assigned for the fluctuations of illness. With progress of time the tendency is for the spells of pain to become more frequent and severe, with shorter intervals of freedom, and less ready relief. In some cases bouts of pain may follow dietary indiscretions or intercurrent illness, but in others they recur in spite of the most careful régime. Great diagnostic significance may safely be placed upon this periodicity of ulcer pain, more especially in the case of duodenal ulcer.

**b) Relation to the taking of food**

The daily rhythm of the pain, as distinct from its longer periodicity, is shown in its clockwork regularity after the taking of food, at an interval varying from a few minutes to three hours or more. The heavier the meal the more severe the pain, which may sometimes only follow the main meal of the day. As with site, the time relation of the pain is no certain guide to the situation of the ulcer. In general, however, pain from duodenal ulcer occurs at a long interval after food, which it often appears to precede rather than to follow. It is an especial feature in the small hours of the morning, often waking the patient from sleep. It is, in fact, a diagnostic principle that pain of sufficient severity to awaken a patient who has once fallen asleep should be regarded as due to organic disease rather than to functional dyspepsia, unless completely proved otherwise. In the same subject considerable constancy is the rule in the character and time relations of his ulcer pain.

**(c) Situation and paths of spread**

Ulcer pain is felt most commonly in the central epigastrium, where it is often sharply localized to a small area. Alternatively, it may be located to one or other hypochondrium or to a combination of these sites. The exact situation of pain is of little or no value in the differential diagnosis of the probable site of ulceration, although in duodenal ulcer the reference is more commonly to the right hypochondrium. In contrast to peptic ulcer, the pain of nervous dyspepsia is less well-defined, and is usually referred widely to the upper abdomen. Radiation of pain through to the back or around the costal margin, especially when severe and resistant in type, commonly indicates involvement of the posterior abdominal wall by a deep penetrating ulcer, with its special dangers of haemorrhage. Jejunal ulcer has a reference of choice to the left mid-abdomen at about the umbilical level, with tenderness at this site. Inflammatory spread beyond the confines of an ulcer, with involvement of the peritoneum, leading to a perigastritis or periduodenitis, may widen the reference of pain, and its intensity and relentlessness, to any degree.

Finally, in regard to pain production, it must be noted that a few active ulcers, for reasons not understood, may fail to cause any pain whatever, and the first evidence of their presence may be severe haemorrhage or perforation.

**(d) Character and severity**

Ulcer pain may be of any grade from a mild discomfort to severe distress. At onset it may scarcely merit the term pain at all, and be no more than a dull upper abdominal discomfort or feeling of emptiness. Later, with established ulceration, definite pain as opposed to mere discomfort is the rule, a point of value in distinction from the many forms of nervous dyspepsia. It is then commonly of burning or boring character, and may from its severity lead the patient drastically to reduce his diet in fear of its recurrence. In degree and
development it is commonly of ingravescent or 'crescendo' character, rising to a maximum severity within a few minutes of onset after food. The pathognomonic linking of pain with a craving for food, and the relief commonly given thereby, has aptly led to its designation as 'hunger-pain,' a feature most characteristic and constant in duodenal ulcer.

(e) Aggravating and relieving factors

The essential relation of ulcer pain to food is concerned no less definitely with the amount and character of the food partaken. An unwise choice of diet, whether of highly-flavoured or unsuitable foodstuffs, or of immoderation in size of meal, will in each case render pain more certain and severe. The immediate effect upon pain of the taking of food will vary with the situation of the ulcer in the patient concerned; in duodenal ulcer relief is characteristically given, with recurrence as the stomach empties; in gastric ulcer exacerbation of pain is the rule.

In no less degree does relief of pain in simple ulcer follow the inception of suitable dietary measures, with accompanying bed rest. So marked and constant is this relief, in fact, as to be practically diagnostic. Should it fail to occur, and pain remain unaltered, one of two conclusions may safely be drawn. Either the diagnosis is in error, and search should be made, in explanation, for some other organic disease; or the ulcer has undergone complications beyond its confines by development of external adhesions, inflammatory changes, leak or obstruction, little relief then being given by dietary measures.

Complications of this order apart, relief by dieting in simple ulcer is fully equalled by the relief from giving alkalis, to which an equal diagnostic significance may be attached. Wherever the site of ulceration, the neutralization of gastric acidity so afforded brings an immediate though temporary cessation of pain.

External factors, less directly concerned with food, may also greatly influence the pain and other symptoms of peptic ulcer. Anxiety, physical and nervous strain of all kinds, general illness, exposure to cold, may all promote exacerbation, or their correction bring relief.

Causation of Ulcer Pain

As with visceral pain in general, the pain of peptic ulcer is primarily of muscular origin, produced either by tension or by stretching of tissues in the ulcer neighbourhood from distension of the stomach or from irregular and violent muscular contractions or spasm, particularly of the pylorus. Relief of pain by antispasmodics is therefore readily explained. Neither the normal mucosa nor the ulcer itself is directly tender or sensitive to touch, but the threshold of pain appreciation may be lowered by inflammatory changes in the region of the ulcer or by excess of acid secretion. Hyperacidity of itself does not produce pain, being frequently present in health, and the severity of pain in ulcer cases is not necessarily related to the degree of acidity present, which in fact often remains unchanged whether the ulcer is in an active or a healing stage. The most severe association of pain with peptic ulcer is that which accompanies involvement of peritoneum or erosion of the pancreas or posterior abdominal wall.

Other Gastric Symptoms

Appetite in uncomplicated peptic ulcer is normally retained or increased, unless an associated gastritis be present, but a common finding is a voluntary restriction of food intake from fear of ensuing pain, and some loss of weight may follow. Nausea is similarly unusual apart from obstruction, and is a more common feature of gall-bladder disease. Vomiting is frequent in severe cases; it may occur reflexly at the height of pain, giving relief, or may indicate an obstruction to the food channel. In some cases the latter is a temporary hold-up from oedema or muscular spasm, a form of obstruction amenable to medical treatment; in others it is of graver issue and signifies an organic stricture from cicatrization of the ulcer base. For a time its effects may be overcome by more powerful peristalsis, visible as waves of contraction proceeding from left to right across the epigastrium, but eventually increasing dilatation follows, leading to forcible ejection of stagnant food and retained fluid, at irregular intervals and often in large amount.

Acid regurgitations into the mouth, with paroxysms of excessive salivation or water-brash, are common accompaniments of ulcer, but are of little diagnostic value, occurring in many other forms of dyspepsia, organic or functional. Gastric flatulence is sometimes present, usually from a subconscous aerophagia to relieve pain, but is again of scant differential significance, and less in evidence than in nervous dyspepsia or cholecystitis.

Constipation is a common finding in peptic ulcer and tends to accentuate the degree of pain. Looseness of bowels may follow excess of laxatives in treatment, while a lienteric form of diarrhoea is worthy of note as tending to follow the performance of gastroentostomy, at least for a time until a nervous adjustment of the altered mechanics is developed.

Anaemia is not a direct feature of simple peptic ulcer unaccompanied by haemorrhage, apart from its possible sequence to prolonged and excessive
restriction of diet, and therefore of iron and vitamin intake.

The subjects of perforation and haemorrhage, the most urgent and important complications of peptic ulcer, are considered separately in another section, but no survey of symptomatology would be complete without reference to the great frequency with which some degree of blood loss occurs. Bleeding of clinical significance is found to occur at some phase, in at least half the total cases of chronic ulceration, either as haematemesis, melaena or both. In acute ulceration it may be the first and only symptom. A large haematemesis much more frequently arises from a simple ulcer than from a carcinoma of the stomach with its more gradual and limited oozing. Other causes of profuse bleeding which sometimes cause confusion in diagnosis include multilobular cirrhosis of the liver, haemorrhagic purpura and splenic anaemia. Differentiation of the site of ulceration, as between gastric and duodenal, from the circumstance of haematemesis or of melaena, is fallacious, the mode of avoidance being dependent more upon the rapidity or otherwise of gastric distension by blood than upon the exact site of bleeding.

What factors determine the hazard of severe haemorrhage in chronic ulceration is often obscure, and the onset of sudden haematemesis is frequently unpredictable. Bleeding sometimes surprises the patient apparently fit and symptom-free; in other instances it follows a heavy meal, or further complicates a phase of acute exacerbation of symptoms.

The danger to life from haemorrhage lies mainly in its repetition; a single haemorrhage, however large, seldom proves fatal. A frequent occurrence, unfortunately, is for the initial bleeding to be followed by further substantial blood loss within an interval of a few hours or days, to which the already exsanguinated patient may succumb. The event of haemorrhage from an ulcer is not always readily discerned. Quite severe bleeding into the lumen of the stomach or duodenum may fail to promote local symptoms, and the history present itself as one of unexplained faintness, collapse and weakness, or of pallor and dyspnoea without apparent reason. The possibility of ulcer haemorrhage may easily be overlooked should there be failure later, on the patient's or the physician's part, to note the dark motions which almost always follow.

In this way recurrent fulminating haemorrhage may dominate the clinical background, but in other cases a prolonged though less obvious loss of blood may lead gradually to the development of an anaemia of milder grade without the signpost of haematemesis. The clue will be given by routine examination of the stools for occult blood, an investigation which in unexplained anaemia should always be made. Reviewing gastric ulceration in its widest sense, a sound rule for clinical guidance is that dyspepsia accompanied by significant anaemia indicates the likelihood of bleeding ulcer or of growth.

To summarize the role of history taking in diagnosis, it may be said that a full survey of symptoms in peptic ulceration will of itself frequently justify a provisional diagnosis, the main place of special investigations being confirmatory. In other cases the confirmation of diagnosis may be afforded not by instrumental means, but by clinical criteria in the development of one of the well-recognized complications of ulceration such as perforation, leak, haemorrhage or obstruction, so modifying the clinical picture as to prove the diagnosis beyond doubt.

Physical Signs

Physical signs in peptic ulceration are less constant in nature and in significance, and routine clinical examination may frequently fail to elicit any abnormal findings, especially during periods of relative quiescence. Although a spare nervous duodenal type is recognized, physique and temperament are too variable to be of diagnostic value. Nutrition is usually preserved and anaemia is not a feature apart from blood loss. Local tenderness upon deep pressure is common in the central epigastrum or to either side of the upper abdomen, usually well-localized and corresponding with the site of pain, and sometimes associated with cutaneous hyperalgesia. The site of tenderness usually remains constant in the individual patient, and is often accompanied by muscular rigidity of the upper rectus to a variable degree. Rarely, a tender mass may be felt where acute inflammation has followed a slow leak through the ulcer base, and may be confused with carcinoma. Obstruction will outline the distended stomach or portion thereof, with peristaltic waves of characteristic type. Splashing is readily elicited in dilatation of the stomach with retention of its contents, but is of no pathological significance within two and a half hours of a meal.

Special Investigations

Radiology. Apart from these sparse findings, diagnosis of peptic ulcer depends upon a combination of careful history and of special investigations. Of the latter radiology takes the lead, and in good hands will reveal a high proportion of ulcers by means of an opaque meal. Thus it should be possible to diagnose some 90 per cent. of gastric and 75 per cent. of duodenal ulcers, the difficulties and errors being higher the deeper and less accessible the site. Of anastomotic ulcers
perhaps the majority will be revealed. Despite the most careful radiological examination fallacies will sometimes occur, and the rule for the clinician should be to accept a diagnosis of peptic ulcer, particularly duodenal, based on strong clinical evidence in the absence sometimes of X-ray confirmation. The same comment applies with regard to tests of cure.

Satisfactory radiological examination of the gastro-intestinal tract requires that the patient shall be fit enough to stand for some minutes without fear of faintness or collapse. Recent haemorrhage will clearly preclude such examination, usually for a period of a month to six weeks. A further requirement is that the stomach must be completely empty at the time of survey, a morning investigation, therefore, being preferable.

Screening rather than films constitutes the more informative aspect of the test, and to be of full value observation will be needed in a series of planes, posterior-anterior, both obliques and sometimes in the recumbent position. Details of the examination are discussed elsewhere, but reference may be made here to its essential objects. The size and type of stomach is revealed, and an estimation made of its tone, peristalsis and the character of its rugae. Direct demonstration of a niche or crater is the most convincing X-ray evidence of an ulcer, either in the stomach or duodenum, but short of this it may be shown indirectly by the muscular spasm by which it is frequently accompanied, especially in its active phases. Thus a fixed localized spasm or incisura may be found opposite the ulcer site, or in other cases a marked spasmodic contraction of the pyloric segment or duodenal bulb, with difficulty and delay in gastric emptying. Repeated examination may in these cases be required after an interval of treatment by antisapmosemics, so as to differentiate the nature of the obstruction, whether spasmodic or organic stricture, as well as to clarify the cause of duodenal deformity, whether simple spasm or distorsion by active ulceration or by scarring. The latter point is greatly helped by the determination of local tenderness or otherwise upon X-ray palpation. Tenderness of the ulcer site is valuable evidence of active ulceration, especially when accompanied by irritability and disordered motility.

Confirmation of obstruction will be given radiologically by dilatation of the affected organ or segment and its delayed emptying, while adhesions to surrounding organs may usually be demonstrated by palpation under the screen.

While not decrying its great value in diagnosis, too much weight should not be given to radiological investigation alone, nor its conclusions regarded as infallible. Negative investigation by no means excludes an ulcer, nor proves its healing. Its greatest value lies in serial observation and in the assessment of progress in the established case.

Gastric analysis. Support for radiological evidence is given by chemical laboratory tests, in chief by gastric analysis. Examination of a single specimen of gastric contents after a one-hour interval is a method of little value and of historical interest only, the fractional test meal being now universally employed. As with X-ray examination, it is best carried out in the early morning and the patient's last meal must have been not later than 8 p.m. the previous evening, all drugs being omitted on the day of test. The fasting stomach, contents or 'resting juice' are completely withdrawn after the swallowing of a Ryle's tube, the meal prepared from fine oatmeal gruel is then given, and samples of about 10 to 15 cc. of gastric contents withdrawn at regular intervals, preferably half-hourly, for a total of 2½ hours, by which time the stomach is normally empty.

The specimen of greatest importance is the resting juice; this is examined for volume, odour, consistency, presence of blood, mucus, and food residues, and microscopically for red cells, pus cells, epithelial and malignant cells, with chemical estimation of free and total acidity. Similarly each specimen is examined for volume, total acidity, free HCl, mucus, bile, blood and starch and the results recorded graphically upon a chart.

The interpretation and significance of the test meal may be briefly described. A wide variation in gastric secretion may be found. In uncomplicated gastric ulcer the curve may either be normal or show a hyperchlorhydria. Sometimes an initial low acidity is found from associated gastritis, the production of acid being increased after gastric lavage. Acidity, moreover, in gastric ulcer increases with proximity of the ulcer to the pylorus. In duodenal ulcer it is the rule to find a marked hyperchlorhydria, with irritability and hypersecretion of the stomach, irrespective of the phase of activity of the lesion. The resting juice also is usually highly acid.

Two types of curve can commonly be distinguished, particularly in duodenal ulceration. In the first, or 'climbing curve,' after an initial fall in acidity due to dilution of the resting juice and fixation of free acid by the meal, there is a gradual rise in its level throughout the whole period of observation. Slow emptying of the stomach from pylorospasm, with delayed bile reflex and little or no regurgitation from the duodenum causes a continued rise in the level of HCl past the 2½ or 3 hours period. In the second or 'hurry' type of curve, a high initial acidity of the resting juice after a slight temporary drop rises sharply to a still higher plateau level, which is
either sustained or shows a premature fall within an hour or so, due to rapid emptying of the stomach unimpeded by pylorospasm.

A further point of value in assessment of test meal findings lies in the volume of resting juice. In the normal stomach being usually of not greater volume than 25 cc., in active ulceration it is commonly increased in volume in like manner with the acidity, so that even without obstruction its amount may rise to a level of 100 to 300 cc. or more, from the combined effect of hypersecretion and pylorospasm.

An alternative method of fractional analysis, now extensively used, is by the substitution of alcohol in place of gruel as an excitant of gastric secretion, giving 100 cc. of 7 per cent. alcohol, and withdrawing samples of gastric contents at intervals. Cleaner specimens are obtained for analysis by this method, easier of filtration and of microscopic examination. Whichever method be used, the giving of histamine as added stimulus of acid secretion when required is a valuable accessory measure in the test. Briefly, histamine is injected subcutaneously in dosage of 0.25 to 1.0 mgm., according to body weight, should the fasting juice and first two or three specimens collected fail to show free hydrochloric acid. Should this be present in the early specimens, the giving of histamine is unnecessary.

In interpretation of these findings, it must be remembered that while many cases of carcinoma of the stomach show an absence of hydrochloric acid, its presence in normal amount or even in excess by no means excludes a diagnosis of malignancy. Other lesions apart from gastric may, of course, be accompanied by achlorhydria. Conversely, a complete lack of HCl production in a test meal which includes the giving of histamine is strong evidence against benign ulceration.

As mentioned in considerations of treatment, the healing of the ulcer has little effect upon the acid secretory levels of the gastric juice; this indeed is one of the potent factors in recurrence. Reference is made later to the means whereby effective neutralization of the gastric acidity may be measured.

Occult blood test. Bleeding detectable only by chemical test is sufficient evidence of active ulceration, granted certain well-known safeguards in technique and interpretation, such as the exclusion of haemoglobin and chlorophyll-containing foods and of bleeding from other alimentary sites such as the teeth and lower bowel. The further fallacy of examining a constipated stool must also be avoided. A positive occult blood test or benzidine reaction in the stools, with these provisos, then indicates a breach of surface epithelium. The test is so sensitive that slight or doubtful reactions may be ignored. The giving of inorganic iron does not cause a positive reaction. Glove washings after rectal examination are a satisfactory substitute in cases of failure to pass a stool for the tests.

In interpreting this simple test, the need for repeated examination should be borne in mind. A single negative test does not exclude peptic ulceration or other organic lesion, but the sustained disappearance of occult blood from the stools is strong evidence of healing of a simple ulcer and makes malignancy an improbability. In converse, repeated positive results, given adequate precautions against fallacy, point strongly to organic disease and throw great doubt upon a diagnosis of functional dyspepsia.

Gastric aspiration. Aspiration of stomach contents, apart from its inclusion in a test meal, is a measure of value both in diagnosis and treatment, especially in suspected obstruction. It has been noted that in the normal empty stomach there should be not more than 25 cc. of resting juice; an excess indicates gastric irritability and hypersecretion, and becomes marked in the event of obstruction of outflow, whether of spasmodic or organic nature. In these circumstances many ounces, rarely pints, of residual stomach contents may be found, perhaps of dirty malodorous fluid containing mucus, blood, stale food or malignant cells, and of high acidity from foreign acids due to putrefactive organisms. Routine aspiration of such fluid and subsequent lavage with 0.1 per cent. HCl will do much to allay the accompanying gastritis and relieve the obstruction present. Even in non-obstructive lesions the removal of highly-acid gastric juice by aspiration is a measure of value, as noted later.

Gastroscopy. Of all methods of examination visual inspection is the most certain, and in this generalization the stomach shares. Direct inspection of the stomach by gastroscopy is fast becoming the most valuable single measure in diagnosis and in assessment of progress of peptic ulcer; feared for long from the undoubted dangers of rigid instrumentation, it has been rendered possible and safe by the introduction and development of the flexible gastroscope by Schindler in Germany 12 years ago, and particularly by the improvements of Hermon Taylor in this country. With premedication and local anaesthesia, combined with skill and experience of the operator, the examination is not unduly uncomfortable or dangerous to the patient. Its value is, of course, greater in the case of gastric than of duodenal lesions. While not infallible, the increased accuracy of diagnosis which it affords, particularly in acute ulcers, should make it a routine measure in the investigation and control of
gastric disease. It in no way replaces or diminishes the importance of radiology, but provides an additional and more exact means of determining pathological changes in the stomach and their course under treatment; the two methods are therefore to be regarded as complementary rather than competitive modes of investigation.

Before gastroscopy is undertaken, a preliminary radiological investigation by barium swallow and meal should always be made, in order to exclude an obstructive organic lesion of the oesophagus. As with X-ray examination, the stomach must be empty, preferably after an overnight fast. Local anaesthesia is employed, so securing the patient's active co-operation, preceded by a premedication of morphia gr. $\frac{1}{4}$ and hyoscine gr. 1/150. Half an hour before the examination the patient is given a tablet of decicaine 0.1 gm., to be dissolved slowly in the mouth and then swallowed, after which the pharynx and pyriform fossae are carefully anaesthetized with 2 per cent. anethane solution. The left lateral position is the one usually employed, and the gastroscope, lubricated with liquid paraffin, is introduced quickly but without pressure, guided by the operator's left index finger and following the movements of deglutition. After entry into the stomach, gentle inflation by a bellows, combined with appropriate rotation of the instrument, enables the interior of the stomach to be visualized, as far as accessibility will allow. After gastroscopy is completed and the instrument withdrawn, the patient should rest recum- bent for at least an hour and refrain from all food and drink until recovery from the local anaesthesia.

Benign gastric ulcers usually show sharp crater-like margins and a smooth or but slightly irregular yellowish-white floor, though after haemorrhage it may be brownish or dark-red in colour. The adjacent mucosa is often normal in appearance, but may show local inflammatory swelling around the margins of the ulcer. Coincident gastritis produces an oedematous dull mucosa with sticky adherent mucus or mucopus, and sometimes petechial submucous haemorrhages, indicating the need for gastric lavage. Rarely, the likelihood of impending haemorrhage may be suspected from an exposed or oozing vessel in the ulcer base. As the ulcer heals it becomes shallower, with cleaning and granulation of the base and subsidence of local oedema at its margins, and a converging stellate pattern develops in the surrounding mucosa from contracture around the ulcer floor.

Too comprehensive a survey must not be expected from gastroscopy, for some areas of the stomach, chiefly the fundus, and sometimes the pre-pyloric region, are inaccessible to direct vision. An area hidden from view on one examination may, however, be revealed at a subsequent in-

pection, and as with radiology the value of the repeated test is often proved in this way. The greatest use of gastroscopy lies in following the progress of a known gastric ulcer through all stages to complete healing, and in limited measures in the diagnosis of innocent from malignant disease.

While in the differentiation of benign from malignant ulcers gastroscopy is of much value in skilled hands, features of malignancy are not necessarily conclusive at a single observation. A carcinomatous ulcer usually has more rounded edges, less well demarcated from the mucosa; its floor is commonly irregular, with nodular prominences or ridges, and is more frequently of a reddish-brown or dirty grey colour than yellow. In contrast with the excavation of the simple ulcer, it is usually elevated above the surrounding mucous membrane, which may, like the ulcer itself, show nodular irregularities. Size alone is of no guide; a small ulcer may be malignant and a benign reach a diameter of several inches.

It follows, therefore, that a single examination is often inconclusive, and no final decision as to malignancy or otherwise should be sought from it. The value of gastroscopy lies rather in serial observation. Wherever the malignancy of a gastric ulcer is in question, gastroscopy should be repeated after a period of three weeks' intensive medical treatment by complete rest, dieting and alkalis. An innocent ulcer will certainly during this time decrease in size, and will show other visual evidence of healing. If, on the other hand, the appearances of the lesion are unchanged, it is right to regard it as probably malignant and to treat the patient, if otherwise suitable, by subtotal gastrectomy. In some cases the later gastroscopy will reveal that the ulcer has extended and become more nodular and infiltrative, and in these its malignancy will not be in doubt. Wherever, therefore, symptoms of peptic ulcer are unrelied or inadequately relieved by medical treatment, serial gastroscopy should be carried out.

Apart from considerations of malignancy, the surest evidence of healing of a simple ulcer is given by periodic gastroscopy. Caution is taught by the observation that weeks or months after the patient is symptom-free and X-ray findings are negative, the ulcer may still be present as a shallow crater with smooth floor and uninflamed margins. Recurrent bouts of pain, thought clinically to be due to fresh ulceration, are revealed as no more than the lighting up of an ulcer which has never completely healed. It follows then that where an ulcer is within the range of vision it should be gastroscopically controlled until it is known to be healed, and that any fixed duration of hospital treatment and dieting is a bad routine and not
necessarily adequate. Where, moreover, it is shown by gastroscopy that an ulcer persistently fails to heal by these means, the indication is clear for surgical treatment.

The duodenum unfortunately remains cloaked from view, and diagnosis of ulceration here must rest upon the indirect means previously described. Gastroscopy nevertheless is not without its value, especially in decisions of appropriate treatment. Degree of hyperacidity bears a close relation to the total acid-secreting surface of the stomach and hence to the degree of rugosity of the mucosa. Where the folds are markedly deep and numerous, as in the hyperplastic type of stomach, difficulties and delay in healing by conservative treatment may be expected, and considerations of radical surgery apply. Simple short-circuit procedures in such a case are likely to be followed by jejunal ulceration, and good grounds are present for a choice of subtotal gastrectomy.

Jejunal ulcer may sometimes be diagnosed by gastroscopy, which is, however, technically difficult in this case and often affords but a partial view of the stoma.

Clinical differentiation of innocent and malignant gastric ulcer. Peptic ulcer may be mimicked by various forms of dyspepsia, but the differential diagnosis of paramount importance is from gastric carcinoma. Some of the points aiding this distinction will have already been noted. Clinical aspects are no sure indication, and differentiation is often difficult. An ulcer of the stomach beginning after the age of 40 should be suspect of malignancy until the converse is proved. Age itself is of untrustworthy significance, however, for carcinoma may occur in the third decade and simple ulcer is not unknown in the sixth or seventh. A prolonged dyspeptic history favours a benign lesion, but carcinoma of the stomach may arise in a patient the subject of long-standing indigestion whether from simple ulcer or any other cause.

Conversely, a worsening of symptoms in a known case of innocent ulcer does not necessarily mean a malignant change. Marked loss of appetite, weight and strength are more likely to occur in malignant disease, as is anaemia not due to blood-loss. A palpable swelling, though a late sign, nearly always indicates carcinoma. Early obstructive symptoms also point to malignancy. Haematemesis and melena may be initial or early symptoms of either disease, but gross bleeding is commoner from a simple ulcer. The continued presence of occult blood in the stools after two or three week's full medical treatment which includes recumbency is suspicious of gastric carcinoma, since most cases of simple ulcer lose this sign within that time upon an efficient régime. Conversely, a persistently negative occult blood test suggests that the ulcer is innocent, although no absolute rule applies. The fallacy of relying upon fractional test meal findings has been noted, 50 per cent. or more of early gastric carcinomata being accompanied by free HCl in the stomach, sometimes in excess. On the contrary, a complete achlorhydria after the giving of histamine practically excludes a simple peptic ulcer.

The value of X-ray and gastroscopic evidence has been discussed. It may be noted that ulcers of the greater curvature are nearly always neoplastic, and the farther away the ulcer is from the lesser curvature the greater is the probability that it is malignant. Proximity to the pylorus similarly carries a proportionate likelihood of malignancy. Carcinomatous ulcers tend in X-ray appearance to be more ragged and irregular in outline, the gastric rugae being distorted and interrupted in precipitate manner instead of converging in radial fashion upon the ulcer site, as in an innocent lesion. The demonstration of a meniscus sign is practically diagnostic of carcinoma. The final judgment of serial X-ray and gastroscopic investigation has been emphasized. Clinical observation is also helpful. If treatment on a medical régime brings about a striking relief of pain and gain in weight, with clearance of the stools from occult bleeding, a benign ulcer is likely, but even this evidence is not absolute, since the improvement of a secondary gastritis in cases of carcinoma by rest and dieting will often lead to symptomatic relief and a temporary regaining of appetite. The value of the visual check by barium meal and gastroscopy, reviewed at appropriate intervals, therefore needs no emphasis.

TREATMENT OF CHRONIC PEPTIC ULCER

Assessment of Method

In their requirements of treatment no two patients are identical, and a correct approach to therapy must, therefore, include a careful assessment of individual circumstances. Many cases call for a balanced decision between medical and surgical methods, and the ideal course is clearly for the closest co-operation in treatment between physician and surgeon.

General considerations of Treatment

In a disease essentially of remission and relapse the problem of treatment falls into two fields; firstly the healing of the ulcer, and secondly the prevention of recurrence, and of these the first is the simpler task. While the response is variable according to site, the general scheme of treatment of an uncomplicated chronic peptic ulcer is
fundamentally the same wherever its position may be. Therapy is essentially medical, and surgery, where indicated, is undertaken for specific complications, which are considered later.

The over-riding principle in the medical treatment of ulcer is to treat the patient and not solely the lesion, and this will include all aspects of his daily life. The importance of the general wellbeing and of complete bodily and mental rest may easily be overlooked by considerations of detail in diet and drugs. How the patient eats, for example, is no whit less cogent than what he eats. Any ambulant treatment at the outset of illness is unsatisfactory and wasteful of time, few chronic ulcers healing while the patient is up and about. A minimum of four to six weeks' complete bed rest, including bed toilet, is essential; followed by a like period of quiet convalescence where progress is satisfactory. It is often difficult to convince the patient of the necessity for this strict régime, the more so when he is of the irritable type. Rapid disappearance of pain and early return of well-being render the enforced recumbency irksome, while anxiety over business or economic affairs often leads to pressure upon the medical attendant to relax restrictions unwisely and prematurely. A clear explanation is required that relief of symptoms does not imply that the ulcer has healed. Factors leading to nervous or emotional upset should be fully elucidated and dealt with.

Sedation
For these reasons, care must be taken to ensure for the patient adequate mental relaxation, with quietness, sleep and freedom from worry, mental rest being no less important than physical. Social adjustments in this will play their part, but sedatives are often required in addition. The full and proper use of sedatives has perhaps not been accorded sufficient place in the medical treatment of peptic ulcer, and is certainly no less important than dieting and the giving of alkalis. Of the sedatives employed, phenobarbitone is usually of more value than bromides, with the more recently introduced barbiturates such as sodium amytal and nembutal. Sleep is essential and should be promoted by liberal dosage where required. Needs will vary with the patient's individual type and circumstances, the aim being by encouragement and advice to promote a wholesome psychological outlook. It is common experience that the required régime is more easily and efficiently carried out in hospital than at home.

Habits
In their relationship to peptic ulcer, both aetiological and therapeutic, habits of eating are of greater importance than variation in diet, and in these the ulcer subject is a well-known offender. Any instructions upon food which are mere lists of what may be eaten fall short of requirement, and advice must be included upon how they are to be eaten. Food must be eaten slowly and thoroughly masticated, with regularity and full allowance of time for meals. Long intervals between meals are particularly harmful, and at no time should the ulcer patient over-eat. Good habits in these regards should be followed permanently. Preliminary attention must be given to the condition of the teeth, to ensure a clean mouth and mechanical efficiency.

Alcohol is a gastric irritant and a powerful stimulator of secretion, as its use in test meals demonstrates. It is best avoided at all stages of ulcer, and in any case should be strictly forbidden at the onset of treatment. Tobacco also should be wholly excluded in the initial stages, and preferably throughout, where the patient can be so persuaded. Where the deprivation causes increased restlessness, however, a single cigarette after a meal as sedative may be good policy.

Principles of Dieting
Opinions upon the fundamentals of dieting in peptic ulcer have been greatly changed in the past few years. Perhaps too much emphasis in the past has been placed upon the relative merits of particular schemes of dieting in peptic ulcer, and upon the neutralizing of gastric acidity, to the neglect of a balanced diet providing sufficient calories, salts and vitamin requirements. Early diets were inadequate to the point of semi-starvation. Treatment is necessarily prolonged, and nutrition and health must be maintained, and progress has been towards the acceptance of more liberal feeding. Frequency of feeds is at least as important as their nature, granted the exclusion of obviously unsuitable foods. While it may be true that the presence of hydrochloric acid in excess is the chief factor in maintaining active ulceration, treatment is not solely a simple chemical equation of its neutralization by appropriate alkalis. Nevertheless, it is by combating the effects of acidity that the main therapeutic result is obtained. Drugs, including alkalis, play an important part in control of hyperacidity and are for convenience considered later.

Food is the primary and essential buffer in virtue of the acid-combining power of its food proteins. To render this maximal the following principles should be observed:

(a) The food must be soft, smooth, fluid when ingested, and free from coarse elements, to avoid irritation of the ulcer area.
(b) The bulk of the individual feeds must be small, to prevent distension of the stomach and excessive secretion of gastric juice.

(c) Feeds must be given frequently, so that the process of neutralization is continuous, the total intake of food sufficient to maintain nutrition, and the stomach is not left empty for prolonged periods exposed to acid gastric secretion.

With regard to the second of these principles, it may be noted that the quantitative differences in gastric secretion produced by various foods is less than formerly thought, and that although fats do inhibit gastric secretion and emptying they play less part in maintaining gastric neutrality than does the acid-combining property of protein foods.

The adoption of these principles still leaves a considerable margin of variety and individual choice within which a satisfactory diet may be chosen. In some quarters, so far has the principle of liberal dieting in peptic ulcer been extended that details are regarded as of small moment, and choice is left entirely in the patient's hands to eat what he likes. For the great majority of patients, however, such a step is unwise and not calculated to impress upon the ulcer subject the discipline and care with which he must adapt, not only his feeding, but his general mode of living to his condition.

The main ingredient of all such diets is milk, itself an efficient alkali, neutralizing an equal volume of gastric juice containing 0.3 per cent. HCl. The systems of diet first introduced in the Lenhartz and Sippy régimes, based chiefly upon milk and eggs and milk and cream respectively, were each deficient in calorie value and are now seldom used in their original form, though modifications are still in favour in many hospitals, details of which are readily available. A more balanced diet with greater variety is that devised by Hurst, the most widely used scheme, the first stage of which is based upon feeds at hourly intervals alternately of citrated milk, 5 ozs., and a fruit, vegetable or carbohydrate purée. More recently a still more generous régime has found favour with many physicians in the form of Meulengracht's diet, embracing whole milk, porridge, barley, rusks, cream crackers, fruit and vegetable purées, eggs, fish and even meat; recommended at first for the more generous feeding of patients after haematemesis, it is also used in the ordinary stages of ulcer treatment, and includes quite large and varied meals. The reaction against semi-starvation after gastro-duodenal haemorrhage is fully justified, and the improved results confirmed statistically, as noted later. Hurst's régime includes a number of drugs, whereas in Meulengracht's scheme these are practically excluded.

The first stage of dieting (the strict ulcer régime) is continued not for any stated number of weeks, but until there is freedom from all spontaneous pain or discomfort, tenderness and muscular rigidity are no longer present, and the stools show a negative test for occult blood on three consecutive occasions.

When tests have confirmed a satisfactory response, this initial stage of dieting is followed by an intermediate one, in which some of the milk feeds are replaced by lightly cooked and easily digested meals allowing greater liberty of choice. This second stage must be maintained as long as any evidence of active ulceration is present, and may, therefore, occupy many weeks or months. It is not possible from clinical observations alone to tell when healing has taken place or to assess its degree, for it is not complete until the defect is closed and covered by a normal glandular mucosa; this stage of recovery is delayed long after the disappearance of pain, and even after vanishing of the X-ray crater. Most failures of medical measures arise from insufficient length of treatment. Duration of the graded stages of dieting, in this as in similar schemes, is not to be fixed by arbitrary periods of time, but controlled by clinical and pathological surveys until evidence of healing is obtained. Then only is it desirable to progress to a more permanent post-ulcer régime of treatment. Control by periodic X-ray and gastroscopic examination is required at intervals of three to four weeks, until complete healing can be demonstrated, or the need for alternative treatment de- cided upon. The value in diagnosis by these means of malignant ulcer has already been mentioned. In duodenal ulcer a greater measure of reliance has to be placed upon radiology alone.

Maintenance of nutrition should be checked by a weekly observation of weight, and where anaemia is present, as after haemorrhage, periodic blood counts are required.

Diet after Haemorrhage

While inadequacy of diet is undesirable at any stage of treatment as being un conducive to healing, after substantial haemorrhage further important considerations apply beyond the obtaining of physiological rest to the stomach. The acute blood loss involved leads to a state of circulatory shock, in which a policy of severe restriction either of food and of fluid is unwarrantable, as increasing mortality and delaying recovery. This better understanding of the problems of bleeding was first obtained by Meulengracht in his advocacy of more liberal feeding directly after gastric haemorrhage. He was able to show that the response to a full mixed diet, supplemented where needed by blood transfusion, was greatly
superior to the results of treatment on more orthodox and conservative lines by starvation and supporting means, or of treatment by operation. In a series of 273 unselected cases of ulcer haemorrhage treated by his method the mortality was only 1 per cent., the effect of early feeding being to prevent death from exhaustion and to provide adequate calories and vitamins for the promotion of healing and recovery. His policy has further proved the detrimental effect of keeping the stomach empty of food and exposed to the free secretion of gastric juice, whereby peristalsis is strongly stimulated, at a time when gastric rest is most desired. Apart from leading to a reduction in immediate mortality, adequate feeding was found substantially to lessen, rather than to increase, the liability to recurrent bleeding, the greatest danger to life in ulcer haemorrhage. Apart from lowering of mortality, moreover, the benefit of more liberal feeding is shown in a shortening of the average stay required by the patient in hospital.

A practical difficulty in the adoption of Meulengracht’s full dietary régime, with its three full meals a day and supplements, has been an inability or disinclination on the part of some acutely ill or weakened patients to accept so large a food intake. This objection has largely overcome in a modified dietary scheme introduced by Witts* which, while accepting the principle of early feeding, provides a more fluid diet with adequate calories of from 2,500 to 3,500 per day upon a two-hourly feed basis, with vitamin supplements and additional measures to restore fluid balance to the body where required.

Continuous Drip Therapy

Whatever care is devoted to ensuring a bland quality of diet, any system of intermittent feeding is open to the objection that at some phases of the day, and still more of the night, the stomach is left empty and exposed to the harmful and excessive secretion of the gastric juice. The fundamental principle of obtaining effective acid neutralization throughout the 24 hours is in this way defeated. The effects are clinically apparent in cases where over-secretion is marked and acidity high, and routine treatment upon a Hurst or Sippy régime may fail to relieve symptoms, and other measures be required. Consideration of this problem led to the introduction, in 1932, by Winkelstein 10 11 12 13 of continuous intra-gastric drip therapy. It is most fruitfully employed where pain is severe and persistent, despite usual methods of dieting, where gastric spasm is a marked feature, or where emptying of the stomach is delayed by a partial obstruction from spasm or oedema. In any circumstances, in fact, where it is desired to afford the stomach the maximum degree of rest, as after haematemesis or melena, this method may well be adopted as an alternative mode of feeding since full calorie and fluid requirements are so provided. Other indications include the intractable pain from a deep penetrating ulcer, resistant gastro-jejunal ulceration, and unsuitability of the patient from age or impaired general condition for operative treatment which would otherwise be indicated. In all these types of patient, rapid relief of symptoms frequently follows the adoption of drip feeding, the results of which, in general, are superior to those of a first-stage Hurst’s diet. Acidity is thereby neutralized throughout the 24 hours by a regular and constant introduction into the stomach of ant-acid and buffer substances in small quantities, avoiding the recurrent stimulus of secretion inevitable with intermittent feeding.

As originally introduced, the continuous drip consisted of the ant-acid buffer itself, the most satisfactory choice for the purpose being an aluminium phosphate gel. The more usual and effective method is for the feeding itself to be by continuous drip, using milk instead of the aluminium gel from a simple gravity flask. Using this method, a Ryle’s tube made non-irritant with 0.25 per cent. cocaine ointment is passed into the stomach, preferably through the nose, alternatively through the mouth, and fixed in position by strapping to the cheek. The tube need not extend deeply into the stomach, but should be long enough to allow the patient to turn comfortably in bed at night. Through this tube, from a height of about 2 ft., the patient is given a continuous drip of citrated milk, day and night, from a suitable container such as a transfusion bottle, fixed to a stand or bed extension and adjusted to a rate of about 40 drops per minute. The patient receives in this way a total of five pints of milk in the 24 hours, and where desired the calorie value and protein content of the diet may be increased by the addition of glucose and of a 10 per cent. solution of casein hydrolysate, a pint of the latter being added to the five of citrated milk. Alkalis and other drugs needed may be given either in the drip or separately by mouth, the latter being generally preferred. Most patients will tolerate feeding in this way for periods up to three weeks, some for much longer. Rest of the stomach is as complete as may be obtained.

Appetite secretion is minimized, and the stomach is never left exposed at night or for other intermittent periods to the action of highly-acid gastric secretion, neutralization of which is made a continuous process. Nutrition is well maintained, and healing is more rapid by this method, in the writer’s experience, than by any other. An initial soreness of nose or throat for the first day or two
is seldom maintained. A period of milk-drip feeding in this way may well be followed by a first-stage Hurst diet.

A few practical points may be noted. Special care in the cleanliness of the mouth and teeth is required, and the tube should be changed every third or fourth day to avoid blockage or perishing and possible loss. Its position in the stomach may be adjusted as needed, and in high ulcers an introduction as far as the lower oesophagus may be sufficient. In subsequent stages of treatment the use of drip feeding may satisfactorily be restricted to the night hours, as a supplemental method to the normal scheme of intermittent ulcer therapy, and maintained if desired even for many months after the ambulant stage is reached.

It must be noted, finally, that any infection of the upper respiratory tract makes the adoption of drip therapy unsuitable.

Drugs in the Treatment of Peptic Ulcer

The administration of drugs does not constitute the chief aspect of treatment, being of less vital import in the programme for healing than general measures of physical rest and dieting, which it can never be made to replace. Nevertheless a rational use of drugs forms a valuable supplementary measure of treatment. It is directed towards three main objects, neutralization of acidity, inhibition of gastric activity, both motor and secretory, and sedation of the nervous system, while other minor forms of symptomatic treatment may also be required.

(a) Acid neutralization. Sippy's aim in neutralizing hydrochloric acid was to inactivate pepsin, but it is now known that high acidity is in itself more destructive upon an ulcer than the solvent action of the peptic ferment. The object, nevertheless, remains unchanged to maintain a neutralization of all free HCl while food and its accompanying secretion is present in the stomach; it is also necessary, and more difficult, to neutralize the continued secretion of acid gastric juice during the night hours when the stomach is empty of food.

Alkalies are the most widely used as well as the most abused remedies in the treatment of peptic ulcer. In their rapid relief of pain lies their danger in ignorant hands; advertisements of proprietary 'stomach powders' fill the daily press and lull their victims into a false security. Properly used, alkalies are of the greatest value and second only to correct dieting in treatment.

A wide range of ant-acids is available, with their special advantages or otherwise according to the case. Two broad groups are recognized according to solubility or otherwise. Those most readily soluble are in consequence the most rapidly absorbed, whilst those that are comparatively insoluble are correspondingly more gradual and prolonged in action, acting as buffer salts or neutralizing agents without the undesirable liberation of free alkali. The latter group is, therefore, greatly to be preferred; any excess above requirement merely remains in the stomach until neutralized, without danger of systemic alkali intoxication or of the stimulation of a secondary secretion of acid by the stomach.

Typical of the first or soluble group is sodium bicarbonate, which has a quick though short neutralizing action, but produces distension of the stomach by liberated CO₂ and a marked subsequent secretion of acid, rendering it unsuitable as an alkali for this purpose. In view of its greater solubility it is, as noted, more prone than are other alkalis to produce alkalosis. The more gradually acting magnesium and calcium salts are fully effective, while free from this risk, and may be combined in proportion to regulate the bowels, the former being mildly aperient and the latter astringent. Magnesium oxide, carbonate and tribasic phosphate are excellent; the trisilicate has come into favour with some, but is a more costly preparation and no more efficient than its fellows. Effective dosage requirement varies with the degree of acidity present; commonly (as in Hurst's scheme) doses of a drachm of one of the above salts in powder form are sufficient, given with water before each of the purée feeds, and one drachm or more of emulsio magnesiae B.P.C. (containing grs. v of magnesium oxide) before each of the alternating milk feeds; a double dose of alkaline powder is given at night. Calcium preparations, in the carbonate or tribasic phosphate, are useful alternatives, and a good case has lately been made for a gel preparation of colloidal aluminium hydroxide, in the form of aludrox in similar dosage. Bismuth salts are feeble alkalis in their degree of neutralizing power, having about a fifth of the potency of magnesium salts, and the idea of their forming a protective coating to the ulcer floor belongs to past days; they are, like calcium salts, mildly constipating. Sodium citrate, besides inhibiting rennin and preventing clotting of milk, is also an effective alkali, and is added to all milk feeds in proportion to two grains to the ounce. As with all other drugs in the treatment of peptic ulcer, alkalies should always be given in suspension or solution and not in tablet form.

Gastric Aspiration

As a supplementary method of ant-acid therapy, alkali administration may be fortified where necessary by a direct removal of the acid gastric juice. Where hypersecretion is marked or a measure of obstruction present, alkali administra-
tion by itself is insufficient to ensure continued neutrality of stomach contents throughout the 24 hours, the more so at night, when nocturnal pain may be a distressing feature. Routine aspiration of the stomach at bed-time, or oftener, should in these cases be carried out, thereby shortening the period during which the ulcer is exposed to the action of the acid gastric juice. It affords, moreover, a means of assessment of correct alkali dosage; if this is adequate, the stomach contents 30 minutes after a dose of the powder should contain no free acid; its presence at that time is a call for more frequent or larger dosage. In non-obstructive cases it is the rapidly emptying stomach which most needs aspiration at night, food contents and alkali having been quickly passed on, and a collection of highly-acid secretion being then poured out into the empty stomach, to remain there during the night. The case is clear also for gastric aspiration in obstructive ulcer, whether from pylorospasm or duodenal stenosis, and this should be continued at least twice a day until the residual contents are not more than 50 to 100 cc. In obstructive cases with foul stomach contents, aspiration may be usefully combined with gastric lavage.

Alkalosis

The indiscriminate giving of alkalis in excess, especially when accompanied by vomiting or independent renal disease, may cause a serious disturbance of the acid-base equilibrium and chloride content of the blood, a condition known as alkalosis. This is seen most often where a continued depletion of chlorides has occurred from low salt intake combined with vomiting, especially in the presence of pyloric obstruction, benign or malignant. Symptoms include irritability, lassitude, mental confusion and headache, with loss of appetite, nausea and distaste for milk, followed by profound vomiting and drowsiness, and in serious cases the development of a state closely simulating uraemia, with low urinary output, albuminuria and high blood urea, perhaps progressing to coma and tetany. The chloride content of the blood is always greatly lowered. Treatment called for is the immediate stopping of alkalis and the giving of large amounts of sodium chloride as normal saline solution intravenously, with glucose and abundant fluids by mouth, supplemented where it can be taken by oral administration of sodium chloride and ammonium chloride in capsules in large doses, or the latter may in urgent cases be given intravenously in 2 per cent. solution. If tetany occurs, intravenous calcium gluconate is given. Prophylactically, in conditions where alkalosis is a likely complication, 3 to 5 grs. of sodium chloride may with advantage be added to the daily milk ration.

(b) Inhibition of gastric activity. The functional over-activity of the stomach in ulcer subjects is at least partly the result of an exaggerated vagal tone, inducing over-secretion and hypermotility. Acid neutralization by alkalis is fruitfully supplemented by measures claimed to diminish this tone and hence the secretion of gastric juice, and of these the giving of belladonna or its alkaloid atropine is the most widely used. Its action in restraining gastric secretion is doubtful, but its effect as an anti-spasmodic and inhibitor of peristalsis is more certain, and it is hence of marked value in inducing relaxation of spasm at the pylorus or at the site of ulceration. It is included as a routine in the Hurst's diet, in doses of 1/150 - 1/100 gr. in a drachm of water by mouth before two of the daily feeds, and a double dose before the 10 p.m. feed, while more may be given if spasm persists, to the point of producing blurring of vision and dryness of the mouth, small doses being ineffective. As evening and nocturnal secretion are the most difficult to check, late afternoon or bedtime is the time of choice for administration. Benefit may be derived in some cases from combining atropine with ephedrine gr. 1/4, further benefit to inhibit vagal overtone, while papaverine gr. 1/2, and pethidine hydrochloride 50-100 mgm. by mouth or by injection are available. Many proprietary combinations of efficiency are available.

Fats in general also inhibit gastric secretion and motility. Olive oil or the more readily obtainable arachis oil, taken twice daily before meals in ounce doses, has this effect, besides forming a valuable food and being mildly laxative. The addition of cream to the milk feeds is of similar benefit.

(c) Sedation. The importance has already been noted of obtaining quietness of the mental state and relief of nervous anxiety or restlessness. A choice of barbiturates is available for this purpose, the most valuable and generally employed being phenobarbitone, given in liberal dosage. Where required, sedation may be combined with analgesia and relief of spasm by employing a drug possessing each of these qualities, such as papaverine grs. 1 to 2, or its equivalent synthetic preparation in the form of perparine 0.04 gm.; atropine gr. 1/100, or novatropine gr. 1/25, are useful supplements in this regard. The place of morphia as more powerful sedative in the shock of major bleeding needs no emphasis.

Apart from these main therapeutic needs, other drugs may in some cases be required, and include the following:—

(d) Haematinic drugs. Anaemia of some grade from slight blood loss over a long period is so...
common in peptic ulcer that regular blood investigation should always be made. Where haemoglobin deficiency is found, iron is indicated in liquid form as iron and ammonium citrate or collirion in appropriate dosage; after frank haemorrhage, early and massive iron administration is required, begun as soon as the bleeding has ceased. In view of the low iron content of ulcer diets, a minimum of 5 grains of a ferrous salt per day as supplement is a good routine, despite the absence of demonstrable anaemia, for all patients upon the restrictive stage.

(e) Vitamins. The most likely deficiency in this regard arises from the limitation of fresh fruits and vegetables, and a long-continued ulcer diet should always be supplemented by vitamin B1, 2,000 units, and vitamin C, as ascorbic acid, 100 mgm. given daily. There is no objection to the giving as well of fresh orange or other fruit juice.

(f) Control of bowels. Straining at stool is obviously undesirable, particularly if recent bleeding has occurred. Where regulation of the diet and additional magnesia do not suffice, agar and liquid paraffin preparations will help towards an easily passed stool. Enemata rather than drugs will sometimes be required, but are to be used with great caution, especially after haemorrhage. The rule should be to leave the bowels undisturbed for at least a week after a haematemesis has occurred.

(g) Histidine. The injection of histidine products recently had a short-lived vogue in the medical treatment of peptic ulcer. It has since been shown to be entirely unsupported by evidence or by results, and its use has now been discarded.

After-Care of Peptic Ulcer: 'Post-Ulcer Régime'

The treatment of the acute ulcer is comparatively straightforward. The most difficult decisions of treatment arise in the chronic or resistant case. The plan of treatment outlined is maintained either so long as any evidence of active ulceration remains, or until the conclusion is reached that medical means alone are inadequate after a prolonged trial. Where healing is established, the patient is allowed up by stages and progresses on to a post-ulcer régime of diet and habits, which he is instructed to follow for a minimum of two years or, if possible, permanently. The dangers of recurrence and the need for long-term care must be emphasized to him. From these instructions he will be taught to maintain small frequent meals with intervals of not more than two hours, to adhere to soft readily-digested foods and avoid hard, irritating or highly-seasoned articles with indigestible residue. Advice upon diet should be positive and not merely a list of forbidden foods; those recommended should also be within a range which he can obtain and afford to purchase. Above all he will be advised to obtain ample time and regularity for his meals, to rest before and afterwards, and to avoid excessive fatigue and, as far as possible, intercurrent infections. He must pay proper regard to his teeth and his bowels and continue to take an alkaline powder after each of his main meals. A patient's own teeth may be more serviceable for eating than an empty mouth, and a programme of clearance should include replacement by efficient dentures. Smoking and alcohol are best avoided altogether. Any return of symptoms calls for a prompt resumption of bed rest and strict dieting.

Could this ideal advice always be followed, the prognosis of medical treatment of peptic ulcer would be much better than it is. Prospects of remaining well vary greatly with social status and economic means. The patient in comfortable circumstances may be able to continue the whole régime religiously, and remain free from symptoms with a careful diet and sheltered life quite impossible for a working man with living to earn and family to support. The occupation followed may be a stumbling block, and its type is not easily changed; the best choice is often that with which the patient is most familiar. Even granted the best of after-care, no guarantee can, in fact, be given of freedom from recurrence of ulceration.

Strong argument obtains, therefore, for the indefinite following-up of all ulcer patients in clinics organized for the purpose, supported by X-ray and other special investigations as required.

Indications for Surgical Treatment

The best efforts of medicine in this disappointing disease are not always blessed with success. Despite a high proportion showing initial improvement, it is certain that a considerable percentage of cases relapse after apparent medical cure, and of all patients treated medically not more than 30 to 40 per cent. remain permanently well. It does not, of course, necessarily follow that of these medical failures all are amenable to successful surgical treatment, but with proper choice many will be benefited thereby. It is pertinent, therefore, to consider what are the indications for surgical treatment. Some will be obvious and are by nature emergency procedures; others should be embarked upon only after carefully weighing the pros and cons of individual circumstances. The most generally agreed indications are as follows:

(a) Failure of Medical Treatment. This is the most frequent reason for operation; it presupposes that medical treatment should have been really adequate, and not a half-hearted trial. It more commonly applies in intractable duodenal
ulcer than in gastric, not considering those complications of dramatic order calling for urgent surgery. The type of patient with prolonged history of pain unrelieved by dieting and alkalis, and interspersed with increasingly frequent and severe relapses, is not best served by repeated vain attempts at medical cure, which serve merely to prolong the duration of his ill-health, but should if otherwise fit be treated surgically to avoid a life-long dyspepsia. Within this group will be many with deep penetrating ulcers embedded in callous scar tissue and adherent to other organs. In some cases the failure to heal of a gastric or jejunal ulcer after gastro-enterostomy will be an indication for more radical surgical treatment. The trend of opinion in these medical failures is increasingly in favour of partial gastrectomy as being the most radical means of extirpating the acid-producing area, but in choice of surgery the degree of hyperplasia and hermotility of the stomach will be a factor. Suitability for operation on grounds of age, pulmonary or cardiovascular condition has, of course, to be considered. Fresh hope of success has recently been aroused in a new measure of surgical treatment aimed at controlling the excessive secretion and muscular activity of the stomach, namely by the operation of vagus nerve resection or vagotomy (Allen, A. W.14). A less drastic and extensive procedure than gastrectomy, it has been shown to be of some value and may acquire a permanent place in the treatment of intractable duodenal and anastomotic ulcer. Sufficient time has not yet elapsed to permit of its proper assessment in therapeutics, but immediate results are encouraging.

(b) Inability or unwillingness to maintain a full measure of efficient medical treatment. Lack of cooperation on the part of the patient will often indicate the advisability of surgery. This is sometimes concerned with psychological type and temperament. Frequently, however, the reasons are economic rather than medical, in the nature of occupation followed, pressure of time for the more prolonged medical treatment or domestic circumstances out of the patient’s control; it may be essential in such a case to restore, where possible, the ability to pursue a heavy or exacting type of employment, the prospects of which are afforded by successful operation alone.

(c) Recurrent haemorrhage. Most of the fatalities from bleeding follow repeated blood loss, and in any event each such episode entails a long and tedious illness. While the immediate treatment of ulcer haemorrhage in most cases is by general agreement medical, it is certain that recurrent haematemesis should be followed by radical operation as soon as the patient’s general state permits. In a small proportion of cases of fulminating bleeding not responding to medical treatment, an immediate gastrectomy after mass transfusion is the one way of saving the patient’s life.

(d) Suspected malignancy. The failure of a gastric ulcer to respond to full medical treatment within, at most, a few weeks, indicates the advisability of exploration, to confirm the diagnosis of malignancy and, where suitable, to carry out a subtotal gastrectomy.

(e) Perforation of the ulcer is an obvious need for immediate surgery.

(f) Organic obstruction. Obstruction which is largely due to oedema and spasm will frequently be relieved by dieting, antispasmodic drugs, aspiration and lavage. Where, however, the obstruction is of organic origin from cicatricial stenosis, as in hour-glass stomach, duodenal or pyloric stenosis, surgical treatment alone can relieve it, and should not be unduly postponed.

To summarize this attempt at balancing the scales of treatment, medical measures then carry the bogy of relapse, surgical of a not negligible immediate mortality and a fairly high incidence of minor post-operative troubles and digestive symptoms. On the other hand, medicine can offer to the chronic sufferer nothing to equal the almost complete immunity from perforation and recurrent bleeding given by a successful gastrectomy.

Perhaps if any lesson may be fruitfully drawn from this discussion, it is to stress the paramount importance of a fusing of medical and surgical opinion in this protean disease. Only in this way may proper assessment be made and the patient’s best interests served.
Method of feeding by continuous milk drip.

REFERENCES

3. ALLEN, A. W., and WELCH, C. E. (1941), 'Gastric Ulcer. The Significance of this Diagnosis and its Relationship to Cancer,' Am. Surg., 114, 489-509.

10. WINKELSTEIN, A. (1942), 'Studies in Gastric Secretion During the Night, with a Preliminary Note on a New Therapy for Peptic Ulcer,' Am. J. Surg., 15, 523-524.