Progress report

Inhibition of gastric secretion by the pyloric antrum

Early Concepts

The observation that the secretion of hydrochloric acid and pepsin by the stomach was markedly increased after ingestion of a meal and virtually abolished during the interdigestive phase formed a basis for the suspicion that gastric secretion was regulated by the interaction of both stimulatory and inhibitory processes.

The credit for recognizing an inhibitory mechanism regulating gastric secretion must go to Pavlov and his coworkers. It was Sokolov, working at St Petersburg, who found that the introduction of 0.5% hydrochloric acid into the canine stomach could diminish the output of acid from a Pavlov pouch in response to a meat meal. But, early opinion regarding the existence of an intragastric mechanism controlling gastric secretion was somewhat divided. Pavlov postulated that gastric juice was secreted at a constant acidity but that alkaline mucus altered the acidity either by dilution or neutralization. Others agreed with Pavlov but felt that acid secretion had to cease before any mucus effect could take place.

MacLean and his coworkers believed that the strength of acid either placed in the stomach or secreted by the stomach itself and allowed to accumulate reached a certain level at which point the parietal cells ceased to secrete hydrochloric acid. Demonstrating this phenomenon in canine innervated fundic (Pavlov) pouches and the intact human stomach, they felt that gastric acidity having reached a certain level was then diluted by the secretion of fluid rich in neutral chlorides.

These views were really modifications of the hypothesis advanced by Rosemann that the gastric glands secreted acid and neutral chlorides in varying proportions according to the intensity of the stimulus. Evidence against such a mechanism however came from the work of Hollander, who found a direct relationship between total chloride and acid concentration in the gastric juices over a considerable range of acidity.

Some investigators attributed the regulation of gastric acidity to the neutralizing effect of alkaline fluid, either regurgitated from the duodenum or secreted by the pyloric mucosa.

Confirmation of Sokolov's finding that the intragastric acidity was of importance in regulating gastric acid secretion was provided by Wilhelmj and others. Collecting acid via a gastric tube they found that the canine gastric secretory response to a test meal was inhibited by adding hydrochloric acid to the meal before its ingestion. This inhibition was proportional to the concentration of hydrochloric acid added to the meal, being pronounced with 0.077 normal acid and virtually complete at a concentration of 0.1 normal.
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They concluded that the inhibitory mechanism was located within the stomach since it persisted following pyloric division.

Significance of the Antrum

DOG
Although the existence of a gastric inhibitory mechanism was evident from these early studies, the vital role of the pyloric antrum in this mechanism was not appreciated until Woodward and his colleagues performed a series of studies using dogs with isolated antral pouches. They showed that the acid response, both of the vagally innervated and denervated stomach, to the introduction of liver homogenate into the antrum or the mechanical distension of the antrum, could be markedly diminished by irrigating the antrum with decinormal hydrochloric acid. This reduction occurred with both innervated and denervated antral preparations.

This prominent inhibitory function of the gastric antrum has been verified by numerous workers, and its mechanism investigated in relation to the cephalic, gastric, and intestinal phases of gastric secretion.

Acidification of the canine antral pouch inhibited the acid secretory response of innervated fundic pouches to sham feeding and to insulin hypoglycaemia.

The gastric phase of acid secretion was also inhibited by antral acidification. The secretory response following antral stimulation by acetylcholine, ethyl alcohol, or antral distension was diminished by the presence of acid in the antrum.

Conflicting views have resulted from attempts to demonstrate antral inhibition of the intestinal phase of gastric secretion. Inhibition was demonstrated by some investigators. The latter workers used dogs with isolated denervated antral pouches and Heidenhain fundic pouches. Inhibition of the acid response to a meat meal followed antral acidification with decinormal hydrochloric acid. Since both the antral and fundic pouches were vagally denervated these investigators believed that the fundic pouch secretion was mediated by the intestinal phase.

Others were unable to reproduce inhibition of acid secretion in response to a meat meal using identical preparations.

MAN
Almost all knowledge of the antral inhibitory mechanism has been derived from canine experiments. There have been few investigations in man and unfortunately the value of the results obtained has been limited by the problem of few tests performed on small numbers of subjects. But these studies have tended to confirm the concepts derived from canine investigations.

Gillespie perfused the antra of three patients undergoing two-stage gastrectomy with sulphuric acid. These perfusions were carried out after the first stage of the operation when access to the antrum was possible. When the antral pH was lowered to 1.5 both spontaneous and histamine-induced secretion was inhibited.

The operation of two-stage gastrectomy also provided an opportunity for Köster and Rune to perform antral acidification studies. They investigated six patients undergoing surgery for duodenal ulcer but used a Visking dialysis balloon in order to achieve antral acidification without concomitant duodenal
acidification. Spontaneous acid secretion was reduced in both vagotomized and vagally intact subjects but histamine-stimulated secretion was not inhibited.

Shapira and State\textsuperscript{33} studied a patient with a Jianu gastrostomy, in which there was an inner fundic mucosal lining and an outer stoma of antral mucosa. By inflating the balloon of a catheter inserted into the gastrostomy the latter could be converted into a pouch. The introduction of meat broth into the pouch stoma stimulated acid secretion from the stomach, but acidification of the broth to pH 1.5 abolished this stimulatory effect.

Antral exclusion operations used in the past for the treatment of duodenal ulcer\textsuperscript{34,35} provided further evidence for antral inhibition of acid secretion in man. These procedures were associated with a high incidence of recurrent and marginal ulceration\textsuperscript{36}. Excluding the antrum from the acid stream abolished the inhibitory influence. Stimulation of the antral mucosa by regurgitated alkaline duodenal contents was probably an additional factor in the production of hyperacidity.

**Mode of Action of Antral Inhibition**

**pH changes**

Although many experiments clearly established the existence of an antral inhibitory mechanism, a more detailed examination of the exact pH changes involved was required before the physiological significance of the mechanism could be assessed.

The changes of pH in the canine antrum, following a test meal of horse meat, were monitored after the insertion of pH electrodes into the antrum via a lateral antral fistula\textsuperscript{37}. Acidification of the meal before ingestion, sufficient prematurely to drop the antral pH below 3.0 reduced the secretory response from a Heidenhain pouch. With an antral pH as low as 1.5 secretion was basal but alkalinization of the meal enhanced and prolonged the secretory response.

**Graded response**

Evidence has been provided suggesting that the release of antral gastrin is directly related to the pH within the antrum\textsuperscript{38}. Using dogs with innervated antral and vagally denervated fundic pouches, liver solutions with pH values ranging between 1.0 and 7.0 were introduced into the antral pouches in order to release endogenous gastrin. Maximal acid secretion occurred with antral perfusion at pH 7.0, but there was a progressive decrease with falling pH until a complete cessation occurred at pH 1.7.

**'All-or-none' phenomenon**

It was postulated by Posey and Franklin\textsuperscript{39} that the antral inhibitory system functioned in an 'all-or-none' manner. They were unable to support the concept of a graded secretory response accompanying pH changes in the canine antrum after observing a complete cessation of acid secretion from a vagally denervated fundic pouch during antral perfusion with a buffer solution below pH 1.8. Between pH 1.8 and 3.0 there was a small but variable response, but above pH 3.0 there was a significant stimulatory effect which did not increase further with increasing pH. As in this experiment the antrum was *in situ* it
was possible for acid to enter the duodenum and influence fundic pouch secretion via the duodenal inhibitory mechanism. Support for an 'all-or-none' concept also came from human investigation when it was noted that there was little inhibition of spontaneous acid secretion until the antral pH fell to 1.5.

The sensitivity of the antral gastrin mechanism has been shown to vary both with the composition and concentration of the stimulant. It was demonstrated that inhibition of the acid secretory response to sham feeding and bathing the antral mucosa with 10% ethyl alcohol required somewhat higher acidity than that necessary to inhibit the response to glycine and choline introduced into the antrum.

In a further experiment Andersson and Elwin examined the secretory responses of canine Heidenhain pouches after irrigation of isolated antral pouches with choline solutions of varying strength. Increasing choline concentrations required lower antral pH levels for suppression of the response, indicating that the degree of inhibition was dependent upon the choline strength. Therefore it appears that studies of the antral inhibitory mechanism are not comparable unless the composition and concentration of the gastrin-releasing agent, as well as its acidity, are known.

Effect of alkalis
The effects of an alkaline pH within the antrum are somewhat variable. A distension stimulus to the innervated antrum, inadequate to result in acid secretion, could be rendered adequate by irrigating the antral pouch with isotonic sodium bicarbonate at pH 8.3. But, when liver extract and ethyl alcohol were used as antral stimulants there was no difference in the secretory response when the pH was raised from 5.4 to 8.1 in the case of the liver and 6.6 to 10.3 with alcohol.

Alkaline antral perfusion was without effect on the secretory response of canine fundic pouches to a meat meal.

Food buffers
The neutralizing capacity of a meal is an important factor in its ability to stimulate gastric acid secretion.

By the addition of alkali, acid and phosphate buffers Williams et al. were able to alter artificially, the neutralizing capacities of meals fed to dogs. An increase in neutralizing capacity resulted in an increased acid secretory response of both innervated and denervated fundic pouches. Conversely, decreasing the neutralizing capacity decreased the acid secretory response. These results were in agreement with those previously obtained by Foerster and DuVal.

Physiological significance
Canine and human studies of the antral inhibitory mechanism have indicated that an antral pH between 1.0 and 2.0 is required for significant acid inhibition to occur. Such postprandial antral pH levels have been observed both in the dog and in man.

Furthermore, Gillespie believed that there was ample opportunity for acid inhibition of the antral phase of gastric secretion to occur as a physiological mechanism.
REGULATING MECHANISMS

**Diminished gastrin release**
The question, How does a fall in antral pH inhibit gastric secretion? has only been partly answered. Some clues were supplied by early studies in which transplantation of the canine gastric antrum to the transverse colon resulted in a profound increase in acid secretion from Heidenhain, Pavlov, and total stomach pouches. When the antral transplant contained a small rim of fundic mucosa, capable of secreting acid, the hypersecretion either did not develop or was less pronounced. Subsequent removal of this acid-secreting rim resulted in marked gastric hypersecretion.

Once Woodward and his colleagues had demonstrated the ability of antral acidification to inhibit gastric, but not cephalic or intestinal phase, secretion, the hypothesis was advanced that high acidity in the antrum suppressed the production or release of gastrin. The importance of this mechanism in the antral inhibitory system has since been stressed by many workers. Since the development of a reliable radioimmunoassay for gastrin it has been possible to confirm the existence of this mechanism and actually monitor the fall in serum gastrin level which follows a lowering of intragastric pH.

Any mechanism regulating gastrin formation or release has added significance since the introduction of the concept of an integration of the neural and hormonal control of gastric secretion.

Exactly how increasing acidity within the antrum regulates the release or formation of gastrin is not understood. The hypothesis that local nerve fibres relayed the inhibitory effect of acid to the gastrin-producing cell seemed plausible as the release of gastrin, in response to chemicals in contact with the antral mucosa, was thought to be mediated via a local nervous mechanism although acetylcholine stimulated the gastrin cell directly.

Redford and Schofield found that local anaesthetic agents were unable to prevent the inhibitory effects of antral acidification on gastric secretion stimulated by acetylcholine irrigation of the antrum. They concluded that there was no evidence for the existence of a local inhibitory nervous mechanism.

Two mechanisms were evoked by Andersson to explain the controlling influence of antral acidification on gastrin release. One was a physicochemical interference with the secretagogue potencies of digestive products such as amino acids, choline, and polypeptides and the other a direct action of acid on the gastrin-releasing cell.

**Antral inhibitory hormone**
Although it is generally accepted that a fall in antral pH diminishes the formation or release of gastrin, not all agree that this is the sole mechanism for antral inhibition of gastric secretion.

Brunschwig and his colleagues found that the intravenous injection of achlorhydric gastric juice from patients with pernicious anaemia or gastric carcinoma inhibited canine gastric secretion stimulated by food. Gastric juice from normal human subjects also had an inhibitory effect upon dogs secreting acid in response to histamine stimulation. Further work has been performed on the inhibitory factor in human gastric juice and canine gastric juice.

The demonstration of an inhibitor substance in gastric juice raised the
possibility that the inhibitory effects of antral acidification might be due to the release of a humoral agent from the pyloric antrum.

The first support for this concept came from Harrison, Lakey, and Hyde. They transplanted the distal half of the antrum to the transverse colon in dogs prepared with Heidenhain pouches in order to produce a continuous state of high gastric secretion. Gastrointestinal continuity was re-established by anastomosing the duodenum to the proximal half antrum. The 24-hour acid outputs from the Heidenhain pouches were monitored and rose by 62% when the proximal antral remnant was excised after 21 days. When the colonic antral diverticulum was excised acid secretion fell to almost basal levels. As acid secretion rose when the antrum in contact with the stomach was excised it was suggested that this portion of the antrum was releasing an inhibitory substance.

In further experiments the release of this inhibitor seemed to be independent of the vagal innervation of the antrum since denervation of the half of the antrum remaining in continuity with the stomach did not influence the pattern of secretory changes.

Other workers were unable to confirm these findings. Dragstedt believed Harrison's results to be due to the inadvertent excision of a rim of acid-secreting mucosa, at the time of excision of the proximal antrum, which resulted in diminished acid inhibition of duodenal origin.

Divided antral pouch techniques were employed by other workers for investigating the antral inhibitory hormone. One pouch was used for the stimulation of gastrin release whilst acidification of the other was performed in the hope of activating a humoral inhibitory mechanism.

Two such experiments produced evidence for and two against the existence of a humoral inhibitory agent. Jordan and Sand used 10% ethyl alcohol as a stimulant of gastrin release and observed inhibition of gastric secretion after one to three hours of antral acidification. In a series of control studies, without concomitant antral acidification, Shapira and State found a biphasic acid secretory response to antral irrigation with 10% ethyl alcohol. These workers believed that this normal pattern of response to ethyl alcohol was sufficient explanation for the findings of Jordan and Sand.

When a purified preparation of gastrin became available it was hoped that the problem of the antral inhibitory hormone would be resolved. Thus if the secretory response of a denervated fundic pouch to exogenous gastrin was suppressed by antral acidification, a mechanism other than the suppression of gastrin release would be responsible. The results of such studies have been conflicting with some investigators finding inhibition and others failing to do so.

First, Gillespie and Grossman, using three dogs with vagally denervated antral and fundic pouches, were unable to suppress the acid secretory response to intravenous hog gastrin by irrigating the antrum with decinormal hydrocholoric acid at a pH of less than 1.3.

Conversely, Thompson et al reported suppression of gastrin-stimulated acid secretion in dogs provided with vagally denervated antral and fundic pouches. They stressed that antral irrigation was performed at a rate of 3 ml per minute and believed that this was the minimum rate which would ensure intimate contact of the perfusate with the antral mucosa. Thompson and his colleagues concluded that the negative results obtained by Gillespie and
Grossman were due to the lower irrigation rate of 1 ml/min used in their experiment.

The synthesis of a pentapeptide (Peptavlon, ICI 50, 123 Imperial Chemical Industries Ltd, England), possessing gastrin-like properties, has permitted further attempts to seek evidence for an antral chalone. Using dogs prepared with innervated antral and either innervated or vagally denervated fundic pouches, submaximal doses of pentagastrin were infused intravenously to stimulate gastric secretion. No inhibition of acid secretion was observed with antral acidification rates of either 1 or 3 ml/min.

It has been argued that the demonstration of antral inhibition active against stimuli which act independently of gastrin would provide evidence for the existence of an antisecretory hormone. Although histamine is believed to be such a stimulus, studies using this agent have unfortunately once again provided conflicting results. Some workers have observed inhibition, whereas others have failed to do so.

As the denervated antrum does not release gastrin in response to vagal stimulation, State and Morgenstern attributed their demonstration of antral inhibition of cephalic phase secretion, in dogs prepared with vagally denervated antral and innervated fundic pouches, to the release of an antral chalone.

Similar conclusions were drawn by others, after observing inhibition of intestinal phase secretion by antral acidification, in dogs with vagally denervated antral and fundic pouches. These authors reasoned that in their experiments gastrin of antral origin was not involved in the stimulatory process.

An alternative argument to explain these findings is that the secretory tone for any stimulus, whether cephalic, intestinal, or histamine is dependent on subthreshold stimulation by antral gastrin and that therefore removing gastrin by antral acidification depresses this reactivity. When such an argument is evoked the case for the antral inhibitory hormone diminishes.

The use of cross circulation and transfusion techniques would seem to provide an alternative method of investigation free from this theoretical objection. A study supporting the concept was carried out on anaesthetized dogs. It was observed that inhibition of spontaneous and histamine-induced acid secretory responses followed the intravenous injection of an extract prepared from blood draining the acidified antrum of other dogs.

Further confirmatory studies were performed on conscious dogs.

In Thompson's experiment pairs of dogs were prepared, the donor animal having an isolated antral pouch and portal vein catheter and the recipient having a Heidenhain pouch and inferior vena cava catheter. The acid secretory response to a test meal was inhibited by 74% in the recipient animal following cross circulation with the donor animal which was undergoing antral pouch irrigation with decinormal hydrochloric acid. Innervated and denervated antral pouch preparations were both capable of initiating inhibition.

More recently Thompson et al. have described an extremely elaborate experiment designed to elucidate the problem of the inhibitory hormone. Dogs were prepared with homotransplanted antral and fundic pouches in addition to denervated antral and fundic pouches constructed from their own stomachs. The acid secretory response of the host and transplanted fundic pouches, to the introduction of acetylcholine into the transplanted antral pouch, was inhibited by acidification of the host antral pouch. In this experiment the host antral pouch gastrin mechanism was not involved in the
stimulatory process. Therefore it was concluded that inhibition was mediated by a humoral agent. The complexity of the preparation and the complicating feature of immunosuppressive therapy, however, reduce the significance of the findings.

Despite the many ingenious attempts to resolve the problem of the hypothetical antral chalone the question of its existence is still unanswered. Furthermore even the most enthusiastic supporters of the concept are sceptical of its physiological significance.

**Neural reflex**

Another possible mechanism for the mediation of antral inhibition of gastric secretion is that of an inhibitory reflex. But, little attention has been directed towards the possibility that inhibition might depend to some extent upon nervous pathways.

The first suggestion of such a mechanism came from Pavlov's laboratory. He was, of course, familiar with Sokolov's early studies of the effect of intragastric acidity upon Pavlov pouch secretion and later postulated that specific inhibitory fibres existed in the vagus nerve.

The classic studies of Wolf and Wolff on Tom demonstrated that emotional states such as fear, sadness, and depression may inhibit gastric secretion collected via a gastric fistula.

The majority of canine antral pouch studies have shown that the vagally denervated antrum is just as effective as the innervated antrum in producing inhibition of gastric secretion.

A few investigators have noted differences between vagally innervated and vagally denervated antra, with respect to the initiation of gastric secretory inhibition. Acidification of the innervated but not denervated antrum suppressed intestinal phase acid secretion in Heidenhain pouch dogs. But, in the same experiment it was noted that inhibition of histamine-stimulated acid secretion followed acidification of both innervated and denervated antra.

Dogs in which one half of the antrum had been excluded from the stomach by a mucosal barrier were studied by DuVal et al. The secretory response to a meal was measured during acidification of this antral segment before and after its denervation. Denervation increased inhibition of gastric secretion at pH 1.0 and increased secretion when the segment was irrigated at pH 7.0. If inhibition had been dependent upon vagal innervation a decrease in inhibition at pH 1.0 would have been expected.

A demonstration of antral inhibition, dependent upon the nervous connections between the antrum and secreting mucosa, was provided by Williams and Forrest. They prepared two dogs with vagally innervated antral and fundic pouches and two with vagally innervated antral and vagally denervated fundic pouches. Antral acidification with decinormal hydrochloric acid inhibited the acid secretory response to a meat meal in both preparations. When the innervated antrum was perfused with hydrochloric acid at a rate of 1 ml per minute, there was inhibition of the acid secretory response, of the innervated fundic pouches, to submaximal doses of pentagastrin. This effect was not observed in the denervated fundic pouches in which the nervous connections between the antrum and secreting cells had been lost. Therefore acidification of the antrum had exerted an inhibitory effect which was independent of the known methods of releasing gastrin from the antrum. It was
concluded that this effect was dependent upon intact nervous connexions between the antrum and the acid-secreting mucosa.

More recently evidence has come from Nyhus' laboratory that preservation of antral innervation in the dog results in enhancement of inhibition of acid secretion produced by acidification of an antral pouch. This enhancement was noted both when the secretory stimulus was provided by irrigation of a second antral pouch with meat extract and when it was provided by a pentagastrin infusion. Full details of this experiment have not yet been published.

In an attempt to elucidate the problem of an antral inhibitory reflex, Preshaw irrigated innervated antral pouches with 50 mN and 100 mN hydrochloric acid in dogs with gastric fistulae. There was no inhibition of the gastric acid response to intravenous porcine gastrin, administered in 1-25 g and 5 g per hour doses. However the sham feeding response was inhibited by antral acidification. Preshaw stated that the result of his experiment provided no evidence for the existence of an antral inhibitory reflex.

Studies of the antrum in situ, although perhaps more physiological than antral pouch studies, unfortunately have also provided controversial results. It was found by de Castella and Irvine that antral denervation enhanced histamine-stimulated acid secretion from vagally innervated but not denervated fundic pouches. As subsequent antrectomy produced no further elevation in output it seemed that a nervous inhibitory reflex rather than antral chalone had been involved.

Studying the effects of denervation of the antrum in situ, on histamine- and pentagastrin-induced acid secretion in dogs, Hunt and Forrest noted an increased response to stimulation in both innervated and denervated fundic pouches. A further increase followed truncal vagotomy in the dogs with denervated pouches. These results suggested that division of the nervous connexions between the antrum and the body of the stomach had disturbed an inhibitory mechanism. The findings of Hunt and Forrest regarding denervation of the antrum in situ are contrary to those of other workers.
Several other studies have provided suggestive evidence for the existence of a neuronal antral inhibitory mechanism. It was reported by State\cite{state} that in certain circumstances the antrum may assume a protective role. He induced experimental ulcers by repeated injections of histamine in dogs after 50% distal partial gastrectomy. When the antrum remained in continuity there was a much reduced incidence of ulceration compared with that in the antrectomized animals. This protective role of the antrum was impaired by antral denervation.

Andersson and Grossman\cite{andersson} further indicated that the antral inhibitory mechanism requires vagal participation for its full operation when they observed a pronounced increase in maximal acid output from canine Pavlov pouches, in response to histamine and gastrin, following antrectomy. As no such augmentation of the maximal response occurred in animals with Heidenhain pouches, it appeared that the antrum was exerting a strong inhibitory influence on vagally innervated fundic glands.

The experimental evidence would indicate that the pyloric antrum acts as an endocrine organ with both stimulatory and inhibitory functions. Inhibition brought about by acid in the antrum could be explained in three ways: diminished gastrin release or formation, release of an antral inhibitory hormone, or the activation of an inhibitory neural reflex. Present knowledge would support the first hypothesis but the other two possible mechanisms require further investigation.

**Conclusion**

Although most of the work described has been performed on dogs it is nevertheless true that much of our knowledge of human gastric physiology has evolved with the help of canine investigation.

An understanding of the physiology of gastric secretion is relevant to the aetiology and pathogenesis of peptic ulcer disease and a necessary prerequisite to both its medical and surgical management. It is generally agreed that the management of duodenal ulcer is essentially medical with surgical intervention being reserved for a comparatively small group of patients\cite{medical}. A little explored aspect of the medical management is that involving the administration of gastrointestinal hormones. It is likely that intravenous administration of secretin which is known to be capable of neutralizing the contents of the duodenal bulb in duodenal ulcer subjects\cite{secretin} will soon be tested in the treatment of this disease\cite{duodenal,secretin}.

If an inhibitory hormone could be isolated from the pyloric antrum then it is possible that such a substance could be incorporated into existing anti-ulcer regimes and perhaps even revolutionize the treatment of the disease.

The surgical management of duodenal ulcer has many shortcomings and as a result there is a continual quest for new, more satisfactory operations. The most recent development is the procedure of highly selective vagotomy in which the vagal innervation of the upper two-thirds of the stomach is interrupted but that to the antral region via the nerves of Latarjet\cite{latarjet} is conserved as is also the extragastric distribution of the vagi\cite{vagi}. It is claimed that this operation is physiologically more satisfactory leaving the gastric emptying mechanism unimpaired and permitting the acid inhibitory mechanism of the antrum and duodenum to function normally. But the assumption is made that vagal innervation is necessary for these inhibitory mechanisms to operate.
to their full extent. As has been shown evidence for this is not yet conclusive. Any investigation firmly establishing the role of vagal innervation in the antral inhibitory system would be of great importance and obviously strengthen the case for employing operations such as highly selective vagotomy in the surgical management of peptic ulcer.

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