# The Production of an Acid Inhibitor by the Gastric Antrum *

R. C. HARRISON, M.D., W. H. LAKEY, M.D., H. A. HYDE, M.D.

*From the McEachern Laboratory and Department of Surgery, University of Alberta, Edmonton, Canada*

THE IMPORTANCE of the antrum in gastrointestinal physiology was first stressed by Edkins in 1906. Since that time, it has been assumed by physiologists and surgeons that it contributed to the etiology of peptic ulcer. It has recently been shown that the amount of acid stimulation by the antrum depends on the pH in the region of the antral mucosa.

Our experiment suggests that the antrum, if in an acid media, produces a substance which inhibits the production of acid. Thus, the preservation of the antrum in continuity with the stomach may be beneficial in gastric surgery. Pavlov's classical work initiated investigation of the mechanisms which control gastric secretion. Since then, the factors which stimulate gastric secretion have been extensively studied, whereas those which inhibit it have not received much attention.

*Stimulation of Gastric Secretion.* It has long been known that the secretion of hydrochloric acid by the parietal cells of the stomach could be stimulated in three ways. These three mechanisms have been called the cephalic, the gastric, and the intestinal phases of gastric secretion, and more recently, it has been postulated that the adrenal steroids are also implicated in the control of gastric secretion.

Pavlov [14] and others found that food was responsible for the stimulation of gastric secretion. The thought, sight, smell, or taste of food resulted in stimulation of acid secretion by the vagi. The presence of food in the stomach resulted in increased gastric secretion, as did the absorption of the products of digestion from the upper intestine.

Edkins [5] on the basis of his investigations, postulated that the antrum produced a hormone, gastrin, which reached the parietal cells by the blood stream and stimulated acid production. Ivy [10] repeated Edkins' experiments and failed to confirm his results. However, data from clinical cases tended to confirm the importance of the antrum in stimulating gastric acid production. The Eiselsberg-Finsterer-Devine exclusion procedure for duodenal ulcer, in which the antrum was retained and left in continuity with the duodenum, resulted in a high incidence of stomal ulceration. Many of these failed to heal until the antrum was excised.[12]

By 1954 it was well established by the experiments of several workers [4, 6, 13, 17, 20] that the antrum is capable of elaborating a substance which stimulates parietal cell secretion. This substance is generally referred to as the hormone gastrin, although it has not yet been isolated or proven to be a true hormone.[8] Moreover, this stimulation is minimal when the antrum is bathed by acid, moderate when the antral pH is relatively alkaline, and maximal when the antrum is in contact with fecal contents, as when it is attached to the transverse colon as a diverticulum.[21]

*Inhibition of Gastric Secretion.* The study of inhibition of gastric secretion has been approached by many workers bearing in

* Presented before the American Surgical Association, White Sulphur Springs, West Virginia, April 12, 1956.

Supported in part by the 'National Research Council of Canada.'

mind the three major mechanisms of parietal cell stimulation.

*Vagal.* There are inhibitory fibres in the vagus nerve, and Wolf and Wolff [19] have demonstrated that emotional states such as fear and anger may inhibit gastric secretion.

*Intestinal.* In 1910 Pavlov noted that a fatty meal inhibited gastric secretion. Kosaka and Lim [11] in 1930 demonstrated that this inhibition was due to the formation of a humoral agent in the mucosa of both the small and large intestine as a result of contact with fat. They suggested the name enterogastrone for this gastric inhibitory agent.

*Duodenal.* Many investigators [3, 7, 18] have confirmed Sokolov's [15] observation that acid in the duodenum inhibits parietal cell secretion.

*Antrum.* In 1942 Brunschwig [2] and his associates demonstrated a gastric secretory depressant in canine and human gastric juice. This inhibitory substance was not present in the gastric juice of patients suffering from pernicious anemia or gastric carcinoma. In dogs that had been recently fed and were showing profuse secretion from a cannulated gastric pouch, the test suspensions of previously obtained gastric juice were injected intravenously and the effect on pouch secretion determined. A significant reduction in acid output from the pouches occurred with the intravenous administration of the gastric juice.

Hood, Code and Grindlay [9] in 1953, extended the work of Brunschwig and attempted to demonstrate that a substance was produced by the gastric antrum, which was capable of inhibiting gastric secretion. They compared the inhibitory action of juice from fundic pouches with that collected from antrum pouches. These were given intravenously to dogs whose fundic pouch output was carefully measured. Their results seemed to indicate that the main source of the gastric secretory inhibitor in canine gastric juice was the antrum mucosa. Although they felt that this intravenous injection produced a minimal pyrogenic effect, they did note some elevation of temperature following injection. In the experiments of both Brunschwig and Hood the inhibition obtained might have been due to the pyrexia resulting from the intravenous injection of gastric juice.[8]

In 1954 Dragstedt and his associates [21] sought evidence for an inhibitor having its source in the antrum. Using four dogs with Heidenhain or total stomach pouches and a marsupialized antrum pouch they stimulated the parietal cell secretion by the injection of 1.0 mg. of histamine. The comparison of the resulting secretion, with that produced by the same dose of histamine while the antrum was irrigated with N/10 HCl failed to demonstrate any difference in acid output by the fundic pouches. On the basis of this experiment they concluded that the antrum was not capable of secreting an inhibitory substance. One wonders, however, whether the artificial stimulant, histamine, may have been of such potency as to completely destroy or mask any inhibitory substance which was being liberated by the acid bathed antrum mucosa.

Further evidence that the pH existing over the antrum mucosa was of extreme importance in determining the amount of hydrochloric acid secreted by the parietal cells was demonstrated in 1954 by Wangensteen and his associates.[1] They demonstrated in a series of dogs that when the antrum was excluded from the acid secreting part of the stomach, gastrojejunal ulcers developed. When the antrum remained in continuity with the rest of the stomach, or was excised, no ulcers occurred. The increase in gastric secretion which occurred in the dogs with the antrum excluded was explained on the basis of increased production of gastrin by the antrum in contact with food and alkaline secretions. He concluded that the antral stimulation of gastric secretion is not nearly so great when the antrum retains its normal relation to the remainder of the stomach as when it is

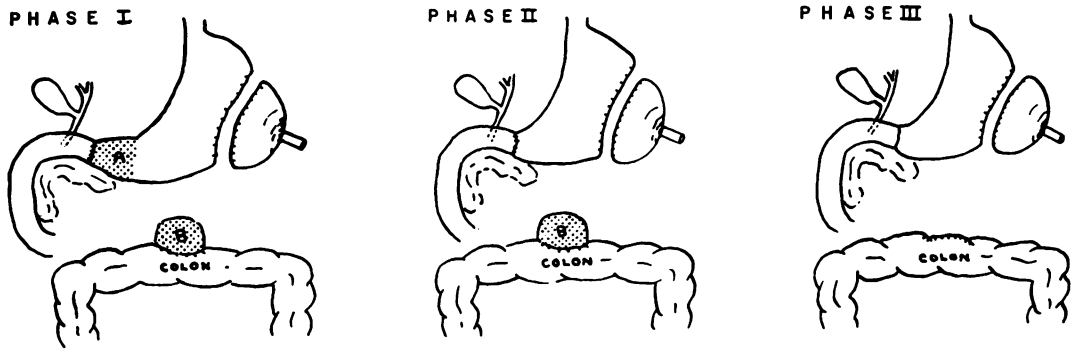


FIG. 1. Illustrating the three operative procedures or phases of the project.

excluded from contact with acid gastric juice.

Interesting evidence that the antrum may take an active role in the inhibition of gastric secretion was provided by the work of State *et al.*[16] in 1955. They demonstrated in a series of dogs that the antrum would protect against duodenal ulceration under histamine stimulation. In their study, with a 50 per cent resection of the acid secreting portion of the stomach, the incidence of histamine induced ulcer was significantly less when the antrum was preserved.

In this project we attempted to investigate any inhibitory mechanisms having their origin in the antrum, which might regulate acid secretion when the stomach had emptied. It seemed desirable that the parietal cell stimulation be as physiological as possible rather than introduce an artificial stimulant such as histamine. Dragstedt had demonstrated that the antrum attached to the colon as a diverticulum resulted in a generous secretion of acid by the parietal cells in a Heidenhain pouch. In addition, we wanted antral mucosa in its normal location to be bathed by this gastric juice of high acidity. An antral pouch on the colon would produce such an effect. One of the solutions to this problem was to divide the antrum, leaving one half in its normal location, transplanting the other half to the colon.

*Methods.* A series of seven adult mongrel dogs were subjected to three operative procedures (Fig. 1). During the first (Phase I) procedure, a Heidenhain pouch was fashioned from the greater curvature and fundus of the stomach. The limits of the pyloric antrum were then defined, the proximal edge of the antrum being marked with two long black sutures to facilitate recognition of its limits at the later operative procedure. The distal half of the antrum was divided from the stomach and duodenum, with care to retain its blood supply from the lesser and greater curvatures. The distal end of this terminal half of the antrum was closed and the pouch so formed was attached to the side of the transverse colon as a diverticulum. The proximal half of the antrum was anastomosed to the duodenum, with care to ensure that an adequate stoma existed.

Heidenhain pouch secretions were collected through a stainless steel cannula into a rubber bladder, after the method of Dragstedt.[20] After a month had elapsed the pouch secretions were collected daily for 21 days, the free hydrochloric acid output being calculated and expressed as milliequivalents per 24 hours. Toepher's method for free hydrochloric acid was used.

The second operative procedure involved the removal of the proximal half of the antrum, which had been left attached to the stomach. (Phase II). Histological sections were taken from the proximal and distal edges of this specimen. These sections showed antral mucosa continuous with duo-

TABLE I. *Change in Pouch Secretion Following Removal of the "Gastric" Half of the Antrum (Phase I to Phase II)*

| Dog No. | Phase I | | | Phase II | | | % Change Phase 1 to Phase 2 | t* | P* |
|---|---|---|---|---|---|---|---|---|---|
| | No. of 24 Hour Collections | Av. 24 Hr. Collection mEq. HCl | Standard Deviation | No. of 24 Hour Collections | Av. 24 Hr. Collection mEq. HCl | Standard Deviation | | | |
| 10 | 22 | 17.3 | 6.5 | 14 | 35.7 | 6.8 | +106 | 7.9 | <.001 |
| 11 | 21 | 14.5 | 3.4 | 21 | 25.2 | 5.1 | + 74 | 7.8 | <.001 |
| 12 | 21 | 54.3 | 4.0 | 16 | 105.1 | 7.3 | + 93 | 26.1 | <.0001 |
| 13 | 21 | 57.4 | 12.6 | 21 | 64.9 | 8.8 | + 14 | 2.2 | <.04 |
| 14 | 22 | 26.3 | 7.7 | 21 | 35.2 | 6.9 | + 34 | 3.9 | <.001 |
| 15 | 21 | 19.8 | 7.2 | 21 | 37.0 | 7.9 | + 87 | 7.2 | <.001 |
| 19 | 21 | 2.4 | 0.8 | 21 | 3.1 | 0.8 | + 29 | 26.9 | <.0001 |
| | Average Percentage Change Phase I to Phase II | | | | | | + 62 | | |

* P is the probability of the difference being due to chance—Student's "t" test.

denal mucosa on the distal side and gastric mucosa on the proximal side. This provided evidence that the antral mucosa had been present in the first Phase and that all the gastric portion of the antrum had been removed in the second Phase. The gastric stump was anastomosed to the duodenum to re-establish gastrointestinal continuity. Following another month's recuperation the 24 hour acid output was collected for a period of from 14 to 21 days.

Removal of the antrum diverticulum from the colon was undertaken as a third operative procedure on three of the dogs (Phase III). Another 21 days of 24 hour acid output was taken following the return of the dog's health.

Throughout the course of the experiment, the dog's daily diet consisted of 500 Gm. of Miracle Dog Food and water ad lib. Serum chlorides were done weekly, and sodium chloride added to the diet to ensure that the chloride intake was adequate.

*Results.* All the dogs in the series showed a significant increase in pouch acid secretion when the antrum, in its normal location, was excised (Phase I to Phase II), Table I. By statistical methods, the difference was very significant in six dogs, and moderately significant in the seventh (#13). The average increase was 62 per cent. Both volume and degree of acidity increased between Phases I and II.

The marked variation in the pouch output of one dog as compared with another is of course explained by the variation in the size of the Heidenhain pouch in each preparation.

The percentage of change from Phase I to Phase II in each dog depends on how much antrum is left attached to the stomach in Phase I. If too much antrum is transplanted to the colon (as occurred in dog 13), the inhibitory effect will be minimal. We believe that the difficulty in accurately dividing the antrum into halves explains the variation in the percentage increases of the seven dogs between Phase I and Phase II.

Following removal of the "colonic" half of the antrum (Phase III), which was done in three dogs only, the pouch output fell to very low levels. The average 24 hour output in these was 1.06, 0.42, and 0.14 mEq. of hydrochloric acid (Dogs 11, 13, and 15). That the "colonic half" of the antrum was the source of stimulation of the pouch is evident when the change is noted between Phase II and Phase III.

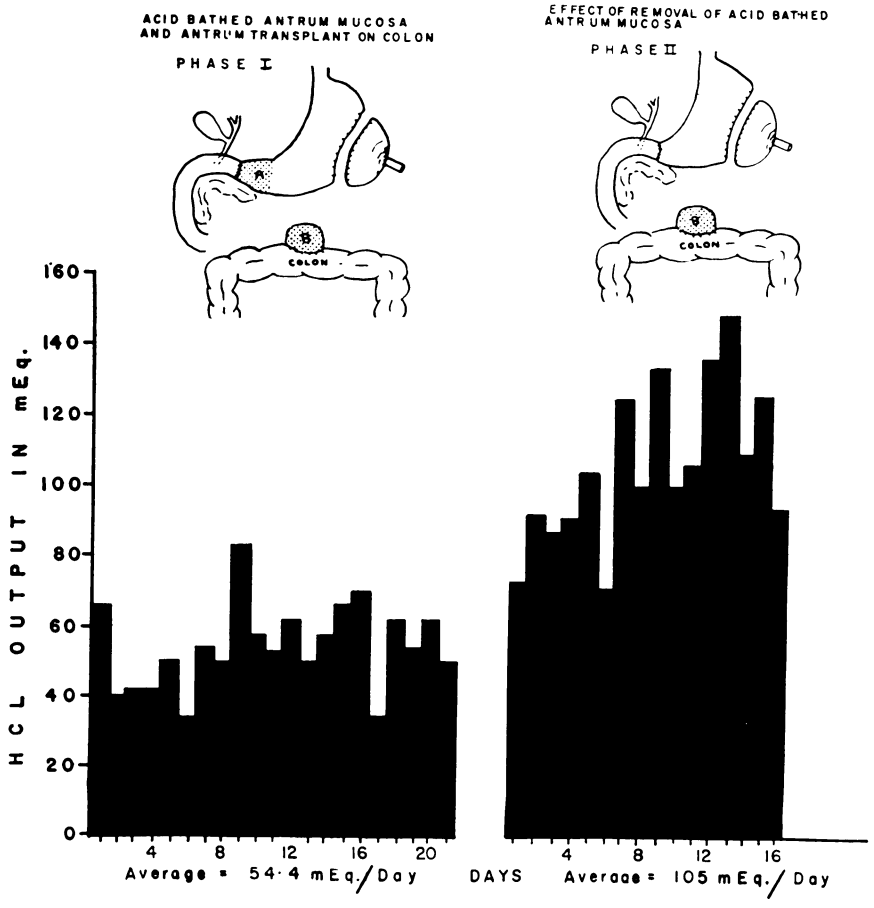


FIG. 2. Results in dog 12, showing the increase in Heidenhain pouch secretion when the "gastric" half of the antrum was removed.

The results are shown diagrammatically in two dogs in Figures 2 and 3.

## DISCUSSION

In an analysis of Phase I, the "colonic portion" of the antrum, it has been shown,[13] will stimulate acid production by both the pouch and the body of the stomach, presumably as a result of the production of gastrin in the "colonic" antrum. This will result in an acid environment for the "gastric" half of the antrum, resulting in little or no gastrin production by it.[21] If gastrin production is the only factor of significance when the "gastric" half of the antrum is excised (Phase II), pouch secretion will remain steady or fall slightly. The fact that the pouch secretion rose markedly influenced us to postulate the concept of an inhibitor having its source in the antrum.

This experiment suggests that in an acidic environment the antrum not only stops secreting gastrin, but produces an inhibitor substance capable of actively interfering with production of acid.

The mechanism whereby this active inhibitor affects secretion is unknown. Three obvious possibilities come to mind. It could interfere with gastrin production, combine with gastrin to render it ineffective, or affect the parietal cells directly. Recent work in our laboratory suggests that it is capable

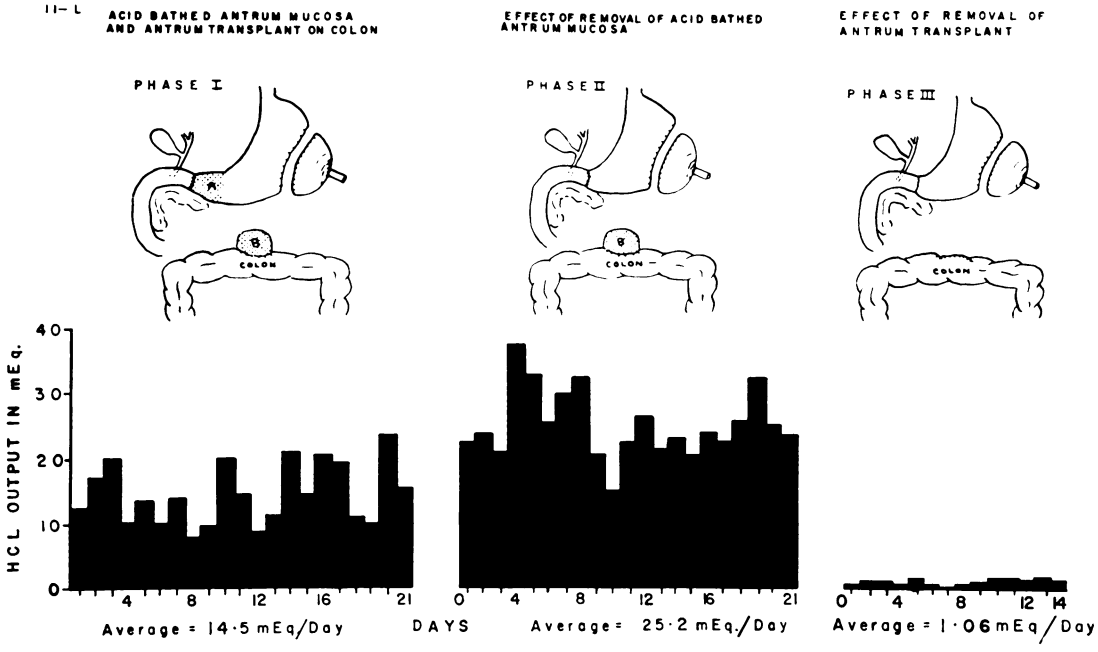


FIG. 3. Results in dog 11. Three phases.

of inhibiting the intestinal phase of secretion as well as the stimulus to acid production provoked by histamine.

If such a substance exists in man, it would provide a very effective regulator of the post prandial flow of hydrochloric acid. It would be much more effective than the mere reduction in gastrin secretion, and would be a major factor in preventing continuous hyperacidity. While a similar mechanism has been demonstrated in the duodenum, the effect of an antral inhibitor should be more significant, in that it would initiate the reduction in flow of unbuffered hydrochloric acid.

It is quite possible that the unhappy results associated with exclusion procedures in which the antrum is left attached to the duodenum (Eiselsberg-Finsterer-Devine) have made us unjustifiably prejudiced against this portion of the stomach. It is of course clear why such an anatomical arrangement resulted in a high incidence of stomal ulceration. The antrum was constantly in an alkaline environment, and gastrin production was continuous and probably large in amount.

Wangensteen has demonstrated in the laboratory and clinically that the antral mucosa in an acid environment is not harmful or conducive to ulcer reformation. If it is not harmful to the ulcer patient, it at least adds to his storage capacity. If it is capable of secreting an acid inhibitor, it may be even more beneficial.

## CONCLUSIONS

(1) In the dog the antrum is capable of producing a substance which will actively inhibit the secretion of acid by the stomach.

(2) It would appear that the effect is humoral, as the only communication between the antrum and the Heidenhain pouch was by the blood stream.

(3) The nature of the material is unknown and its site of action is unknown. Three possibilities regarding its method of action have been considered.

SUMMARY

A series of dogs with Heidenhain pouches with half the antrum left in continuity with the stomach, and half as a colonic diverticulum have been studied to show the inhibitory effect produced by the antrum mucosa bathed in an acid environment. When the portion of antrum in its normal location is excised, a definite rise in the acid output of the Heidenhain pouches occurred in all dogs, this increase averaging 62 per cent.

This study has confirmed previous work, demonstrating that the antrum in an acid medium does not result in significant stimulation of gastric secretion. Moreover, this experiment suggests that the antrum in such an environment is capable of producing an inhibitory substance which will actively reduce acid output. The antrum in its normal location may act as an important mechanism to reduce the postprandial secretion of hydrochloric acid. Failure of this mechanism may play some role in the development of peptic ulceration.

BIBLIOGRAPHY

1. Brackney, E. L., P. S. Campbell and O. H. Wagensteen: Role of Antral Exclusion in Development of Peptic Stomal Ulcer. Proc. Soc. Exper. Biol. and Med., **86**: 273, 1954.
2. Brunschwig, A., R. A. Rasmussen, E. J. Camp and R. Moe: Gastric Secretory Depressant in Gastric Juice. Surg., **12**: 887, 1942.
3. Day, J. J. and D. R. Webster: The Autoregulation of the Gastric Secretion. Am. J. Dig. Dis. and Nut., **2**: 527, 1935.
4. Dragstedt, L. R., E. R. Woodward, E. H. Storer, H. A. Oberhelman and C. A. Smith: Quantitative Studies on the Mechanism of Gastric Secretion in Health and Disease. Ann. Surg., **132**: 626, 1950.
5. Edkins, J. S. and J. M. Tweedy: The Natural Channels of Absorption Evoking the Chemical Mechanism of Gastric Secretion. J. Physiol., **38**: 263, 1909.
6. Evans, S. O., J. M. Zubiran, J. D. McCarthy, H. Ragins, E. R. Woodward and L. R. Dragstedt: Stimulating Effect of Vagotomy on Gastric Secretion in Heidenhain Pouch Dogs. Am. J. Physiol., **174**: 219, 1953.
7. Griffiths, W. J.: The Duodenum and the Automatic Control of Gastric Acidity. J. Physiol., **87**: 34, 1936.
8. Grossman, M. I.: Gastrointestinal Hormones. Physiol. Rev., **30**: 33, 1950.
9. Hood, R. T., C. F. Code and J. H. Grindlay: Source of a Possible Gastric Secretory Inhibitor in Canine Gastric Juice and Effects of Vagotomy on its Production. Am. J. Physiol., **173**: 270, 1953.
10. Ivy, A. C. and J. E. Whitlow: Gastrin Theory put to Physiologic Test. Am. J. Physiol., **60**: 578, 1922.
11. Kosaka, T. and R. K. S. Lim: Demonstration of the Humoral Agent in Fat Inhibition of Gastric Secretion. Proc. Soc. Exper. Biol. and Med., **27**: 890, 1930.
12. McKittrick, J. S., F. D. Moore and R. Warren: Complications and Mortality in Subtotal Gastrectomy for Duodenal Ulcer. Ann. Surg., **120**: 531, 1944.
13. Oberhelman, H. A., E. R. Woodward, J. M. Zubiran and L. R. Dragstedt: Physiology of the Gastric Antrum. Am. J. Physiol., **169**: 738, 1952.
14. Pavlov, I. P.: Work of the Digestive Glands. London, Charles Griffin and Company, 1910.
15. Sokolov, as quoted by Babkin, B. P.: Secretory Mechanism of the Digestive Glands. New York, Paul B. Hoeber, Inc., 1950.
16. State, D., A. Katz, R. S. Kaplan, B. Herman, L. Morgenstern and I. A. Knight: The Role of the Pyloric Antrum in Experimentally Induced Peptic Ulceration in Dogs. Surg., **38**: 143, 1955.
17. Storer, E. H., E. J. Schmitz, L. R. Sauvage, E. A. Kanar, D. H. Diessner and H. N. Harkins: Gastric Secretion in Heidenhain Pouches Following Section of Vagus Nerves to Main Stomach. Proc. Soc. Exper. Biol. and Med., **80**: 325, 1952.
18. Wilhhemj, C. M., F. T. O'Brian and F. C. Hill: The Inhibitory Influence of the Acidity of the Gastric Contents on the Secretion of Acid by the Stomach. Am. J. Physiol., **115**: 429, 1936.
19. Wolf, S. and H. G. Wolff: Human Gastric Function. Oxford University Press, 1943.
20. Woodward, E. R., R. R. Bigelow and L. R. Dragstedt: Effect of Resection of Antrum of Stomach on Gastric Secretion in Pavlov Pouch Dogs. Am. J. Physiol., **162**: 99, 1950.
21. Woodward, E. R., E. S. Lyon, J. Landor and L. R. Dragstedt: The Physiology of the Gastric Antrum. Gastroenterology, **27**: 766, 1954.