Mechanism of Gastric Hypersecretion Following Massive Intestinal Resection

Clinical and Experimental Observations

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Craig and Stewart [6] noted the favorable course of a man who previously sustained a massive bowel resection. He had undergone gastrectomy and vagotomy for duodenal ulcer. They reported a description of this patient in 1960.

Case 1. (U.H. (Columbus, Ohio) 34616X.) A 58-year-old man, with superior mesenteric artery thrombosis, required resection of bowel from a point 15 inches distal to the ligament of Trietz to the splenic flexure of the colon. A jejunocolic anastomosis was performed. He was achlorhydric because of a gastrectomy and vagotomy performed 4 years previously for gastric ulcer. The postoperative course was remarkably favorable, with a minimum of diarrhea and a return to within 8 pounds of his ideal weight in 6 months. He died one year later of unrelated causes.

Craig and Frederick initiated an investigation vagotomy and pyloroplasty after massive bowel resection in dogs at Ohio State University. Frederick completed the demonstration of improved survival and decreased weight loss of these dogs at the Harvard Surgical Unit of the Boston City Hospital.

In 1963 we noted marked gastric hypersecretion in a 16-year-old boy who had undergone nearly total small bowel resection for midgut volvulus.[12, 13] A disastrous course was halted and anastomosis healing with a normal gastric secretory rate followed vagotomy and pyloroplasty.

Case 2. (B.C.H. (Boston, Massachusetts) 1815190.) A 16-year-old boy with midgut volvulus and secondary bowel infarction required a massive small bowel resection. Anastomosis disruptions and fistula formation required multiple re-resections until ultimately he retained only 5 inches of jejunum, distal to the ligament of Treitz, which was anastomosed to the remaining 2 inches of ileum proximal to the ileocecal valve. Gastrostomy drainage ranged up to 4,600 ml. and 465 mEq. of free acid per day. At the final closure of an anastomosis fistula, vagotomy and pyloroplasty were performed. Gastric acid output dropped to normal range, the fistula repair healed and diarrhea was controlled. Within one year his weight went from 82 to 102 pounds, and diarrhea was not a

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problem. He then developed pulmonary tuberculosis from which he is now recovering.

This case suggested that the mechanism of improved survival after gastrectomy and vagotomy in Craig's case and after vagotomy and pyloroplasty in Frederick's dogs may have been control of gastric hypersecretion and this led us to its study. Hypersecretion from Heidenhain pouches was shown to occur in proportion to the amount of small bowel resected in preliminary studies reported with Frederick and Sizer in 1964.[12, 13] These animals maintained normal liver function and showed no elevation of urinary corticosteroids. Simple bowel transection and re-anastomosis did not cause hypersecretion. Animal studies confirming this finding were subsequently reported by Landor and Baker [25] from the University of Missouri, by Westerheide, Elliot and Hardacre [43] at the Ohio State University and by Reul and Ellison [34] of of Marquette. We were also able to describe an additional case which suggested the benefits derived from previous ulcer surgery by a 43-year-old woman with massive bowel resection seen at the New England Baptist Hospital.[12, 13]

Case 3. (N.E.B.H. (Boston, Massachusetts) A52951.) A 43-year-old woman with a superior mesenteric artery embolus required resection of bowel from a point 18 inches distal to the ligament of Treitz to the midtransverse colon. A jejunocolic anastomosis was performed. She had no free acid on overnight gastric analysis, having required a gastric resection 10 years previously for duodenal ulcer and a vagotomy for marginal ulcer 3 weeks before. Diarrhea was easily controlled, and she gained to within 10 pounds of her ideal weight. Three and one-half years after bowel resection she was doing well and underwent elective cholecystectomy.

An additional case of measured gastric hypersecretion following extensive bowel resection in an 87-year-old woman was added from the Boston City Hospital.[12, 13]

Case 4. (B.C.H. (Boston, Massachusetts) 2005247.) An 87-year-old woman, with superior mesenteric artery thrombosis and failure of endarterectomy, had a resection of bowel from a point 24 inches distal to the ligament of Treitz to the midtransverse colon. A jejunocolic anastomosis was performed. She had undergone no previous gastric surgery. Postoperative diarrhea was profuse and gastrostomy drainage ranged up to 2,200 ml. and containing 130 mEq. of free acid per day. She died of sepsis 14 days after bowel resection.

In 1966 Winawer and associates in the Gastrointestinal Research Laboratory at the Mallory Institute of Pathology reported on the detailed metabolic studies which permitted solution of many of the problems which our first patient, the boy with subtotal small bowel resection, sustained.[44]

We have observed two additional cases which relate to this problem. A 30-year-old woman under the care of Dr. Cornelius Sedgwick at the Lahey Clinic had previous small bowel resection because of regional enteritis. She required removal of two thirds of the small bowel and subtotal colectomy for combined recrudescent enterocolitis, and developed inanition and cachexia because of ileostomy diarrhea up to 9 liters daily and an intractable hypokalemic alkalosis. A jejunal segment had been reversed. Only after gastric irradiation to reduce gastric secretion did this patient appear to have been salvaged.[2]

Case 5. (N.E.B.H. (Boston, Massachusetts) A58107.) A 30-year-old woman underwent a resection of the distal four feet of her ileum and proximal ascending colon for regional enteritis. An ileocolic anastomosis was performed. Two years later she underwent a further resection of small bowel and subtotal colectomy with construction of an ileostomy and a sigmoidal mucous fistula for recurrent enterocolitis with diarrhea, rectal stricture, and rectovaginal fistula. Severe ileostomy diarrhea occurred. Drainage of as much as 4,800 ml. per day with 114 mEq. of chloride and 16 mEq. of sodium per 1,000 ml. resulted in severe metabolic alkalosis. Minimal control of the problem was obtained by medical and dietary manipulations. Five months later she underwent reversal of a 2½-inch segment of small bowel immediately proximal to the ileostomy, and at that time it was felt that she had three feet of small bowel remaining distal to the ligament of Treitz. Postoperatively, ileostomy drainage remained very

TABLE 1. *Acid Secretion by Heidenhain Pouch Dogs after Different Amounts of Upper and Lower Small Bowel Resection*

	Bowel Resection							
	Control Period				Following Bowel Resection			
Dog No.	No. Determ.	Mean Free Acid H-Pouch (mEq./24 hr.)	S. D.	% Bowel Resected	No. Determ.	Mean Free Acid (mEq./24 hr.)	S. D.	*p*-Value
518	8	1.1	±0.7	0% simple transection	15	0.7	±0.4	n.s.
471	15	7.2	±3.0	25% distal resection	3	10.7	±1.0	<0.010
515	19	2.4	±1.3	50% distal resection	15	5.4	±4.8	<0.050
735	19	1.7	±1.0	75% distal resection	13	4.7	±1.8	<0.001
1210	7	1.6	±1.3	25% proximal resection	19	2.4	±2.4	<0.300
518	56	4.8	±4.0	50% proximal resection	29	8.5	±4.6	<0.001
518	—	—	—	75% proximal resection	20	11.4	±5.9	<0.100

* Comparisons of mean acid secretion before and after bowel resection are made with varying statistical significance of results but increased secretion in all cases.

high with volumes up to 6,600 ml. per day. The pH of this fluid ranged between 6 and 1 and serum electrolytes reflected metabolic alkalosis. Gastric output ranged up to 3,300 ml. per day, and one measured overnight secretion of 350 ml. contained 56 mEq. of acid. Supervoltage gastric radiation of 600 rad was given. Ileostomy drainage decreased and her weight rose from 60 to 70 pounds at the time of discharge. Four months later she weighted 105 pounds, only 10 pounds less than her previous maximal weight.

The second case showed no gastric acid secretion in gastrostomy drainage when a 62-year-old woman underwent subtotal small bowel and partial colon resection at the Boston City Hospital. This seems to be explained by the absence of parietal cells; there was no acid secretion after histalog administration, and at autopsy the stomach showed atrophy and absence of parietal cells.

Case 6. (B.C.H. (Boston, Massachusetts) 20011379.) A 62-year-old-woman with superior mesenteric artery thrombosis required a resection of bowel from a point 7 inches distal to the ligament of Treitz to the midtransverse colon. A jejunocolic anastomosis was performed. She had had no previous gastric surgery, and the pH of gastrostomy drainage was 8. There was no free acid after histalog stimulation. Her postoperative course was stormy, and she died of sepsis in the fifth postoperative week. Autopsy section of the stomach showed no parietal cells.

Since the foregoing data suggests the clinical importance of gastric hypersecretion associated with massive bowel resection, factors concerned with this phenomenon were studied experimentally.

Materials and Methods

Under intravenous sodium pentobarbitol anesthesia Heidenhain pouches were constructed in mongrel dogs varying in weight from 15 to 40 Kg. The antrum was mapped at operation to be sure that it was excluded from each pouch.[31] We employed a new and inexpensive cannula.* Small bowel resection or exclusion was the performed prior to, simultaneously with, or following the resection or explantation of the gastric antrum. Closed aseptic intestinal anastomoses were made after small bowel resections using Halstead matters sutures over Bainbridge clamps. Open two-layer gastroduodenal reconstructions were made after antral resection or explantation (with mapping of the antral margins). Thiry-Vella stomas and those of the explanted antrums were primarily matured by suture of the entire thickness of the bowel wall to the subcuticular fascia with fine chromic

* Available from F. W. Dixon Co., Cambridge, Massachusetts.

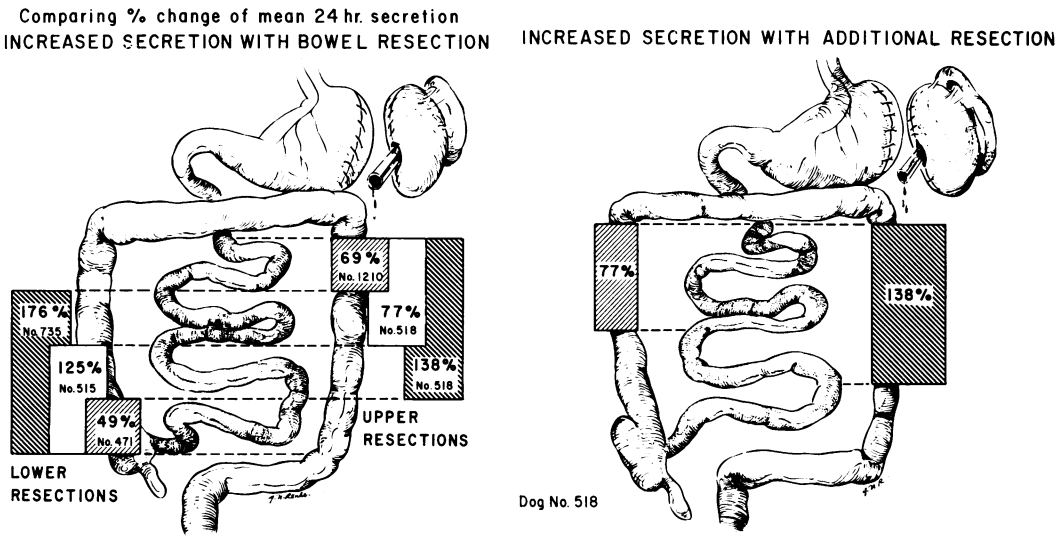


FIG. 1. Heidenhain pouch acid secretion is increased in rough proportion to amounts of small bowel resected.

FIG. 2. Acid secretion which had increased from Heidenhain pouch after bowel resection increased further after additional resection.

catgut. Intra- and postoperative saline and glucose infusions of 1 liter per day were given 3 days along with transfusions of unmatched canine blood as was indicated. One million, two hundred thousand units of procaine penicillin were given for 5 days. Oral fluids were restricted for 3 days with an increase to a regular diet after 5 days. After postoperative stabilization on a standard laboratory diet plus supplements * 24 hours pouch collections were made. Sepcimens were titrated for free acid with 0.1N NaOH using Topfer's reagent (0.5% alcoholic solution of dimethyl-amino-diazobenzene) as an indicator. X-ray studies to determine gastric emptying time were performed following the feeding of 100 Gm. of micro-paque barium mixed with a standard meal using a portable x-ray unit. Anteroposterior and lateral films were made hourly, and complete emptying was considered to have occurred when only traces of barium remained in the stomach. Basal secretion of Heidenhain and Pavlov pouches before and after small bowel resection was determined by a modification [40] of the irrigational method of Savage *et al.*[36] 0.01N NaOH was used to titrate free acid in 15-minute collections made by this method.

* ½ can of Hills Dog Food, 1 can of Purina Chow dog food, 1 can of Kibled dog food, mixed with a 2 multivitamine capsules with mineral oil and 1 gram of potassium chloride and 5 grams of sodium chloride distributed throughout the food. Smaller animals which could not eat this amount of food were fed a reasonable fraction of this diet regularly.

Results

Five dogs had bowel resections varying from 25 to 75 per cent of the upper or lower small bowel (Table 1). As the amount of bowel resected increased, so did the 24-hour acid secretion from the Heidenhain pouches (Fig. 1). Upward revision of the amount of bowel resected in one animal resulted in an additional increase in acid (Fig. 2). Lower small bowel resections usually resulted in a greater increase of secretion than comparable upper small bowel resections (Fig. 3). Statistical analyses of the differences between these groups show highdegrees of significance in some cases. One animal showed no significant

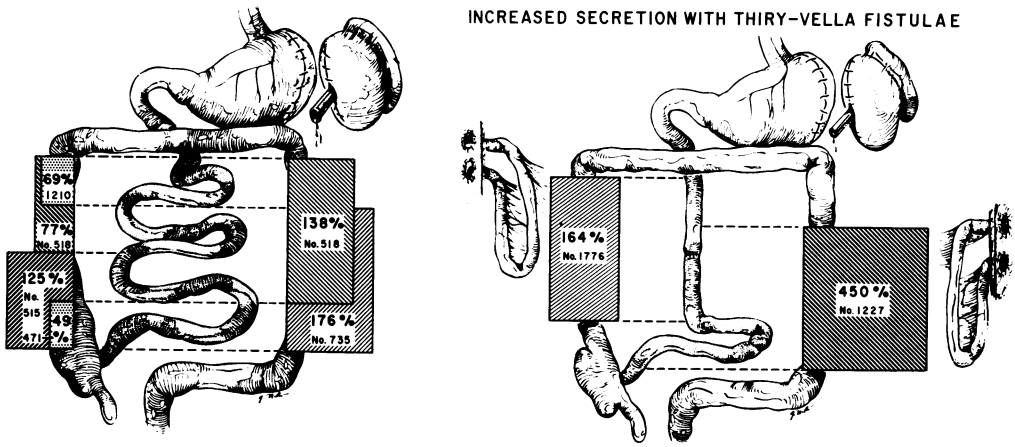


FIG. 3. Lower small bowel resections are associated with greater increases of Heidenhain pouch acid secretion than are comparable amounts of upper resections (with one exception).
FIG. 4. Heidenhain dogs show increased mean daily acid secretion when Thiry-Vella loops are made.

change in secretion, as one would expect, after simple bowel transection and reanastomosis. All animals showed increased secretion after resections.

When Thiry-Vella loops were constructed to exclude the upper 75 per cent of small bowel in one animal and the lower 75 per cent of small bowel in another, marked hypersecretion occurred (Table 2). This was greatest with distal bowel exclusion (Fig. 4). The observed differences were significant.

Gastric emptying time was determined in two animals before and after Heidenhain pouch construction, and after 75 per cent distal small bowel resection. Three studies of emptying were made at each stage (Fig. 5). Emptying time was not prolonged; it was slightly reduced.

The effect of body wall explantation or resection of the gastric antrum after massive small bowel resection was studied in five animals (Table 3). After explantation of the antrum in four animals, the hypersecretion following upper or lower 75 per cent small bowel resection fell to preresection levels or lower (Fig. 6). The same reduction in acid secretion occurred after antral excision in the remaining animal (Fig. 6). Significant differences were recorded.

Two animals showed decreased pouch secretion after antral explantation before bowel resection had been done (Table 4).

TABLE 2. *Acid Secretion by Heidenhain Dogs with Thiry-Vella Loops*

	Bowel Exclusion							
	Control Period				Following Bowel Resection			
Dog No.	No. Determ.	Mean Free Acid H-Pouch (mEq./24 hr.)	S. D.	% Bowel Excluded (Thiry-Vella Loop)	No. Determ.	Mean Free Acid (mEq./24 hr.)	S. D.	*p*-Value
1227	25	0.4	±0.4	75% distal	23	2.2	±1.7	<0.001
1776	21	4.4	±3.8	75% proximal	17	11.6	±2.9	<0.001

One of them subsequently had a 75 per cent small bowel resection which was not followed by hypersecretion (Fig. 7). Another animal showed no hypersecretion when antral resection was performed at the same time as the 75 per cent proximal small bowel resection (Fig. 7), while another showed low secretion after antral excision and no hypersecretion when 75 per cent distal resection was done.

Under carefully controlled basal conditions, four fasting Heidenhain and awo Pavlov pouch dogs showed no free acid secretion during 15-minute fractional hour collections (Table 5). Similar observations were made after 75 per cent distal small bowel resections in one Heidenhain and two Pavlov pouch dogs (Table 5).

The Heidenhain dogs showed no acid secretion during fasting basal state study after bowel resection. Pavlov pouch dogs showed the expected small amount of basal state acid production before resection with similar very low secretion rate in animals which had been resected. Acid values and numbers of animals were too small to permit statistical comparison.

Discussion

Hypersecretion of gastric acid is an established phenomenon after massive

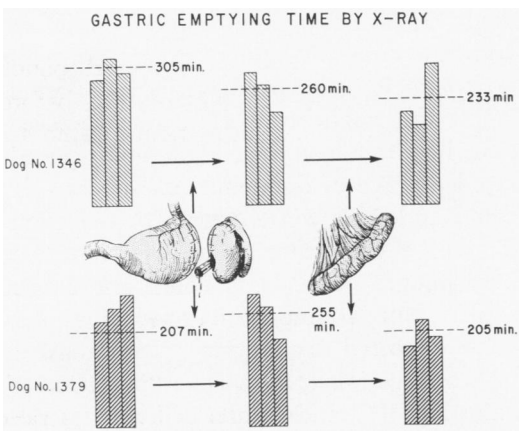


FIG. 5. Barium mixed meal shows no delay in gastric emptying when Heidenhain pouches are made, and slightly accelerated emptying after massive small bowel resections.

TABLE 3. *Heidenhain Pouch Secretion before and after 75% Upper or Lower Small Bowel Resection and after Body Wall Explanation of the Mapped Gastric Antrum or Antral Excision*

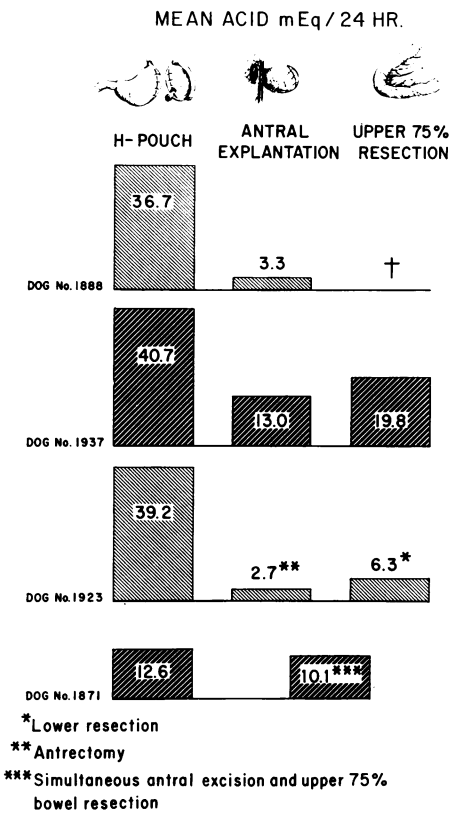
	Bowel Resection and Antral Manipulation											
	Control Period				Following Bowel Resection					Following Antral Manipulation				
Dog No.	No. Determ.	Mean Free Acid (mEq./24 hr.)	S. D.	% Bowel Resection	No. Determ.	Mean Acid Acid (mEq./24 hr.)	S. D.	*p*-Value	Antral Manipulation	No. Determ.	Mean Free Acid (mEq./24 hr.)	S. D.	*p*-Value
1346	7	4.0	±2.9	75% distal	11	19.9	±11.2	<0.150	Explant	12	4.0	±3.5	<0.001
511	20	4.4	±2.9	75% proximal	32	9.4	± 4.2	<0.001	Explant	13	1.2	±0.9	<0.001
1906	—	—	± —	75% proximal	8	20.5	± 4.5	—	Explant	9	0.15	±0.19	<0.001
1907	6	3.5	±1.3	75% proximal	6	22.7	±10.8	<0.001	Explant	10	0.6	±0.2	<0.001
1886	6	1.7	±0.7	75% proximal	6	5.6	± 2.5	<0.001	Excision	8	1.0	±0.5	<0.001

TABLE 4. *Effect of Antral Explantation or Excision in Heidenhain Dog Pouch Secretion with Subsequent Bowel Resection or Simultaneous Antral Excision and Bowel Resection*

Dog No.	Control Period			Antral Manipulation and Bowel Resection									
					Following Antral Manipulation				Following Bowel Resection				
	No. Determ.	Mean Free Acid (mEq./24 hr.)	S. D.	Antral Manipulation	No. Determ.	Mean Free Acid (mEq./24 hr.)	S. D.	p-Value	% Bowel Resection	No. Determ.	Mean Free Acid (mEq./24 hr.)	S. D.	p-Value
1888	10	36.7	± 8	Explant	17	3.3	±1.9	<0.001	Died	—	—	—	—
1937	11	40.7	±23.5	Explant	17	13	±7.8	<0.001	75% proximal	13	19.8	±10.7	n.s.
1923	7	39.2	± 5.2	Excision	10	2.7	±2.4	<0.001	75% distal	12	6.3	± 4.1	n.s.
1871	11	12.6	± 5.4	Simultaneous Antral excision and bowel resection 75% proximal	19	10.1	±5.4	n.s.	—	—	—	—	—

bowel resection.[12, 13, 25, 34, 43] It has been described in patients and is consistently seen in Heidenhain dogs. This must be due to some mechanism involving increased stimulation or decreased inhibition of gastric acid secretion. Our observations on antrectomy in bowel resected animals and on Thiry-Vella loops are similar to those of Landor and Baker.[25]

Consideration of Secretagogues. Gastrin is released with antral distention. It was to evaluate the possibility that prolonged gastric emptying and consequent antral distention with increased gastrin release followed Heidenhain pouch construction or bowel resection that radiologic emptying times were measured. These studies showed no gastric stasis, making excessive antral effect due to delayed emptying unlikely. Increased corticosteroid effects have been suggested as a cause for increased secretion by Gray *et al.*[16] This has been disputed by other observers [7, 42] and is ruled out in our experiments by measurements of urinary corticosteroids, which were not increased.[12, 13] Howe and others implicated infection as a cause for increased pouch acid secretion, a factor which was not noted in our animals.[21] Diversion of pancreatic secretions away from the duodenum or obstruction of the pancreatic ducts [15, 30] are two circumstances which are known to cause increased acid secretion but do not seem to be pertinent here. Shortening of the small bowel by extensive resection, however, could be thought to permit rapid passage of duodenal content into the colon and, in a sense, represent diversion. Similar effects after bile diversion [30] or liver injury [37] have been noted but do not explain our findings. Liver histology has been reported as normal after massive bowel resection in hypersecreting Heidenhain dogs [25, 34] and results of liver function studies made in our experiment remained normal.[12, 13] Sircus [39] and Landor, Baker and Hite [26] showed that bowel distention



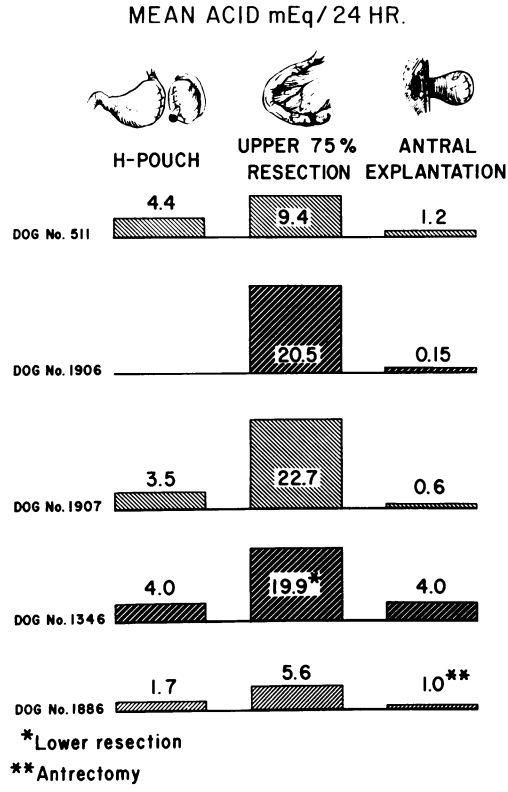


FIG. 6. Mapped antral explantation or excision is followed by fall to preresection or lower levels of Heidenhain pouch secretion in 75% small bowel resected dogs.

FIG. 7. Mapped antral explantation or excision before or at the same time as 75% small bowel resection abolishes the increased secretion otherwise observed in Heidenhain pouch dogs.

TABLE 5. *Fasting Basal State Secretion of Heidenhain and Pavlov Pouch Dogs without Bowel Resection and of Others after Bowel Resection (Made by Irrigation of Pouches to Recover 15 Minute Secretion)*

Bowel Resection—Basal State						
	Control Period				Following Bowel Resection	
Dog No.	No. Determ.	Mean Free Acid H or P Pouch (mEq./15 min.)	Type of Pouch	% Bowel Resected	No. Determ.	Mean Free Acid (mEq./15 min.)
506	13	0.0	H	Not resected	—	—
744	8	0.0	H	Not resected	—	—
511	12	0.0	H	Not resected	—	—
743	9	0.0	H	Not resected	—	—
2104	—	—	H	75% proximal	8	0.0
2120	9	0.08	P	Not resected		
2151	4	0.008	P	Not resected		
2154	—	—	P	75% proximal	8	0.007
2143	—	—	P	75% proximal	4	0.003

is followed by an increase in pouch secretion, a finding which Sircus proposed as the explanation of the intestinal phase of gastric secretion. Compensatory dilatation of the small bowel is seen in patients and in animals after bowel resection, and this relationship to increased secretion deserves further study. Since antral explantation or excision was consistently associated with a reduction to low levels in our hypersecreting bowel resected animals, it seems that an antral factor, probably gastrin, is involved as the proximate stimulus to hypersecretion in these Heidenhain pouch dogs. This need not imply any increase of gastrin, and could represent absence of an inhibiting factor.

Consideration of Inhibitors. Enterogastrone has been proposed as an inhibitor of gastric secretion.[10, 19, 22, 24] Its existence has been questioned increasingly through many years of study.[17] It is thought to be elaborated in the upper small bowel. Our lower bowel resections and exclusions showed a greater rise in secretion than upper bowel resections. Histaminase is known to occur throughout the gastrointestinal tract except for the stomach.[5] Loss of its inhibition of histamine at the parietal cell level could play a role in permitting hypersecretion.[18, 38] However, no role for this substance has ever been proved, and antihistamine drugs have no effect on parietal cell acid secretion unless applied directly to the mucosa where they inhibit secretion by local toxicity.[1, 23, 27] Similarly, serotonin does arise in the gut,[8, 9, 33, 35] has the effect of inhibiting gastric secretion and might merit consideration as the inhibitor which has been lost after massive resection.[20] However, Rosenberg's studies showed reduced amounts of 5-hydroxy-indol-acetic acid after bowel resections.

Basal state studies which showed no increase of acid secretion after bowel resection in Heidenhain pouch dogs (no secretion of acid measured) and in Pavlov pouch animals (low secretion rates with or without resection) also fit the hypothesis that an inhibitor has been lost. If a secretagogue had been gained, either or both of these preparations might have been expected to show some basal state secretion rise. Gastric juice itself contains one or more substances which inhibit secretion,[4] and loss of absorption of such factors after massive resections could also represent the mechanism permitting hypersecretion. Menguy *et al.*[29] have showed that an acid inhibitor is derived from the gastric antral mucous while Thompson and associates[41] have studied a possible antral chalone extensively. Our animals stopped hypersecreting with antral explantation or antrectomy. Since antral gastrin was lost at the same time as the inhibitor might have been, it becomes difficult to assess whether an antral factor might be the inhibitor which is not absorbed after bowel resections.

Matthews and others[28] have shown that acid introduced into the gut causes diarrhea. Parker, Soergel and Ellison[32] confirmed this finding. Severe diarrhea is well known in many cases of ulcerogenic pancreatic tumor. The mechanism of diarrhea with abnormal absorption from the gut depending on pH changes has been studied by Goldenberg and Cummins[14] and by Broitman and associates.[3] Two cases described in this report responded favorably to such dissimilar measures for control of acid secretion as vagotomy[12, 13] in one case and gastric irradiation[2] in the other. Whatever may be the alteration in control of acid secretion after massive bowel resection which leads to marked hypersecretion, it is clear that control of this may be essential in the management of patients after such resections.

Summary and Conclusions

Hypersecretion of gastric acid occurs after extensive bowel resection in human

patients and from the pouches of Heidenhain dogs.

In Heidenhain dogs:

1) The amount of hypersecretion increases as the amount of bowel resected increases.
2) Lower small bowel resection is followed by greater increase in secretion than an equal upper bowel resection.
3) Long Thiry-Vella loops (75 per cent of the small bowel length) are associated with acid increase.
4) Massive bowel resection does not alter gastric emptying time as determined by barium meal.
5) Explantation or resection of the mapped gastric antrum abolishes this hypersecretion.
6) Basal levels of pouch secretion during fasting are similar with or without bowel resection in Heidenhain and Pavlov dogs.

Our data suggests the loss of an inhibitor rather than the gain of a secretory stimulus.

Since control of gastric acid hypersecretion is necessary and after massive bowel resection helpful for some patients and permits improved survival of experimental dogs, further knowledge of the incidence of such hypersecretion and the mechanism of this phenomenon is needed.

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Discussion

Dr. Lester R. Dragstedt (Gainesville, Fla.): Pavlov and his pupil, Sokolov, made the initial discovery that the introduction of acid into the duodenum inhibits the secretion of gastric juice. This discovery was confirmed many years ago by Dr. Webster and his associates in Montreal and by Pincus and his associates in Philadelphia.

Since the introduction of acid into the duodenum inhibits the secretion from a vagus denervated Heidenhain pouch the effect must be brought about by some humoral agent. Pancreatic secretin is released from the duodenal mucosa into the blood stream on contact with the acid gastric content from the stomach. It occurred to me that the humoral agent released from the duodenum and which inhibited gastric secretion might well be pancreatic secretin. When, therefore, pancreatic secretin in fairly pure form was made available by the Eli Lilly Company, my associate, Dr. Greenlee, and I decided to determine the possible effect of intravenous pancreatic secretin on gastric secretion. We found that the intravenous injection of pancreatic secretin did indeed inhibit this secretion of gastric juice from the Heidenhain pouch while simultaneously stimulating the secretion of pancreatic juice. The effect of the secretin was more marked on gastric secretion induced by endogenous gastrin than it was on vagus stimulated gastric secretion of that produced by histamine. These findings are, of course, in harmony with those of Dr. Osborne.

Since pancreatic digestion goes on best in an alkaline medium this dual action of pancreatic secretin in inhibiting gastric secretion while stimulating pancreatic secretion is a purposeful one.

According to our present information, pancreatic secretin is obtained chiefly, if not entirely, from the duodenum and upper gastro-intestinal tract. Lesser amounts have been found in the