Progress report
Small bowel resection and gastric acid hypersecretion

Resection of a large segment of small intestine in the dog is associated with an increase in gastric acid secretion. However, the occurrence of gastric acid hypersecretion after small bowel resection in man remains in doubt. The benign postoperative course of patients who have undergone an extensive intestinal resection after having had a previous gastric resection was first observed by Craig and Stewart (1960). Since then, the beneficial effect on survival of measures to control gastric acid secretion after extensive small bowel resection has been well documented.

An acute syndrome consisting of the aspiration of copious quantities of acid from the stomach after small bowel resection has been reported in man. The copious aspirate usually subsides in the first few weeks after surgery. There are few reports of long-term changes in acid secretion after small bowel resection or exclusion. A low pH of the jejunal contents in six patients of Krone, Theodore, Sleisinger, and Jeffries suggests that hypersecretion exists after small bowel resection. However, the work of Shibata, McKenzie, and Long, Salmon and Wright, and Buchwald and Varco has not confirmed the increase in acid secretion in patients undergoing small bowel bypass. In man, therefore, the circumstantial evidence that is available suggests that there is a syndrome of hypersecretion after small bowel resection but the few studies of acid secretion which have been reported have not verified the presence of this syndrome.

Although 50 years have elapsed since gastric acid hypersecretion after extensive small bowel resection was first demonstrated experimentally, knowledge of the mechanisms by which hypersecretion occurs is still fragmentary. The increase in gastric secretion has been found to be proportional to the length of the intestine resected. Controversy exists over which segment of the intestine, when removed, produces the greater increase in gastric acid secretion. A greater increase in gastric acid secretion was found after resection of the upper small intestine compared with the lower small intestine, whereas other authors have demonstrated a greater increase in gastric acid secretion after resection of the lower small intestine.

The acid response to exogenous stimulation of the parietal area either by histamine or gastrin is essentially unaffected by small bowel resection, suggesting that the increase in acid secretion is confined to the acid response from a meal and is not related to a change in parietal cell function. The marked prolongation of the acid response to a meal after intestinal resection provides additional evidence that it is the later part of the meal response which is abnormal. A similar observation has been made by other authors, who reported difficulty in achieving a basal secretory state in dogs which had undergone an extensive intestinal resection.

In dogs with an antrectomy and a vagally denervated gastric pouch, an
increase in acid secretion of the same relative magnitude has been found after small bowel resection as in dogs with an intact gastric antrum. These studies suggest that the gastric antrum is not essential for the production of gastric hypersecretion, and that it is the remaining stimulus to gastric acid secretion, namely the small intestine itself, that is important in the production of the increase in acid secretion.

An increase in gastric acid secretion was observed after a reversal of short segments of the small intestine, whether alone or in combination with small bowel resection, thus suggesting that stasis of food in the antrum or in the intestine is of importance in the production of hypersecretion which follows the reversal of an intestinal loop. Although gastric acid hypersecretion was found to follow intestinal resection or reversal in these experiments it is possible that the hypersecretion could be the result of two different mechanisms.

A recent series of experiments in the dog into the relationship between extensive small bowel resection and gastric hypersecretion confirmed that there was a prolongation of the acid response to a meal after intestinal resection. Further, an abnormal stimulatory mechanism occurred when food passed into the remaining segment of the small intestine and stimulation from the antrum and vagus was essentially unchanged after intestinal resection. In another series of experiments, using dogs with a duodenal fistula, macroscopic faecal contamination of the duodenal contents was found in all dogs which were demonstrating gastric acid hypersecretion after small bowel resection. In addition, there was a delay in transit of food through the remaining segment of the small bowel. These experiments also cast doubt about the importance of loss of intestinal inhibition in producing hypersecretion. In a parallel series of experiments, the magnitude of the intestinal phase of gastric acid stimulation was re-appraised and found to be of greater magnitude than previously recognized, and after resection of the small intestine, stimulation from the remaining small bowel was even greater.

It is interesting to speculate how such an increase in stimulation after an extensive small bowel resection might occur when food is present in the remaining segment of the small intestine. Stasis of food in the upper small intestine could result in the increased breakdown of protein in the upper small bowel. Peptide fragments and amino acids in contact with the mucosa of the small bowel are known to produce secretion of acid from the stomach in the same way that these substances produce stimulation of acid when in contact with the antral mucosa. Gastrin-like substances have been isolated from the mucosa of the upper small intestine in both man and dog. The amount of intestinal gastrin is greatest in the duodenum and decreases down the length of the small intestine. Increased breakdown of food substances in the duodenum and proximal small bowel after intestinal resection as a result of intestinal stasis could result in a greater stimulation of acid through the greater release of an intestinal humoral stimulant.

Abnormal contamination of the upper small bowel after extensive intestinal resection has been confirmed in both man and the dog. In our experience, the gastric acid hypersecretion was periodic in nature and corresponded to changes in the bacterial flora of the upper small intestine. Normally, the upper small bowel contains relatively few bacteria, consisting of predominantly Gram-positive aerobes of the oral type with a total concentration of
less than $10^8$ organisms per ml, whereas the terminal ileum has a substantially
greater number of bacteria, between $10^6$ and $10^8$ organisms per ml, comprising
a mixture of Gram-positive and Gram-negative organisms bearing a greater
resemblance to caecal flora than does the flora of the jejunum$^{41-50}$.

The presence of bacteria in the intestine can affect the intestinal wall. The
intestinal wall of a germ-free or antibiotic-treated animal is thinner and
lighter in weight than that of appropriate controls$^{51,52,53}$. When the enteric
flora is reduced or eliminated, marked reduction is noted in the numbers of
leucocytes, plasma cells, lymphocytes, histiocytes, and macrophages present
in the lamina propria$^{51,52,54,55,56}$. Increased numbers of lymphocytes and
reticulocytes appear in the lamina propria when the germ-free animal is
contaminated with \textit{Cl welchii}$^{51,54}$ or \textit{Strep faecalis}$^{51}$. These changes in the
lamina propria have been called 'physiological inflammation'$^{54}$. Sprinz$^{54}$
has also associated changes in the intestinal villous architecture with the
presence of enteric bacteria. The villi of germ-free animals are slender and
regular in comparison with the thicker, shorter, and irregular processes of
conventionally reared animals. Release of a stimulatory substance,
possibly gastrin, from the mucosa of the duodenum and upper jejunum by
the action of colonic bacteria (or their products), which are not normally
present in the upper small intestine, is another possible mode of stimula-
tion from the upper small bowel.

Release of a humoral stimulant from the intestinal mucosa might be caused
also by the presence of 'toxic' products from microbial action on dietary
foodstuffs. Such products include hydroxystearic acids which are similar to
ricinoleic acid, the main constituent of castor oil$^{57-61}$, acetic, lactic, and
formic acids$^{62}$. Normally, bacterial degradation of food substances occurs
in the lower small bowel and colon, where bacterial populations are greatest;
intestinal stasis and bacterial overgrowth in the duodenum and upper
jejunum after small bowel resection might produce these 'toxic' substances
at a more proximal level in the intestine.

The action of bacteria on the bile acids in the upper jejunum and duodenum
suggests yet another possible mode of release of a humoral stimulant from
the upper small bowel mucosa. Recent studies have shown that a wide range
of intestinal bacteria, particularly Gram-negative anaerobic organisms, can
decomjugate and transform bile acids by dehydroxylation, oxidation, and
reduction$^{62-63}$. Other studies have shown that intestinal bacteria increase
turnover and the metabolic rate of cholic acid in germ-free animals$^{64,65}$. 
Free bile acids are abnormal in the upper small intestine$^{66-70}$ although they
are present in the terminal ileum, from where both conjugated and uncon-
jugated bile acids are normally absorbed into the portal circulation$^{71-100,59,81,101,102,90}$. Increased concentrations of deconjugated or free
bile acids have been found in the upper gastrointestinal tract, in association
with abnormal bacterial flora, in patients after an extensive small bowel
resection$^{62}$.

Free bile acids and their derivatives have a high degree of lytic activity on
the walls of certain bacteria$^{103}$. These substances also produce inflammation
when injected intramuscularly; lithocholic acid and its derivatives are
particularly potent$^{104}$. A similar toxic effect was observed when bile
acid derivatives were placed in contact with the duodenal and jejunal mucosa
in sufficient concentration$^{87,70}$. However, this effect is not demonstrable by
light microscopy if physiological concentrations of bile acid derivatives are
used. More recently, changes have been demonstrated by electron microscopy in the mucosa of a blind small bowel loop in rats. These changes are similar to those caused by feeding small amounts of deconjugated bile salts to normal rats.

Inflammation of the lamina propria or contact of the mucosa with potentially toxic bile acid derivatives could release a stimulatory substance which acts on the parietal cell area in a way similar to that in which normal conjugated bile acids can release gastrin from the antrum. Support for the belief that bile acids normally play an intermediary role in stimulation of acid secretion arising from food in the small bowel is provided by the experiments of Nahrwold and Grossman, which showed a decrease in the acid response to a meal after temporarily diverting the bile from the intestine. They postulated that the presence of bile salts in the intestine facilitates the intestinal phase of gastric secretion. Their findings are at variance with those of Menguy, Menguy and Mings, and Landor, Behringer, and Wild, who found an increase in acid secretion after chronic biliary diversion.

Unlike the experiments of Nahrwold and Grossman, Menguy found that restoration of the normal bile flow was not associated with a return of gastric secretion to normal. Also, in dogs with chronic biliary diversion, liver function studies were abnormal, suggesting that liver dysfunction might account for some of the changes in acid secretion. An alternative explanation for the different result of Menguy might be that bacterial overgrowth occurs in the intestine as the result of interference with the normal controlling influence of bile in the intestine, which, in turn, might produce increased acid stimulation.

Abnormal stimulation from food in the upper small intestine could account for the prolongation of the acid response to a meal and difficulty in achieving a basal secretory state after intestinal resection, and also for the prolonged response to a meal after truncal vagotomy. The wide fluctuations in the 24-hour acid secretions after intestinal resection might be explained also by changes in the bacterial flora in the upper small bowel.

Many small bowel disorders which are associated with steatorrhoea have been found to have associated gastric hypersecretion. For example, steatorrhoea and acid hypersecretion have been observed after small bowel resection, reversed intestinal loops, blind loops of the Mann and Williamson type, and after truncal or extragastric vagotomy.

Bacterial overgrowth in the upper small intestine is found frequently in conditions associated with steatorrhoea. Similarly, bacterial overgrowth has been found in conditions associated with gastric acid hypersecretion, small bowel resection, and truncal or extragastric vagotomy.

Steatorrhoea due to bacterial overgrowth in the small intestine is generally attributed to the effect of deconjugated or degraded bile salts. However, altered bile salt metabolism alone does not entirely explain the steatorrhoea in patients with small bowel bacterial overgrowth. Complete biliary obstruction or diversion often produces only modest faecal fat losses, whereas steatorrhoea in the blind loop syndrome may be severe. These observations suggest that bacteria in the upper intestine exert harmful effects other than by disturbance of bile salt metabolism. Coincidental gastric hypersecretion in the bacterial overgrowth syndrome might account for the severe steatorrhoea observed occasionally in these conditions. A
relatively acid pH in the jejunum impairs micelle formation and lipolysis and also reduces the solubility of fatty acids in bile micelles\textsuperscript{124,22}. In addition, carbohydrate metabolism is inefficient in the presence of an acid pH\textsuperscript{125}.

Figure 1 is a diagrammatic representation of the possible interrelationships between some small bowel disorders, gastric hypersecretion, and steatorrhoea. Abnormal release of an intestinal stimulatory substance as the result of bacterial overgrowth could account not only for most of the observations made in our experiments\textsuperscript{28-32} but also for many hitherto unexplained findings.

The increased acid response to a meal after reversal of a small bowel loop was attributed to antral stasis and greater release of antral gastrin\textsuperscript{26,27}. An alternative hypothesis is that excessive stimulation from food in the upper small bowel is the result of intestinal stasis. It would be interesting to test this hypothesis by seeing if hypersecretion occurred after reversing a small intestinal loop in antrectomized dogs.

The increase in acid secretion after truncal vagotomy or extragastric vagotomy in dogs with Heidenhain pouches cannot be explained satisfactorily on the basis of the knowledge that is currently available\textsuperscript{126-130}. This led Emas and Grossman\textsuperscript{131}, Stening and Grossman\textsuperscript{132}, Spencer and Grossman\textsuperscript{133}, and Korman, Hansky, and Scott\textsuperscript{134} to postulate that the vagus normally exerts a controlling influence on a stimulatory substance, outside the stomach, which is released in greater quantities after section of the extragastric branches of the vagi. The increased acid secretion after extragastric vagotomy could also be explained on the basis of an abnormal

\textsuperscript{*}Known to be associated with acid hypersecretion

\textsuperscript{****}Documented

\textsuperscript{*****}Hypothetical

Fig 1  Hypothesis showing the possible interrelationship of various small bowel disorders, gastric acid hypersecretion, and steatorrhoea.
excitatory process in the upper intestine, occurring as a result of a motility disturbance created by vagotomy.

The acid hypersecretion and the peptic ulcer diathesis which occurs in dogs which have the duodenal loop transplanted into the terminal ileum (the Mann-Williamson preparation) have not been explained satisfactorily. Loss of the neutralizing effect of alkaline duodenal secretions from the region of the gastro-jejunostomy does not seem important because McCann, Ivy, and Fauley found that ulceration still occurred when the duodenal secretions were returned to the stomach. Furthermore, a different explanation is required to account for the actual increase in gastric acid secretion which occurs in this syndrome.

The proximity of the blind duodenal loop to the ileo-caecal valve was pointed out by Mann and Williamson in their original paper. Transplantation of the duodenal loop to the middle and upper small intestine was found to be associated with lesser degrees of ulcer formation, and, so far, this difference has not been adequately explained.

The gastric antrum is not necessary for the occurrence of hypersecretion in the Mann-Williamson model, implying that the abnormal mechanism does not necessarily involve antral gastrin.

Interference with the fat inhibitory mechanism as a cause of the hypersecretion found in the Mann-Williamson preparation was proposed by Menguy and Mings. They provided evidence that gastric hypersecretion could result from diversion of bile or pancreatic juice alone to the lower small bowel, but they could not explain the acid changes without involving the gastric antrum. This led Menguy to examine the effect of pancreatic and biliary diversion on liver function. Although abnormalities in liver function were found, their relevance to acid hypersecretion was unknown.

Evidence that there is loss of duodenal inhibition elicited by acid following transplantation of the duodenum to the terminal ileum was produced by the study of Manzano, de la Rosa, Woodward, and Dragstedt. However, like Menguy and Mings, they concluded that the importance of this mechanism is in doubt because it is thought to act through inhibition of antral gastrin and the presence of the antrum has been found to be unnecessary. Manzano, de la Rosa, Woodward, and Dragstedt therefore, postulated that there was a true increase in acid secretion as well as interference with inhibition to account for the hypersecretion.

The profound increase in acid secretion in the Mann-Williamson preparation can be explained readily by the current hypothesis. Colonization of the blind duodenal loop occurs because of the proximity to the colon. The presence of colonic bacteria alone or the effect of these bacteria on food substances or bile salts in the upper small bowel could release a stimulatory hormone from the mucosa of the duodenum.

Intestinal stasis and overgrowth of bacteria, leading to increased stimulation when food is present in the upper small bowel, might provide a common explanation for the increased gastric acid secretion which follows small bowel resection or exclusion, reversal of intestinal loops, extragastric vagotomy, or the construction of a blind loop, such as in the Mann-Williamson preparation.

It will be interesting to await the results of gastrin estimations in patients with small bowel resection, exclusion, reversal, or in patients with a blind intestinal loop, to see if the proposed extragastric or intestinal humoral
Small bowel resection and gastric acid hypersecretion

stimulant is in fact gastrin as would appear to be the case in patients who have undergone truncal vagotomy.

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References


Small bowel resection and gastric acid hypersecretion


