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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

jejunum and lower small intestine. I am consequently puzzled by the finding of Dr. Osborne and his associates that removal of the ileum produced a greater increase in gastric secretion than occurred from excision of the jejunum. If this increase is due to removal of an inhibitory agent than it would appear that pancreatic secretin is not responsible and that we may have to look for some other substance like, for instance, enterogastrone, to account for the effect. The physiological status of enterogastrone is still in some doubt.

DR. ANDRE MONSAINGEON (Paris, France): Knowing Dr. Osborne's interest in the field of pancreatic activity in connection with gastric secretions, I would like to ask him what he thinks of the pancreatic status of his dogs. We have been interested in that particular aspect in dogs who had a total diversion of bile from gallbladder to urine bladder, with ligature of the choleocus. They develop not only a metabolic acidosis, but: 1) a hypersecretion of previous-made Heidenhain pouches, in volume as well as in acid output; 2) an increased number of the Langherans islets—with no change in their relative dimensions; 3) an increased number of *not* B cells; and 4) an increased number of Gorder cells of the gastric fundus.

There are also unexpected changes of I. V. glucose tolerance tests. So a hyperactivity of the islets of the pancreas connected with gastric hypersecretion seems possible not only in tumor of the pancreas but in some metabolic conditions.

DR. WALTER F. BALLINGER (Baltimore): Considerable credit is assured Dr. Osborne and Dr. Frederick for their persistence in attempting to elucidate the exact mechanism for the increased secretion of acid by the stomach after resection of small intestine. There is a complex world of reciprocal neuro-humoral relationships between the gut and the stomach, and Dr. Osborne has mentioned some of these today.

Our findings in similar experiments indicate to us several points of agreement and of variance with those of Dr. Osborne and his associates, points which help us toward a working hypothesis to explain the hypersecretory mechanism. First—and in agreement—there is no question that the stomach does indeed secrete more acid in a greater volume after intestinal resection. Second—and at variance—and possibly in agreement with Dr. Dragstedt's very lucid hypothesis—this hypersecretion is *pronounced* after a proximal-third resection, as confirmed by others; *variable to absent* after a mid-third resection; and *absent* in all experiments after a distal third resection.

The dogs were followed in groups of three for a month following the usual 3-week control period after resection. The same response occurs with similar segments excluded from the alimentary tract by Thiry-Vella loops.

That the response is due either to an increased stimulation or to a decreased inhibition of gastric acid secretion has been emphasized today.

The proximal portion of the gut contains large stores of serotonin, and as Rosenberg has pointed out, there are decreased amounts of breakdown products of serotonin following intestinal resection.

Thus it would seem plausible to us that loss of the inhibitory activity of serotonin could account in part for gastic hypersecretion reported by numerous observers under these conditions. Furthermore, the interrelationships and interdependences of the actions of serotonin, gastrin, histamine, and vagal activity could well explain the interesting finding of Dr. Osborne and his associates, when they recorded, as did Landor, the abolition of the hypersecretory response by removal of the antrum.

DR. DAN W. ELLIOTT (Pittsburgh): Dr. Tom Craig was a Senior Resident in General Surgery in 1960 at the Ohio State University when he published in *Surgery* a description of the Ohio State patient that Dr. Osborne mentioned. Dr. Paul Frederick, the second author of today's paper, was a First-Year Resident there at that time. Dr. Craig pointed out to us the earlier observations of Jackson and Lindner that duodenal and jejunal aspirates were strongly acid after massive small bowel resection, and the stools often had a pH as low as 2 to 3. He suggested to us the possibility that hypersecretion of gastric acid might be present. We were unaware of Dr. Paul Frederick's continuing interest in this area after he moved to Boston when last year we published some experimental studies indicating that extensive small bowel resection would produce hypersecretion of gastric acid.

We actually resected the upper half of the small bowel from a point just below the pancreatic duct, so that the portion of the duodenum releasing secretin was still left intact proximal to this point. After this small bowel was excised, we found a modest degree of acid hypersecretion averaging 223% of base line in six animals with Heidenhain pouches. However, if the same segment of bowel were not excised but set to one side as an inactive Thiry fistula in this manner, we could produce the effect of excision on digestion, but preserve any endocrine activity of this segment. Under these circumstances acid hypersection occurred which was comparable to that after excision, and perhaps a little bit greater. Then, if the gastric antrum is removed this hypersecretion goes away, which is in substantial agreement with what Dr. Osborne showed you. This suggests that removal of this large portion of intestine from the digestive stream removes an inhibitor of antral gastrin.

If the antrectomy is done first, and then the inactive fistula made later, there is a definite rise in acid seen following formation of the fistula, which seems very slight and small, but in relation to the base line after antrectomy, this hypersecretion did occur quite regularly in all six ani-

mals. Further, after excision of the inactive fistula this small rise in acid went away. This suggested to us the possibility that this segment of the upper small bowel might also be capable of stimulating acid directly.

Extracts of mucosa from this region of the small bowel will yield small quantities of gastrin. This fact seems also to confirm the possibility that acid stimulation could occur through endocrine mechanisms in this area of the mucosa. This is theoretically important, since if the upper small bowel has the potential of direct acid stimulation, then disease in this area could account for hypersecretion of acid in man. In general, our results are in agreement with those presented this morning by Dr. Osborne.

DR. WALTER H. GERWIG, JR. (Clarksburg, W. Va.): During the past year, Dr. Alfred Ghaphery and I reported and subsequently published our findings on dogs that were prepared in a manner similar to but not quite identical to those that have just been described.

Our studies encompassed three phases: First, the Thiry-Vella defunctionalized loops were prepared, which involved all of the small bowel and half of the large intestine. Next, we added a vagus resection to animals prepared as in the first phase. The third phase involved the creation of the extensive Thiry-Vella loop, vagotomy, and then, by taking a segment of the greater curvature of the stomach, we prepared a conduit which we interposed as an antiperistaltic segment between the duodenum and the transverse colon.

Rapid death resulted in all Phase 1 animals. The abolition of parasympathetic innervation in the Phase 2 animals resulted in a definite and appreciable increase in survival time. The addition of the antiperistaltic gastric tube in the Phase 3 group further prolonged longevity.

Obviously, the excessive gastric secretions play a major role that is extremely detrimental when the animal is deprived of its small bowel. By the same token, I can not help but think that some decrease in motility might also play at least a minor part.

I would like to ask the authors if they think that the defunctionalized Thiry-Vella loop, which might be the site of the inhibitor that has been referred to, ceases to exert any influence in their preparations, in view of the fact that blood flow to and from this area remains intact.

DR. LLOYD M. NYHUS (Seattle): Dr. Semb of our group confirmed the work of various authors concerning an inhibitory substance in gastric juice. Dr. Rudick found an inhibitor substance in thoracic duct lymph; recently he has found in mucous secretions from jejunum and ileum a similar substance which inhibits acid secretion after histamine and gastrin stimulation. He has also found this substance in colon mucous secretion.

Wyllie, of our laboratory, has found that with the colon inhibitory substance, there is a definite pyrexia. We know that less than 1° C. of rise in fever will inhibit gastric secretion. This factor of pyrexia seems to be less of a factor in inhibition by jejunal and ileal juice; thus, this material may contain a real inhibitor substance. Massive intestinal resections may thus remove a large amount of this inhibitory material.

DR. MELVIN P. OSBORNE (Closing): I wish to say it has been a thrill to be able to present this work to Dr. Dragstedt, the world authority of this century in this field. And, Dr. Dragstedt, secretin, I guess, might come from lower down in the intestine; if it did, it would permit us to understand our preparation.

We avoided getting very near the duodenum, and I think had a simpler experimental preparation than those of Dr. Elliott, although it looks as though some of the phenomena may be the same.

Mr. Monsaingneon, I appreciate your interest in this. We have not studied the pancreas in these animals, and should do so by biopsy and function studies. Pancreatic islet function may be quite relevant.

Dr. Ballinger, regarding the question of the effect of lower as compared with upper resections, I would not say that we are sure that lower bowel resection is associated with markedly greater effect than resection of the upper bowel. In fact, in one of our comparisons a 25% lower resection did not produce more hypersecretion than an upper 25% resection. We have sufficiently detailed data in the manuscript to permit study of these comparisons. We will restudy this, perhaps making Thiry-Vella loops sequentially involving upper and then lower bowel in the same animals, replacing the loops into intestinal continuity and observing sequential changes in the same animal. Perhaps there will not be so much variance seen then.

Dr. Gerwig, I do no know whether a Thiry-Vella loop which is just in place with its vascular supply intact functions or not. Surely it does not function as much as it would if it were actively dealing with the fecal stream. We plan to put a variety of substances in these loops and see what happens to secretion.

Dr. Nyhus, thank you for a good suggestion. If the inhibitor of which Dr. Menguy speaks, coming from the antrum, also comes from similar mucous cells lower down in the intestinal tract, we might have a very simple explanation for this phenomenon.

Speaking of this, I was talking with Dr. Menguy—who unfortunately had to leave yesterday—in the hall. There was a crowd of people around; he mentioned gastric mucus and everyone looked around and said: More of this gastric secretion talk? The crowd then dispersed very rapidly. (Laughter) I am glad this was not the case this morning.