The pancreas and gastric secretion: failure of pancreatectomy to prevent inhibition of gastric secretion by secretin

JOSEPH A. KENNEDY and GEORGE A. HALLENBECK

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota

EDITORIAL SYNOPSIS A second commercially prepared secretin has been found to inhibit the acid secreted by Heidenhain pouches in dogs in response to a meal but not to histamine. This inhibition is not affected by pancreatectomy.

Greenlee, Longhi, Guerrero, Nelsen, El-Bedri, and Dragstedt in 1957 reported that a commercially prepared secretin (Eli Lilly and Co.) given intravenously decisively inhibited the gastric secretory response of Heidenhain pouches in dogs to a meal and to perfusion of antral pouches with liver extract. Secretin did not inhibit secretion of hydrochloric acid by Heidenhain pouches in response to histamine or inhibit the responses of innervated total gastric pouches or Pavlov pouches to hypoglycaemia induced by insulin. Goelzer (1960), reporting that pancreatectomy in dogs with Heidenhain pouches was followed by an increased gastric secretory response to a meal, mentioned briefly that secretin (Lilly) caused gastric secretion to diminish in two dogs after removal of the pancreas.

The present study was made (1) to learn the effect of a different commercially prepared secretin on gastric secretion and (2) to answer more definitively the question, Is the presence of the pancreas necessary for inhibition of gastric secretion by secretin? than is the case when the parietal cells are secreting maximally to histamine (Code, Blackburn, Livermore, and Ratke, 1949). In other experiments the stimulus for gastric secretion was a meal that consisted of 220 g. of lightly cooked ground beef.

The volume of samples of gastric juice was measured and free acidity was determined by titration with Töpfer's reagent (dimethylaminobenzene) as an indicator. The output of hydrochloric acid in milliequivalents was calculated by multiplying the volume in litres by the concentration of hydrochloric acid in milliequivalents per litre.

Experiments with and without secretin were alternated. During some control experiments, physiological saline solution was given intravenously in place of secretin.

Secretin (Vitrum A.B., Stockholm, Sweden) was supplied in ampoules of 75 clinical units and was described by the manufacturer as assayed in anaesthetized cats against a standard preparation of secretin as described by Mutt and Söderberg (1960). Fifteen units of the material given intravenously to a dog prepared for collection of pancreatic juice by the Thomas cannula technique stimulated a copious flow of pancreatic juice. To test its effect on the gastric secretory response to histamine, secretin was given intravenously in doses of 16 units, either as a single injection or over a period of 15 minutes. To test its effect on the secretory response to a meal, 60 units of secretin were given continuously intravenously for the first 60 minutes after feeding.

During one test in each of the four dogs concentrations of glucose in the blood were measured by the Nelson-Somogyi method before, during, and after administration of secretin, to learn whether glucagon might be liberated.

After these data had been collected, the four dogs were subjected to total pancreatectomy. They were maintained in good condition by feeding a commercially prepared dog food (Hills) plus 50 g. of fresh-frozen hog pancreas twice daily and by giving regular insulin in doses that varied between 6 and 8 units twice daily. Beginning three weeks after operation, tests to determine the effect of secretin on gastric secretion were repeated.

METHODS AND MATERIALS

Four dogs were prepared with Heidenhain (vagally denervated) gastric pouches.

In one series of tests, gastric secretion was stimulated by a solution of histamine hydrochloride given continuously intravenously by a motor-driven syringe at a rate found to cause the pouches to secrete hydrochloric acid at 25 to 30% of their maximal rates, rates at which inhibitors of secretion can be demonstrated more easily.
The pancreas and gastric secretion

RESULTS

EFFECT OF SECRETIN ON GASTRIC SECRETORY RESPONSE TO HISTAMINE Secretin, given intravenously in a single injection or over a period of 15 minutes in doses of 16 units, failed to influence the rate of secretion of hydrochloric acid from two dogs with Heidenhain pouches secreting at 24 and 28% of their maximal capacity to respond to histamine (Fig. 1). This confirms the similar findings of Greenlee and his associates (1957).

EFFECT OF SECRETIN ON GASTRIC SECRETORY RESPONSE TO A MEAL OF MEAT Preliminary experiments indicated that in doses of 16 to 32 units given as single injections intravenously secretin modified the gastric secretory response to a meal of meat transiently. In a dose of 60 units given continuously intravenously for the first hour after feeding secretion was decisively inhibited. In the table are presented mean values from four to seven tests on each dog with and without secretin; Fig. 2 graphically presents mean data from one dog. Before pancreatectomy, inhibition of secretion of acid ranged from 79 to 97% during the time secretin was being given. Subsequently, the rate of secretion of acid tended to increase, compared with that in control tests, so that in three of the four dogs acid secreted during the first five hours after feeding was virtually the same whether secretin had been given during the first hour or not. No significant change in concentration of blood glucose occurred during or after administration of secretin after feeding meat in any of the four dogs.

After pancreatectomy, secretin still inhibited gastric secretion of hydrochloric acid after the meal: indeed, the percentage inhibition during the first hour tended to be a little greater and the recovery of secretion of acid during the next four hours a little less than that seen before pancreatectomy.

The animal described in Fig. 2 secreted more than twice as much acid from its Heidenhain pouch in response to the standard meal after pancreatectomy than before the operation. This was true of three of the four dogs and is in harmony with the data of Barcena, Bravo, Baugh, Mountain, and Dragstedt (1957), Elliott, Taft, Passaro, and Zollinger (1961), Goelzer (1960), and Steinberg (1921).

COMMENT

When duodenal contents are made acid, secretion of hydrochloric acid by the parietal cells is inhibited in a variety of experimental situations. The fact that acid in the duodenum can inhibit secretion from vagally

TABLE

<table>
<thead>
<tr>
<th>Dog</th>
<th>Before Pancreatectomy</th>
<th>After Pancreatectomy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HCl (mEq.) First Hour</td>
<td>% Inhibition First</td>
</tr>
<tr>
<td></td>
<td>after Feeding</td>
<td>Five Hours after</td>
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<tr>
<td></td>
<td></td>
<td>Food</td>
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<tr>
<td></td>
<td>Without Secretin</td>
<td>With Secretin</td>
</tr>
<tr>
<td>U-439</td>
<td>0.64</td>
<td>0.02</td>
</tr>
<tr>
<td>T-675</td>
<td>0.63</td>
<td>0.13</td>
</tr>
<tr>
<td>U-464</td>
<td>0.12</td>
<td>0.02</td>
</tr>
<tr>
<td>U-438</td>
<td>0.11</td>
<td>0.02</td>
</tr>
</tbody>
</table>

1Sixty units of secretin given continuously by vein during the first 60 minutes after feeding.
denervated (Heidenhain) pouches (Andersson, 1960) makes it probable that at least part of the mechanism is humoral, assuming that inhibition mediated by sympathetic nerves to the pouch is unlikely.

Acid in the duodenum is also the most effective known stimulus for release of the hormone, secretin, from duodenal mucosa. On learning that secretin (Lilly) could inhibit gastric secretion as well as stimulate pancreatic secretion, Greenlee et al. (1957) suggested that secretin might represent the means by which acid food in the duodenum inhibits gastric secretion. The validity of this thesis will be tested to a certain degree as information accumulates to permit comparison of the characteristics of inhibition by acid in the duodenum and by commercial secretin.

Yet, as Greenlee et al. clearly recognized, commercial secretin, though highly purified, is still an extract of duodenal mucosa that could contain active material other than that which stimulates the pancreas to secrete. Knowledge whether the agent that inhibits gastric secretion is the same as that which stimulates pancreatic secretion would require availability of secretin known to be pure or, conceivably, separation of present extracts into fractions having different activities. The present study shows that secretin (Lilly) and secretin (Vitrum A.B.) share the ability to inhibit gastric secretion.

Since the pancreas is the established target organ for secretin, it was logical to ask whether gastric secretory inhibition by commercial secretin was mediated through the pancreas. Measurement of blood glucose failed to reveal hypergylcaemia and eliminated the possibility that secretin might cause the pancreas to liberate glucagon, a known inhibitor of gastric secretin (Clarke, Neill, and Welbourn, 1960). Tests after removal of the pancreas showed conclusively that inhibition of gastric secretion by commercial secretin persisted in the absence of the gland.

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The pancreas and gastric secretion: failure of pancreatectomy to prevent inhibition of gastric secretion by secretin
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doi: 10.1136/gut.4.1.58

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