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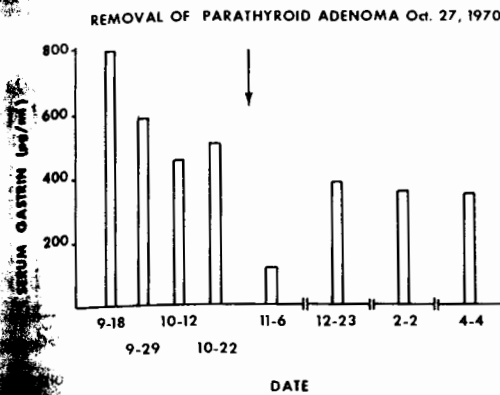


Fig. 1. Serum gastrin measurements from September 1970 through April 1971.

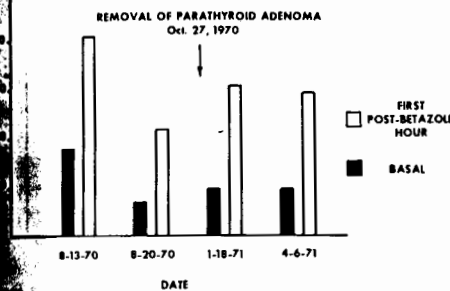


Fig. 2. Basal and betazole-stimulated gastric acid secretion.

ed from 9.5 to 10.2 mg per 100 ml. Serum phosphorus increased to 4.2 mg per 100 ml. Because of hypergastrinemia, hypersecretion of gastric acid, and low pH in the distal duodenum, a clinical diagnosis of ZE syndrome was made.

Special Studies

Gastric secretion. After an overnight fast, gastric juice was collected with a duodenal pump through either a fluoroscopically placed nasogastric or double lumen gastroduodenal tube. During the procedure, when a double lumen gastroduodenal tube was in place, duodenal juice was simultaneously collected. Gastric juice volume was measured and acid concentration determined by titration to pH 7.0 with an automatic titrator. Pepsin concentration was determined by the method of Grossman and Marks.³ Gastric secretory studies were performed with betazole (1.5 mg per kg subcutaneously) stimulation (fig. 2). Mean

prebetazole acid concentration was 108 mEq per liter (range 98 to 117 mEq per liter). After betazole, mean peak acid concentration was 147 mEq per liter (range 134 to 154 mEq per liter): basal acid concentration ÷ peak acid concentration = 0.73. Mean prebetazole gastric acid output was 22 mEq per hr (range 15 to 35 mEq per hr). During the 1st post-betazole hr gastric acid secretion increased to 44 to 82 mEq per hr (fig. 2). After parathyroidectomy, there was no apparent change in acid secretion. Feeding a standard meal of two eggs, toast, and orange juice failed to increase serum gastrin in our patient. In normal subjects this standard meal produced at least a 2-fold increase in serum gastrin.⁴ This standard meal failed to increase serum gastrin in 4 other subjects with ZE syndrome (*unpublished observations*). Four secretin infusion tests were performed: two before and two after removal of the parathyroid adenoma. In addition, two control tests with isotonic saline alone were performed after removal of the parathyroid adenoma.

After at least four 15-min basal collections, 3 U per kg-hr of Gastrointestinal Hormone (GIH) secretin (Karolinska Institutet, Stockholm, Sweden) were added to an isotonic saline infusion, 25 ml per hr.

During each secretin infusion test gastric acid secretion increased significantly ($P < 0.05$) above basal and saline control tests (fig. 3). Concentration of titratable acid did not change significantly above basal during secretin infusion (fig. 4).

The effect of graded doses of secretin (3, 6, and 9 U per kg-hr), given on a single day was studied. Acid secretion increased to a plateau during the 6 U per kg-hr infusion. There was no evidence of inhibition of acid secretion during the 9 U per kg-hr infusion (fig. 5).

Mean pepsin secretion increased from approximately 11 kilounits per 15 min basally to a mean peak of 47 kilounits per 15 min during secretin infusion.

Calcium gluconate (Ca^{++} , 5 mg per kg-hr) produced an increase in gastric

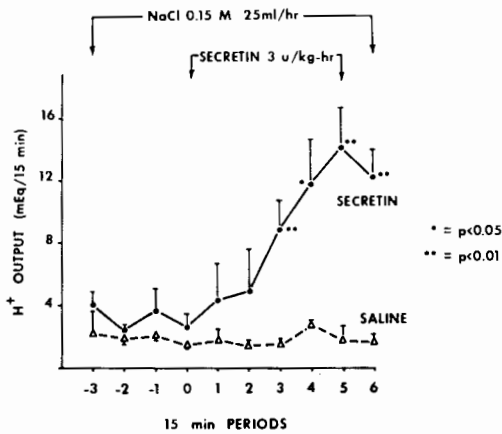


FIG. 3. Mean gastric acid output during secretin infusion and during isotonic saline alone. Each point represents the mean; vertical bar, 1 SE.

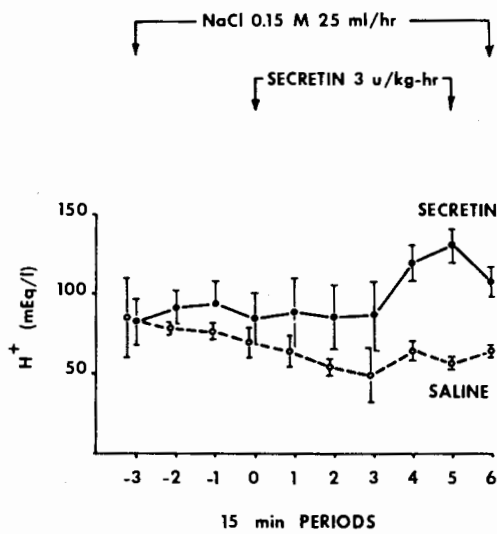


FIG. 4. Mean (\pm SE) hydrogen ion concentration during secretin infusion tests and during isotonic saline alone.

acid secretion to levels similar to those seen with betazole or secretin (fig. 6).

Since glucagon is structurally similar to secretin, the effect of graded doses of glucagon (1, 4, and 16 μ g per kg-hr) was studied. During glucagon infusion gastric acid secretion decreased from a basal of 2.1 mEq per 15 min to 0.1 mEq per 15 min. In addition, during glucagon infusion, pepsin secretion decreased from 11 kilounits per 15 min to a low of 1.5 kilounits per 15 min.

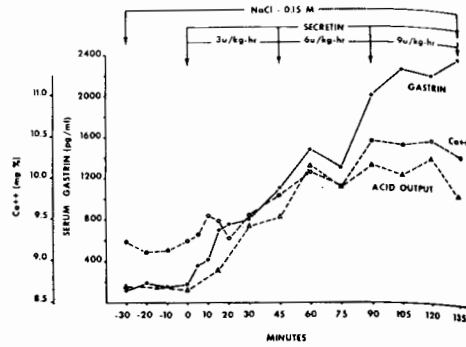


FIG. 5. Serum gastrin and gastric acid output during graded doses of secretin.

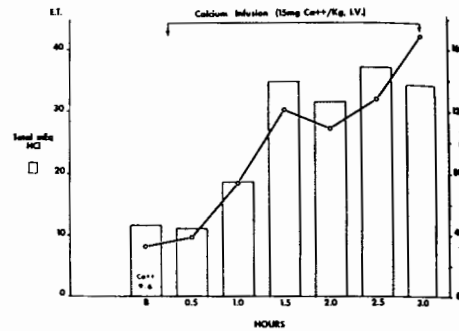


FIG. 6. Serum gastrin (open circles) and gastric acid output during calcium infusion (5 mg per kg-hr).

Pancreatic secretion. During infusion of 3 U per kg-hr of secretin, pancreatic carbonate⁵ output increased from a mean basal of 0.2 mEq per 15 min to a mean peak of 11.6 mEq per 15 min. During the saline control tests, bicarbonate output ranged from 0.1 to 0.4 mEq per 15 min.

During the graded dose glucagon tests there was no significant ($P > 0.05$) change in pancreatic bicarbonate output from the basal which was 0.2 mEq per 15 min.

Serum gastrin. During infusion of 3 U per kg-hr of secretin, mean basal serum gastrin increased significantly ($P < 0.05$) from 333 pg per ml to a mean peak of 850 pg per ml. During infusion of graded doses of secretin serum gastrin increased from 200 to 2300 pg per ml (fig. 5).

During calcium infusion serum gastrin increased from 320 to 1675 pg per ml (fig. 6). During the highest dose of glucagon, 16 μ g per kg-hr, serum gastrin decreased from a mean basal of 283 pg per ml to 163 pg per ml.

The effect of a rapid (30 sec) injection of GIH secretin, 2 U per kg of body weight, was studied in Mr. T, 3 other patients with ZE syndrome, and 8 control subjects. In Mr. T the secretin produced a prompt, brisk rise in serum gastrin (fig. 7). In the 8 control subjects serum gastrin did not change significantly (fig. 7).

Serum calcium. Serum

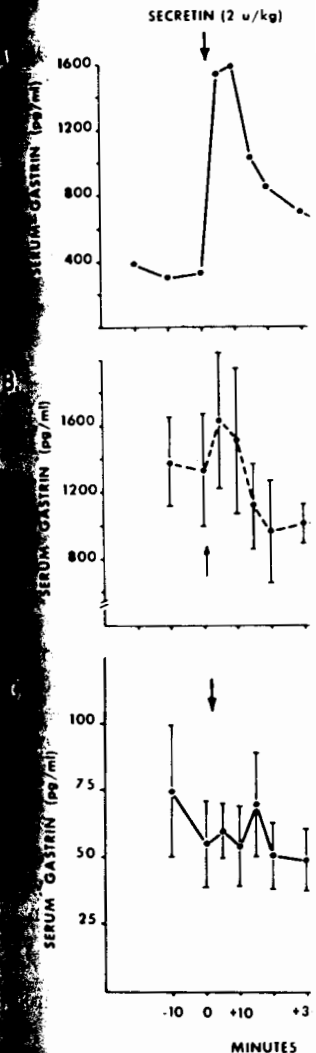


FIG. 7. Serum gastrin response to rapid injection of (2 U per kg of secretin) in (A) 1 patient with ZE syndrome, (B) 3 other unoperated patients, and (C) 8 control subjects.

The effect of a rapid (30 sec) intravenous injection of GIH secretin, 2 U per kg, was studied in Mr. T, 3 other unoperated patients with ZE syndrome, and 8 control subjects. In Mr. T the secretin injection produced a prompt, brisk increase in serum gastrin (fig. 7). In the 3 other ZE subjects serum gastrin decreased (fig. 7). In the 8 control subjects serum gastrin did not change significantly ($P > 0.05$) (fig. 7).

Serum calcium. Serum calcium was

measured by atomic absorption spectrometry. During the test with graded doses of secretin, serum calcium increased significantly ($P < 0.05$) above basal and also above a control test with isotonic saline alone (fig. 8).

During a secretin infusion test ionized calcium, measured with an ion exchange electrode,⁶ increased significantly ($P < 0.001$) above basal (fig. 9). Thirty minutes after discontinuing secretin, ionized calcium had returned to basal level. There was no significant ($P > 0.05$) change in serum calcium during either the glucagon infusion test or the saline control test.

Discussion

Brooks and Grossman demonstrated that in man pentagastrin-stimulated gastric acid secretion was inhibited by secretin.¹ Berstad and Petersen⁷ showed that

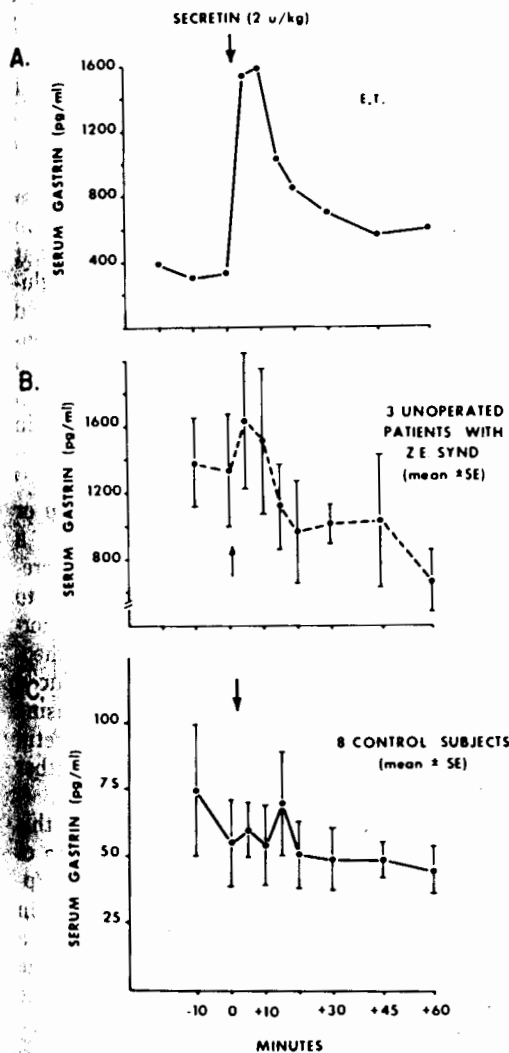


Fig. 7. Serum gastrin response to rapid intravenous injection of (2 U per kg of secretin) in: (A) Mr. T, (B) 3 other unoperated patients with ZE syndrome, (C) 8 control subjects.

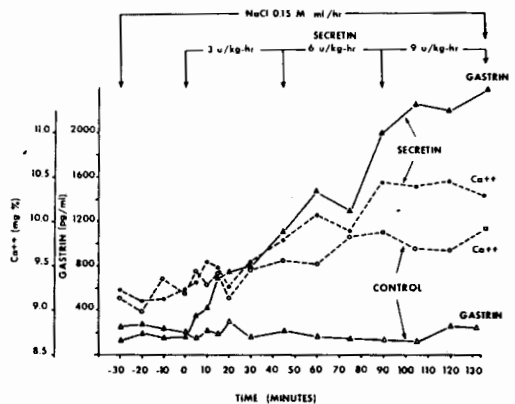


Fig. 8. Serum gastrin and serum calcium during graded doses of secretin.

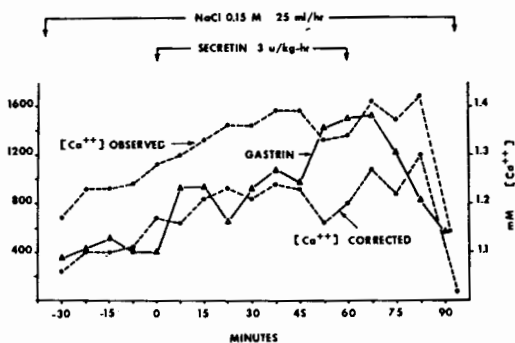


Fig. 9. Ionized calcium observed, pH- and temperature-corrected, and serum gastrin during secretin infusion.

this inhibition followed competitive kinetics in man. The increased acid secretion observed in our patient after the administration of secretin was therefore unexpected.

The paradoxical acid secretory response to intravenous secretin in our patient was due at least in part to the release of gastrin, probably tumor gastrin. Two additional patients with ZE syndrome (without hyperparathyroidism) have also shown an increase in serum gastrin concentration after secretin administration (J. C. Thompson, P. H. Jordan Jr., *personal communications*). Secretin does not induce gastrin release in all patients with ZE syndrome. In the 3 other ZE patients we studied, secretin failed to produce an increase in serum gastrin. Rapid intravenous injections of secretin have been reported to decrease gastrin concentrations in patients with pernicious anemia,⁸ and in normal subjects.⁹

The increase in serum calcium concentration which occurred during secretin infusion is of special interest. It is possible that changes in serum gastrin were mediated by changes in the serum calcium. After parathyroidectomy, our patient's serum gastrin decreased, but infusion of calcium produced an increase in serum gastrin and acid secretion similar to that produced by secretin infusion. Calcium infusion studies were not done before removal of the parathyroid adenoma. Trudeau and McGuigan¹⁰ reported a patient with ZE syndrome whose blood gastrin decreased markedly after removal of three hyperplastic parathyroid glands, but was restored to high levels by calcium infusion. Calcium infusion has produced modest increases in serum gastrin and gastric acid secretion in normal subjects and patients with duodenal ulcer disease.¹¹ Basso and Passaro¹² presented further evidence to suggest gastrin release from ZE tumors by calcium infusion. In 4 patients with ZE syndrome they found that calcium infusion produced a marked increase in acid secretion, approaching the response to maximal betazole stimulation. In Mr. T, calcium infusion produced greater than a 3-fold increase in serum

gastrin and gastric acid secretion. In addition, calcium has been shown to potentiate pentagastrin-stimulated gastric acid secretion in ferrets.¹² It is not known whether calcium augments gastrin-stimulated acid secretion in man.

Calcium is thought to play a role in the second messenger system, cyclic adenosine monophosphate, and to produce degranulation of some hormone-containing cells.¹³ Calcium infusion has produced hormone release from other endocrine tumors including calcitonin from medullary carcinoma of the thyroid¹⁴ and serotonin from malignant carcinoid tumors.¹⁵

An increase in serum calcium as a result of secretin infusion has not been reported previously, and the mechanism is unknown. The effect of secretin on parathyroid hormone release has not been studied. Cushard et al.¹⁶ reported that two other polypeptide hormones, glucagon and adrenocorticotropin, increased circulating parathyroid hormone concentration in man. Recently, Care and Bruce¹⁷ reported that cholecystokinin or the octapeptide of cholecystokinin produced an increase in calcitonin secretion in pig. In addition, Cooper et al. observed that an intravenous injection of infusion of pentagastrin produced a marked increase in thyrocalcitonin secretion in pig. Therefore, there is evidence to suggest that the gastrointestinal hormones may play a role in calcium homeostasis. It is possible that secretin produced hypercalcemia in our patient by releasing parathyroid hormone. The role of secretin in calcium homeostasis deserves further study.

The patient who is the subject of this study has not had surgical exploration of the abdomen and his present mild symptoms do not warrant such intervention. In the absence of direct demonstration of a pancreatic islet cell gastrinoma, the diagnosis of Zollinger-Ellison syndrome remains presumptive.

Addendum

Since submitting the manuscript, we have studied another patient with the di-

agnosis of Ze (whom secretinously) produced gastrin, serum secretion. During serum gastrin basal of 695 t Serum calcium basal of 9.14 t ml, and gastrin from a mean 1 mEq per 15 n Secretin-infused gastrin, serum calcium secretion in Zollinger-Ellison syndrome uncommon. This phenomenon in parathyroid syndrome defined by secretin infusion in patients with Zollinger-Ellison syndrome.

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secretion. It has been shown to stimulate gastrin-secreting cells.¹² It is not clear whether gastrin-secreting cells play a role in the pathogenesis of cyclic adenosine triphosphatase-containing gastrinomas. The release of gastrin has produced other endocrine effects in from medullary thyroid¹⁴ and malignant carcinoid

Calcium as a result of the release of gastrin has been reported. The mechanism is uncertain. The effect of secretin on parathyroid hormone has not been reported. It has been reported that parathyroid hormone, glucagon, increased parathyroid hormone concentration, and cholecystokinin cholecystokinin calcitonin secretion. Cooper et al.¹¹

Secretin-induced increase of serum gastrin, serum calcium, and gastric acid secretion in some patients with Zollinger-Ellison syndrome does not appear to be uncommon. The frequency of this phenomenon in patients with Zollinger-Ellison syndrome deserves further study. Secretin infusion may be of diagnostic value in patients with suspected Zollinger-Ellison syndrome.

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The subject of this case report is a patient with the clinical exploration of the present mild symptoms and intervention. In the demonstration of a gastrinoma, the Zollinger-Ellison syndrome

manuscript, patient with the di-