MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

February 16, 1967

ULCEROGENIC TUMORS

CASE I. [redacted], 47-year-old female

[redacted]. 1960 - Admitted with typical ulcer pain
X-ray: Duodenal ulcer
Ca^{++} 12.1, 13.0, 11.7
2.5 liters gastric juice/12 hours
[redacted] 1960 - Subtotal gastrectomy
[redacted] 1961 - Marginal ulcer - vagotomy
[redacted] 1964 - Pain, melena. 48 and 78 mEq HCl/12 hours
Surgery: 2 perforating marginal ulcers
3.5 cm. pancreatic nodule - islet cell adenoma
All but 15% stomach removed
Ca^{++} 11, 9, 14, 13
[redacted] 1966 - Neck exploration - 1.25 cm. chief cell parathyroid adenoma.
Other glands normal
[redacted] 1966 - Marginal ulcer - total gastrectomy
Ca^{++} 10.9, 11.7
[redacted]. 1966 - Severe malnutrition, death

Postmortem:

1. Multiple islet cell adenomas of pancreas, some showing malignant changes
2. Metastatic islet cell tissue in regional lymph nodes
3. Two islet cell adenomas in duodenum
4. Two parathyroid adenomas
5. Nodular hyperplasia of adrenals
6. Normal pituitary

The association of non-insulin producing islet cell tumors of the pancreas, with marked gastric hypersecretion, and fulminating ulcer diathesis was first recognized by Zollinger and Ellison in 1955 (1). In both their original cases, gastric hypersecretion could not be controlled by medical or usual surgical measures and marginal ulceration recurred until total gastrectomy became mandatory. More than 450 articles on this subject have been published in the last 12 years (2), and it has been estimated that ulcerogenic tumors are implicated in approximately 10% of problem ulcers (18).

Gregory (3) first demonstrated the presence of a potent gastric secretagogue in a pancreatic islet cell tumor removed from a patient with the Zollinger-Ellison syndrome. This substance has the same physiologic effects on the GI tract as the stomach antrum hormone gastrin, which is, along with the vagus nerve, primarily

responsible for regulating gastric acid secretion. Purified antral gastrin and extracts of Zollinger-Ellison tumors both 1) stimulate secretion of stomach acid, 2) increase gastric motility, and 3) stimulate pancreatic enzyme secretion (relatively little effect on pancreatic bicarbonate secretion) (4,5). Tauber and Madison have shown that Zollinger-Ellison tumors contain a material that is biochemically identical to gastrin (6,7).

In addition to isolation of gastrin from tumor tissue, a gastric secretagogue has been found in blood (8) and in urine (9) of these patients. A 6- to 8-fold increase in the parietal cell mass of the stomach has been demonstrated by direct counting techniques (10). This is presumably due to constant parietal cell stimulation by gastrin, and occurs with other stimulants, such as repeated histamine injections.

Electron microscopy has shown the ultrastructure of these ulcerogenic islet cell tumors to be similar to that of the alpha cells of normal pancreatic islets (11), although not all workers agree with this interpretation (12).

Multiple hormones may rarely be secreted by a single islet cell tumor—insulin, ACTH, MSH, a diarrheagenic agent (see Case 4), an agent causing severe flushing (not serotonin), as well as the gastrin-like substance (13,14,15,17).

Although there is excellent evidence that non-beta islet cell tumors of the pancreas may secrete gastrin, most of the evidence suggests that normal islet tissue does not secrete this material (5). Similarly, gastrin-like substance has not been found in adenomas of other endocrine glands (5).

The following statistics on Zollinger-Ellison syndrome are taken from a registry of 260 patients reported by Ellison and Wilson:

Sex: Male to female 6:4

Age: Highest in 3rd through 5th decades. 8% < 20 years of age

Familial: In at least 12 families

Ulcer: Present in 93% of patients. 3/4 are of "fulminating type", 1/4 have usual ulcer symptoms

Location of Ulcer (before surgery): 75% are located in usual site in duodenum. Gastric ulcer relatively rare (6%) and many of those with gastric ulcer have associated duodenal ulcer. 25% have ulcer in unusual location, such as jejunum

Diarrhea: This is the only manifestation in 7% (see Case 4). It occurs in 36% of the cases, and precedes ulcer in 18% when both are present.

Associated Endocrine Disease	21%
Parathyroid adenoma	12%
Clinical hyperparathyroidism	5%
Pituitary adenoma	6%
Functional adrenal adenoma	1%
More than two tumors	3%

X-ray: Hypertrophy of gastric folds, large amount of fluid in stomach, and unusual location of ulcer may suggest diagnosis

Tumor:

a. When primary is in pancreas, 50% are multiple. 10% have diffuse hyperplasia of pancreatic islets or "microadenomatosis" without a solitary tumor.
b. 2/3 have tumor in more than one location at time of surgery. Multiple primary tumors are common.
c. 3/5 are malignant.
d. 44% have metastasis when diagnosis first made.
e. Primary tumor in duodenum, 3%*

It is interestng that stomach antrum (the normal site of gastrin production) tumors have apparently not been associated with Zollinger-Ellison syndrome.

The presence of generalized microadenomatosis, the frequent finding of multiple tumors, and the high incidence of malignancy with metastasis serve to limit the importance of tumor resection as the preferred method of controlling this disease.

Ellison strongly believes that total gastrectomy should be the initial surgical treatment, for the following reasons:

1) Death in the disease is almost always relative to ulcer disease, and not due to the malignancy per se.
2) Complete removal of tumor is usually not possible.
3) Islet cell tumors, even if malignant, grow slowly and are compatible with long life.
4) It has been tentatively suggested that removal of all the stomach may induce remission of the primary tumor (2).

Wilson and Ellison have analyzed the results of 248 operative cases (2). Only 29 of 106 (27%) patients are still living in whom all gastric mucosa remains. Slightly more than half (79 of 164) the patients with subtotal gastrectomy are alive. On the other hand, 45 of 63 (73%) patients who had total gastrectomy are still alive. The best result, that is 13 of 15 patients (87%), occurred when the initial gastric resection was a total gastrectomy. Most of the deaths after total gastrectomy occur in early post-operative period. There have been only 4 deaths in this total gastrectomy group (of 78 patients) that can be attributed to tumor growth per se.

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* Other reports (12) and experience at PMH strongly suggest that islet cell tumors in duodenum are much more frequent than 3%.

CASE 2. [redacted] 48-year-old male

This is a patient who has had ulcer symptoms since 1945. In 1957 he perforated a duodenal ulcer, which was treated surgically by simple closure.

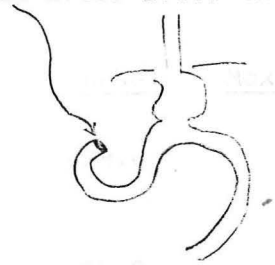
In [redacted] 1964, he was admitted to the [redacted] with exacerbation of pain, frequent vomiting, and mild hematemesis. Physical examination and laboratory work were normal, including serum calciums of 10.1 and 8.8 mg.%. X-ray showed deformity of the duodenal bulb and an active crater. Medical treatment resulted in prompt improvement, and it was decided to place him in a controlled study of gastric freezing. By random selection, he was placed in the control group, and in March of 1964 he received a "sham freeze"; this consisted of intubation similar in all respects to gastric hypothermia except that the coolant bypassed the gastric balloon at the level of the lower esophagus. He returned for follow-up interviews at 1, 3 and 6 months, considered himself definitely improved, and was working full time.

Review of his gastric secretory studies, at the time the freezing study was published, showed the following:

Time	Basal mEq/hr	Maximum Histamine Response mEq/hr	Basal / Maximum Histamine
[redacted]/64 Just before sham freeze	29.0	47.5	0.61
[redacted]/64 3 months after sham freeze	26.0	55.2	0.47
[redacted]/64 6 months after sham freeze	83.7	71.7	1.10

This high basal secretion, relative to maximum output with histamine, suggested Zollinger-Ellison syndrome. Other conditions which may cause high basal, relative to maximum, output are:

1) Retained gastric antrum after Billroth II anastamosis.



2) Portacaval shunts - Gastric histamine bypasses liver, stimulates parietal cells (19,20,21). Peptic ulcer is the commonest cause of GI bleeding after portacaval shunt (8/14 according to Reynolds, NEJM, March 31, 1966, and 6/20 according to Liebowitz, Arch. Int. Med., March 1965).
3) Small bowel resection, especially distal part (22,23,24)
4) Occasionally foregut carcinoid tumors secrete enough histamine to cause massive gastric hypersecretion (25,26). (Carcinoid tumors may also be very difficult to distinguish from islet cell tumors histologically.) Theoretically, mast cell tumors or systemic mast cell disease might also be associated with gastric hypersecretion due to histamine release (27).

5) Pancreatic duct ligation, pancreatic fistula, and pancreatitis (29). Marked hypersecretion occurs in dogs, correctable in part by feeding pancreatic enzymes with food (28). Does not occur with total pancreatectomy. Not clearly established as a cause of hypersecretion in man.
6) Occasionally after vagotomy and pyloroplasty in duodenal ulcer patients. In 12 cases reported by Bank, et al., basal secretion in 3 patients was 58, 65 and 80% of maximum histamine output (30). Average in all 12 patients was 35.6%.
7) Hypercalcemia - See Case 3.
8) ? Pyloric obstruction

Generally these conditions do not result in the massive basal hypersecretion seen in Zollinger-Ellison syndrome, but they may, on occasion, do so.

Since none of these seemed operative in Case 2 ([redacted] on [redacted] 1964, he was subjected to laparotomy in search of islet cell tumor, even though he had been asymptomatic for several months. A 1.5 x 1.0 cm. nodule was found in the gastro-hepatic ligament. This was excised, and a frozen section was interpreted as "lymph node". Careful exploration did not disclose a mass in the pancreas or elsewhere. The pylorus and proximal duodenum were quite deformed. A pyloroplasty and vagotomy were performed.

The histologic diagnosis from the permanent section made from the previously described tissue was "islet cell tumor contained within lymph node".

For the past 2-1/2 years the patient has worked full time, and has only occasionally had pain that may be related to ulcer. Repeat x-rays do not show an ulcer crater, although the bulb area is still deformed (due to old ulcer disease and pyloroplasty).

Gastric secretory studies, done mostly by Dr. Ross Harrell, are shown in the following table:

	Basal	Maximum Histamine	Ratio
[redacted]/64, 6 months prior to surgery, just before sham freeze	29.0	47.5	0.61
[redacted]/64, 3 months prior to surgery; 3 months after sham freeze	26.0	55.2	0.47
[redacted]/64, just before surgery, 6 months after sham freeze	83.7	71.7	1.10
[redacted]/64, 2 weeks after surgery	1.6	11.4	0.14
[redacted]/65, 2 months after surgery	1.0	8.1	0.12

	Basal	Maximum Histamine	Ratio
[redacted]/65, 6 months after surgery	7.4	23.9	0.31
[redacted]/66, 18 months after surgery	6.3	15.4	0.30
[redacted]/66, 21 months after surgery	3.4	13.7	0.24
[redacted]/66, 2 years after surgery	5.8	11.8	0.49

These post-operative secretory studies make it likely that all of the gastrin secreting tumor was removed. The vagotomy itself probably could not produce this effect since it is known that vagotomy reduces the response to gastrin infusion by only 33%, whereas it reduces the response to histamine by 63% (33). Therefore, if gastrin secreting tumor remained, the basal output should still be as high as with histamine.

Thus, the source of the gastric secretagogue appears to have been removed, even though the only tumor removed was in a lymph node. It seems logical to assume that a small primary tumor remains in the pancreas or elsewhere. However, Christleib, et al. reported a patient with Zollinger-Ellison syndrome with islet cell tumor in 3 peripancreatic lymph nodes, and serial sectioning of the pancreas from head to tail at intervals of 1 to 2 mm. failed to reveal a primary, and no primary could be found in the GI tract (31). However, diffuse hyperplasia of the pancreatic islets was present. These authors postulate that there must have been some stimulus present in their patient which caused hyperplasia of the islets, not only in the pancreas, but also in aberrant islet cells located in lymph nodes.

It seems pertinent also that in primary islet cell tumors of duodenum associated with the Zollinger-Ellison syndrome, hyperplasia of islets was present in the pancreas itself (12). One patient has been reported who had the Zollinger-Ellison syndrome apparently due to islet cell hyperplasia of the pancreas, and responded very well to "blind" distal pancreatic resection, subtotal gastrectomy and vagotomy. Adequate studies to rule out primary tumor elsewhere were not done (32).

The excellent response in this patient to removal of tumor, which avoided the necessity of total gastrectomy and the severe nutritional problems often associated with this procedure, prompts a re-evaluation of the generally recommended total gastrectomy in this disease.

The following seems to be a logical approach:

1) It is essential that adequate gastric secretory studies be carried out pre-operatively so that there can be no doubt that an endogenous secretagogue is present.
2) Gastric secretion should be measured during the operative procedure. It is very likely that acid secretion will decrease promptly when the source of gastrin (i.e., the islet cell tumor) is removed, since acid secretion stops in 10-15 minutes after IV infusion of purified gastrin is stopped in patients with duodenal ulcer (44).

3) If a tumor is found (either in pancreas, duodenum or in lymph node) which appears resectable, it should be removed:
   a) If prompt and definite decrease in acid secretion occurs, do a pyloroplasty and vagotomy or leave the stomach intact. Do not do subtotal gastrectomy. This procedure will only remove antral mucosa, and the gastrin secreted by the stomach antrum would be insignificant compared to the large amount of gastrin secreted by any tumor which is left behind. Furthermore, if tumor is left behind, the Billroth II anastomosis has now placed acid gastric juice in direct contact with the jejunum, which is much more susceptible to peptic ulcer than the duodenum, and stomal ulcer with bleeding or perforation will almost certainly develop.
   b) If acid secretion does not decrease after removal of tumor, do a total gastrectomy. This is preferable to total pancreatectomy.
4) If multiple primaries or metastasis makes tumor removal impossible, do a total gastrectomy.
5) If no tumor can be found: This is when disaster may result unless the pre-operative gastric secretory studies were carefully done.
   a) If ulcer diathesis and/or diarrhea (see Case 4) have been very severe, do a total gastrectomy.
   b) If symptoms have not been very severe, do a vagotomy and pyloroplasty.
   c) Do not do a subtotal gastrectomy for reasons given under #3.

It is well to remember that x-ray treatment of stomach, and intensive anticholinergic therapy (34,35), even if a vagotomy has been done (30), may decrease acid secretion in these patients. During pre-operative workup and post-operative observations, it is essential that gastric acid be neutralized, by continuous drip of antacids if necessary.

If available, angiographic studies may help localize a tumor in pancreas (36, 37).

Also, when and if gastrin assay becomes available, measurement of gastrin level in blood may obviously help guide surgical therapy.

Although treatment of Zollinger-Ellison syndrome by any means other than total gastrectomy is contrary to recommendations of Zollinger and Ellison, others have also had success by removal of tumor (12,45) and one case has been reported where surgery and lymph node biopsy was followed by remission for at least 20 months, even though primary tumor and stomach were left intact (46).

CASE 3. [redacted], 27-year-old male

This man was well until 1961, when he developed ulcer symptoms. An upper GI series showed a gastric ulcer. He improved on medical therapy, but in [redacted] 1962 the pain recurred and he vomited blood. He was seen in Medicine Clinic, where hemoglobin was 8.9, Ca 10.8 and PO4 3.5. An upper GI showed a large ulcer crater on the lesser curvature and probably a duodenal ulcer.

He was not seen again until [redacted] 1964, when he returned to PMH because of pain and melena. On [redacted] 1964, x-ray showed both gastric and post-bulbar ulcer. Serum calcium 11.2, PO4 3.1. He had two 12-hour nocturnal gastric analyses on this admission:

	Volume ml.	pH	$[H^+]$ mEq/L	Total Acid per Specimen mEq	mEq/hour
[redacted]/64	510	1.5	66	33	2.7
[redacted]/64	2200	0.9	112	246	20.5

The patient signed out [redacted] but returned 5 days later with massive hematemesis. On [redacted]/64, he had 65% gastric resection. A "massive 4 cm. ulcer" on the lesser curvature had perforated, and he had, in addition, an ulcer in the duodenal bulb. Two weeks post-op he had another 12-hour nocturnal gastric analysis:

Volume ml.	pH	$[H^+]$ mEq/L	Total Acid per Specimen mEq	mEq/hour
650	1.2	95	62	5.1

On [redacted], 1965, 7 months post-op, he vomited blood and returned to [redacted]. An x-ray on [redacted] was negative, but he was explored on [redacted] and found to have two penetrating marginal ulcers and a retained gastric antrum. The pancreas felt normal, but two masses were excised from the lateral wall of the duodenum which were later shown to be non-beta islet cell adenomas. An additional 10% of the stomach was removed.

Twelve-hour nocturnal gastric analyses on this admission showed the following:

	Volume ml.	pH	$[H^+]$ mEq/L	Total Acid per Specimen mEq	mEq/hour
[redacted]/65	2100	1.4	62	130	10.8
[redacted]/65	2340	1.4	85	199	16.6
[redacted]/65	SURGERY				
[redacted]/65	100	1.7	45	4.5	0.4
[redacted]/65	550		49	26.95	2.2

During this admission he had serum calciums of 10.2 and 10.2 and PO4 2.1 and 3.0.

Post-operatively he gained 20 pounds, and generally felt well until [redacted], 1965, when he had recurrent ulcer pain. An upper GI series showed a marginal ulcer. He was admitted in [redacted] of 1966, and three serum calciums were above 11 mg.%.

An augmented histamine test showed basal secretion of 2.9 and maximum histamine response of 3.1 mEq/hour, which was strongly suggestive of recurrent islet cell tumor, and total gastrectomy seemed indicated.

However, the serum calcium was elevated, and it has been shown that hypercalcemia may at times cause gastric secretion. Review of the literature on the relationship of parathyroid adenoma, ulcer and gastric secretion reveals the following conclusions:

1) Intravenous calcium infusion consistently increases stomach acid secretion in normal human subjects and in patients with duodenal ulcer (38-42). The mean secretory response to acute hypercalcemia is 30% of the peak acid response to histamine, and 4-1/2 times the basal acid output. The calcium induced hypersecretion varies from 18 to 52% of the peak acid output with histamine (42). Vagotomized patients also show this response, but anticholinergic drugs will block it (42). Also, induction of hypermagnesemia will block the effect of calcium infusion (42).
   Hypercalcemia does not raise the peak response to histamine (42).

2) Calcium infusion in dogs produces the opposite effect, i.e., inhibition of gastric acid secretion (39).

3) Patients with hypoparathyroidism are achlorhydric until Ca^{++} is raised to or above 7.5 mg.%. Serum Ca^{++} between 7.5 and 11 mg.% exerts a permissive effect on gastric secretion (38).

4) The relationship of chronic hypercalcemia to gastric secretion is not entirely clear. Ostrow (43) reviewed the literature up to 1960 and concluded that hyperparathyroidism was not associated with hypersecretion, and the incidence of ulcer in this disease is only slightly increased (43).
   However, 5 of 9 patients with hyperparathyroidism studied by Ward, et al. (39) and 2 of 5 reported by Barreras and Donaldson (43) had basal hypersecretion. One of the patients reported by the latter group was particularly striking--basal acid secretion was 20 mEq/hour, which was about 40% of maximum Histalog response. After the parathyroid adenoma was removed, basal secretion fell to 2 mEq/Hour, and the patient's ulcer healed without other therapy (42).

Therefore, chronic hypercalcemia is associated with hypersecretion in perhaps 20 to 30% of cases. Since all patients show an effect with IV infusion of calcium, the fact that many patients with chronic hypercalcemia do not show hypersecretion suggests that an adaptation to the hypercalcemic state may occur (43).

Because it seemed possible that basal hypersecretion in Case 3 might be due to hypercalcemia rather than to recurrent Zollinger-Ellison tumor, and in the hope of avoiding total gastrectomy, additional tests were carried out.

First, disodium versenate, 40 mg./kg./hour, was infused intravenously for 2 hours, to note the effect of reduction of serum Ca^{++} to normal levels:

Versenate Infusion

Time	Volume ml.	pH	Serum Ca^{++} mg.%	Versenate
30 min.	71	1.5	11.4	
1 hr	74	1.65	11.1	
1-1/2 hrs	26	2.75	9.8	
2 hrs	26	5.90	9.3	↓
2-1/2 hrs	55	6.65		
3 hrs	26	6.90	9.8	

Having found that gastric acid secretion stopped when serum Ca^{++} was decreased to normal levels, a neck exploration was carried out on [redacted] 1966, and a large 2x3 cm. parathyroid adenoma was removed. Secretory tests pre- and post-op are shown below:

Augmented Histamine Tests

	Basal mEq/hour	Maximum Histamine mEq/hour
[redacted]/66	2.9	3.1
[redacted]/66	PARATHYROID ADENOMA REMOVED	
[redacted]/66	0.0	1.8
[redacted]/67	0.1	4.2

Calcium Infusion Tests*

	Basal mEq/hour	Calcium Infusion mEq/hour
[redacted]/66	0.9	4.3
[redacted]/66	0	2.0

* As calcium gluconate 15 mg./kg. in 0.9% saline over a 4-hour period

The patient has been asymptomatic for the past year, and a recent x-ray shows no evidence of marginal ulcer.

This case illustrates the usefulness of gastric secretory studies in directing treatment of difficult ulcer problems, and the interrelationships between serum calcium and gastric secretion in a patient with two ulcerogenic tumors.

CASE 4. [redacted],
52-year-old male

This 52-year-old [redacted] male [redacted] was admitted to the [redacted] on [redacted]/66 with nausea, vomiting and weakness of 2 days' duration. He gave a history of chronic watery diarrhea which had been present with variable severity since hemorrhoid surgery in 1956, which apparently left him with anal sphincter incompetence. Worse at night and generally consisting of 4-5 brown liquid stools without blood or pus, the diarrhea was occasionally associated with vomiting and necessitated hospitalization at least twice in the 10 years prior to admission for dehydration and weakness. No diagnosis was made at these times. He had always been thin and denied massive recent weight loss prior to admission. He also complained of vague epigastric distress, usually relieved by Alka-Seltzer or eating, which symptoms had likewise been present intermittently for many years. On the day prior to admission he developed pernicious vomiting and noted a coincidental increase in his chronic diarrhea.

Admission physical examination disclosed an extremely thin man with poor tissue turgor, evidence of dehydration and weight loss. Abdominal examination was negative.

Admission laboratory work disclosed: Hemoglobin 11.5, WBC 8100, BUN 37 mg.%, Na 140, Cl 99, CO_2 30, K 2.1, A/G 2.7/4.0. Blood sugar, Ca, P and liver battery were normal; urinary 5HIAA was negative.

He was begun on IV fluid therapy with supplemental K^+ and a nasogastri tube was inserted and placed to suction. Large volumes of gastric juice were returned—over 5 liters in the first 24 hours, and 3040 ml. on a subsequent 12-hour overnight collection. Gastric juice pH was 1.3 with a basal secretion rate of 27.3 mEq/hour. It was further noted that while on nasogastric suction, the patient's profuse diarrhea ceased. A maximum histamine test was done, the results as follows:

		Volume	pH	mEq/L	mEq/hour
Basal	1st hour	338	1.36	73.0	24.7
	2nd hour	170	1.35	73.5	12.5
Post-Histamine (1 hour)		280	1.32	77.5	21.9

A repeat study gave similar results.

The nasogastric tube was D[illegible]d after 3 days of suction, and severe diarrhea ensued once again. Attempts to suppress gastric secretion with atropine were unsuccessful, gastric output being 2 liters in 12 hours, with pH 1.32 and 18.3 mEq/hour. An upper GI series demonstrated marked enlargement of the gastric rugal folds, rapid transit through the small bowel, questionable deformity of the duodenal bulb, with no evidence of obstruction.

Despite careful monitoring of gastric secretion and diarrheal stool output, it became increasingly more difficult to control the patient clinically. Hypotension, dehydration, hypokalemic alkalosis, and malnutrition were constant problems. On the 9th hospital day he was taken to surgery and explored, whereupon a small, 1 cm.

diameter nodule was found distal to the pylorus in the proximal duodenal wall; the pancreas was normal without palpable masses. A pecan-sized lymph node was found below the pancreas. There was no evidence of peptic ulcer. A total gastrectomy with Roux-en-Y anastomosis was performed. Histological examination of the surgical specimen showed typical non-beta islet cell tumor of the duodenal wall, as well as in the regional lymph gland. A jejunal biopsy, taken at the time of surgery, was normal.

The patient's post-operative course was somewhat turbulent initially with fever, abdominal pain and evidence of a left subdiaphragmatic abscess developing in the first 10 days. He was re-explored and a phlegmon drained from the left subdiaphragmatic space on [redacted]/67. Since his second surgery, he has done well without abdominal pain, vomiting or diarrhea, but has remained anorexic and has been extremely slow to regain his normal weight. The patient weighed approximately 120 lbs. prior to the onset of his pre-admission symptoms, dropped to 80 lbs. following surgery, and currently weighs 90 lbs.

As already noted, diarrhea occurs in 36% of patients with Zollinger-Ellison syndrome, and in 7% of cases is the only manifestation of the disease.

Diarrhea due to islet cell tumors has two distinct etiologies, apparently depending on the nature of the hormone secreted by the tumor.

A) Diarrhea, as a feature of the Zollinger-Ellison syndrome, caused by enormous volume of highly acid gastric juice.

The diarrhea can be controlled by nasogastric suction (48,51). Re-infusion of gastric juice after neutralization does not reproduce diarrhea.

The severity of diarrhea is variable, usually not fulminating, but may be as illustrated by Case 4. Hypokalemia is not common (52), and apparently occurs only if the patient has also vomited excessively.

Steatorrhea is common, and may be severe. It is usually attributed to inactivation of pancreatic lipase by low intraduodenal and intrajejunal pH seen in these patients (48,49,50,51) (as low as 1.4). The optimum pH for pancreatic lipase is 7.0. The mucosa of the upper small bowel is usually normal, although some patients have mild sprue-like changes, presumably related to the acid insult (52).

One problem with the above explanation of diarrhea and steatorrhea in these patients is why some patients get diarrhea and others do not. For instance, E.P. (Case 4) had life-threatening diarrhea but secreted only 27 mEq/hour HCl; on the other hand, A.P. (Case 2) secreted as high as 83.7 mEq/hour HCl, but did not have diarrhea. One possible explanation is that duodenal secretin may become depleted in some patients, with the result that the pancreas is inadequately stimulated to secrete bicarbonate and thus to neutralize gastric acid in the proximal small bowel. Thus, patients whose duodenal mucosa is depleted of secretin would be exposed to much larger amounts of acid in the proximal small bowel than in patients with normal duodenal secretin release. Conceivably such patients might benefit from IV secretin therapy (53).

B) Diarrhea due to non-gastrin secreting islet cell adenomas of the pancreas (54-58).

The islet cell tumors in this group of patients have all been in the pancreas. Histologically they are also non-beta cell in type. At least two of these tumors

have been assayed for gastrin with negative results. Seven of the 15 cases reviewed by Matsumoto, et al. had malignant tumors (54). Multiple endocrine adenomas (parathyroid, thyroid and pituitary) were present in 3 of the 15 patients.

The patients have low or normal gastric acidity (54) or even achlorhydria (55).

The relationship of diarrhea to these tumors seems well established, since in at least 4 cases a benign tumor has been resected with complete cure of the diarrhea.

Clinically, these patients present with variably severe, but usually progressive diarrhea. The duration of diarrhea is also very variable (from several months to 15 years) (54). When the diarrhea is fulminant, the stools are cholera-like, having very little odor, a tea-like color, no blood, and very large volumes. Hypokalemia, and its complications, are very common (52). When the diarrhea is less severe, stools are mushy in consistency, and still not excessively foul.

Steatorrhea is very rare in this syndrome, but weight loss is always present, and often severe (52,54).

The only way to diagnose this syndrome is exploratory laparotomy. In addition to finding the islet cell tumor, the small bowel is characteristically filled with clear watery fluid.

A most interesting feature in 2 of these patients (54,57), one reported by Drs. Chears, Thompson, Hutchinson and Patterson of Dallas (57), was the finding of hypercalcemia that disappeared after the islet cell tumor was removed. In another patient with hypercalcemia, neck exploration and subsequent autopsy failed to reveal a parathyroid adenoma (58). Perhaps the islet cell tumors in these patients were also secreting parathormone. In any case, it may be wise to postpone neck exploration in these patients until after the islet cell tumor is removed, if the latter is possible.

Another interesting feature in some of these patients is a beneficial response to adrenal steroids. This is variable, and usually not of prolonged benefit, however. One patient noted that pregnancy relieved her diarrhea on three separate occasions. This patient had no response to estrogens or adrenal hormones, however (54).

The pathogenesis of this disease is unclear. Most workers postulate that secretion of fluid by the small bowel causes the diarrhea. However, extracts of the tumor do not affect water and electrolyte transport in laboratory animals (54).

Diarrhea and Islet Cell Tumors

	Zollinger-Ellison Type	Cholera-Like
Basal acid secretion	> 15 mEq/hour	< 5 mEq/hour
Steatorrhea	Common	Rare
Hypokalemia	Rare	Common
Control with nasogastric suction	Common	Rare
Diagnosis	Maximum histamine test	Exploratory laparotomy

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