

# The Zollinger-Ellison Syndrome: \*

## Re-appraisal and Evaluation of 260 Registered Cases

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NEARLY TEN YEARS have passed since Robert M. Zollinger and one of us (E. H. E.) proposed that a fulminating ulcer diathesis could result from an ulcerogenic or gastrin-like hormone elaborated from an associated non-beta islet cell tumor or tumors of the pancreas.<sup>264</sup> Since that time more than 250 publications have appeared in the World literature and a gastric secretagogue has indeed been isolated in 17 of 26 tumors assayed.\*\* Dr. Gregory has reportedly indicated that his most purified material is 1,000 times more potent by weight than histamine phosphate.<sup>109</sup> A registry of 260 patients including 190 reported cases\*\*\* along with 70 collected and including several personal cases was established to study further the nature and preferred treatment of this disease entity. The year of publication and/or reporting

of the cases are shown in Figure 1. The study was programmed for IBM and computer analysis of 109 questions with 640 possible answers.

One hundred forty-four or 57 per cent of the 260 patients are dead and 111 or 43 per cent are living. Twenty-four patients came to autopsy without operation. One hundred eleven or 49 per cent of the 230 patients operated upon for gastric hypersecretion and/or islet cell tumors of the pancreas are dead and over one-half of these (62 of 111) died in less than 30 days following operation. For the most part, these deaths occurred as a result of complications arising from recurrent ulceration

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\*\* References 3, 40, 43, 47, 60, 68, 82, 83, 106, 109, 111, 116, 122, 134, 147, 159, 185, 196, 207, 221, 257, 263.

\*\*\* References 2-4, 9, 12, 13, 16, 19, 21, 22, 24, 26, 27, 30-32, 34, 36, 38, 40, 42, 44, 45, 47, 50-52, 55, 57, 60, 61, 64, 68, 70, 71, 74, 75, 77, 78, 80, 91, 94, 101, 102, 104, 110, 112, 114, 115, 117, 122, 124-127, 129, 130, 134-137, 140, 142, 147, 148, 150, 152-153, 157, 159, 160, 162, 163, 165, 167, 168, 171, 174-176, 183, 184, 187, 188, 192, 194, 196-198, 201, 206-208, 210, 212, 217, 221, 224, 227, 229, 231-233, 237-267, 239, 244, 246, 248, 251, 252, 254, 263, 264, 268, 269.

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**CASES REPORTED OR RECEIVED BY YEAR**

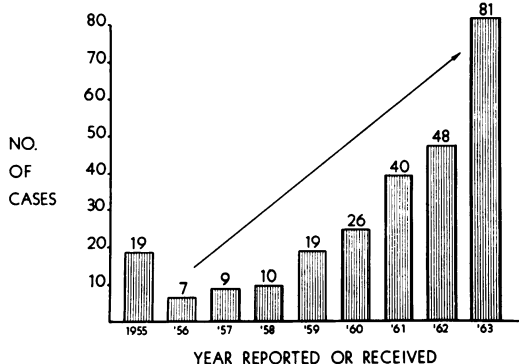


FIG. 1. Number of cases published and/or registered by year. The large number of cases in 1963 resulted from questionnaires sent to hospital surgical services maintaining approved residency programs in general surgery.

including perforation and subsequent peritonitis, obstruction, and hemorrhage and could be attributed either to a misdiagnosis and/or an inadequate operation for ulcer.

**Sex Incidence and Age at Onset**

The sex incidence is now predominantly male with a male to female ratio of 6:4 (Fig. 2). The age of onset of symptomatology is greater in the third through the fifth decades of life and therefore is not unlike that seen in the patient with duodenal ulcer resulting from vagal stimulation of the gastric antrum. On the other hand, it is pertinent that 8 per cent of those studied were under 20 years of age and 12 had not yet reached their 15th birthday. This begins to raise the question as to whether or not the syndrome may be the basis of a considerable number of those peptic ulcerations requiring operation in the child.

**Duration and Character of Symptomatology**

Two hundred thirty of the 260 patients or 88 per cent came to operation and although the syndrome is currently considered the basis of fulminating ulcer dis-

**DURATION OF SYMPTOMS TO FIRST SURGERY**

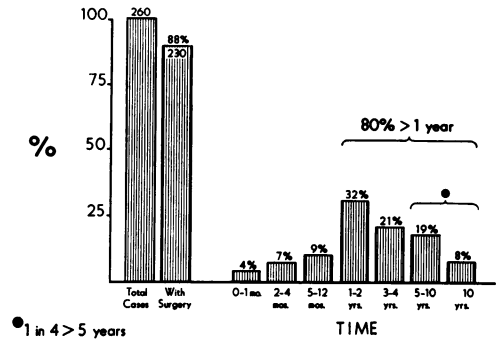


FIG. 3. Note that 80 per cent of the operated patients had been ill one year or longer and 27 per cent for over five years.

ease, 80 per cent of those operated upon had been ill longer than one year and as shown in Figure 3, over one in four had been troubled five years or longer and 8 per cent for ten years.

*Pain* was a predominant presenting symptom in nearly all of the patients and was related to peptic ulceration in at least four out of five and to diarrhea in 15 per cent (Fig. 4).

Acute abdominal pain was attributable to perforation in 18 per cent of the total patients. Symptomatology resulting from excessive fluid loss was recorded frequently

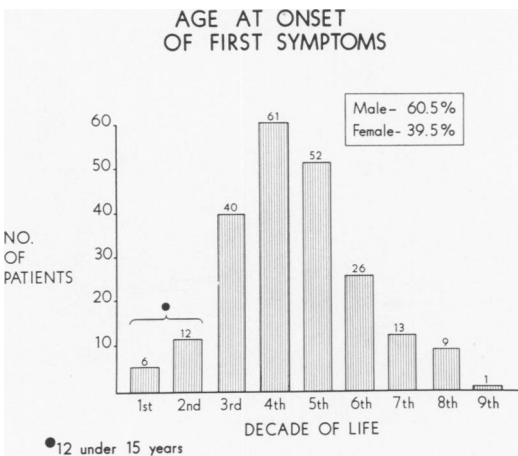


FIG. 2. The age at onset is not unlike that of the usual duodenal ulcer with the peak occurring between the ages of 30 and 50. Six patients were under ten years of age and one was over 80.

**CHARACTER OF PRESENTING SYMPTOMS**

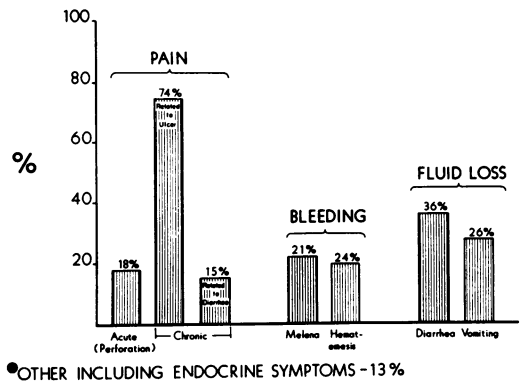


FIG. 4. Pain, fluid loss, and bleeding from the gastro-intestinal tract were among the more prominent initial complaints.

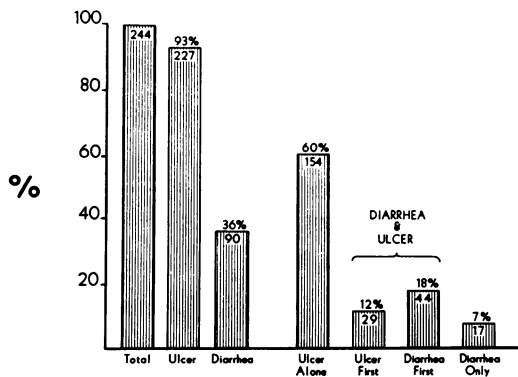
RELATIVE SIGNIFICANCE OF  
ULCERATION AND DIARRHEA

FIG. 5. Diarrhea is a prominent symptom and occurred in 36 per cent of the patients studied. Its pathogenesis remains debatable; however hypersecretion of acid gastric juice does play a major role.

and was attributable to *diarrhea* in 83 or 36 per cent and *vomiting* in 63 or 26 per cent. *Gastro-intestinal hemorrhage* was the third most common complaint; melena was present in 57 patients (22%) and hematemesis had occurred in 50 or 19 per cent.

Ulcer played a significant role in 93 per cent of the studied patients and diarrhea was recorded in 36 per cent (Fig. 5). Ulcer occurred alone in three out of five patients and with diarrhea in 30 per cent. In these instances, diarrhea frequently was the first manifestation. Diarrhea alone was noted in 17 or 7 per cent of the total. The number of clear watery stools exceeded six per day and the serum potassium had fallen to less than 2.9 mEq. in over 50 per cent of the 90 diarrhea patients. Seven patients had 11 to 15 loose bowel movements per day and a similar number reported 16 or more within a 24-hour period. The serum potassium was less than 1.9 mEq. per liter in eight patients.

## Location of Primary Ulcer

The relative frequency of abnormally located primary ulcerations of the gastrointestinal tract continues to be of impor-

tance. About one in four have occurred in the distal duodenum or the proximal jejunum (Fig. 6). It may be significant in a consideration of the etiology of gastric ulcer that only ten or 6 per cent of the 149 single ulcerations occurred in the gastric bag. Eight of the 17 multiple ulcerations were gastric and six of these had an associated duodenal ulcer. Although the finding of an abnormally located peptic ulcer is of significance in the diagnosis of the Zollinger-Ellison Syndrome, it seems pertinent to point out that three-fourths of the primary ulcers are *not* abnormally located.

## Associated Endocrine Disease

Although associated endocrine disease was noted in 21 per cent or 56 of the 260 patients, the syndrome of multiple endocrine adenomatosis (Wermer's disease) was recorded in only eight patients or 3 per cent of the total and included only those with non-beta islet cell tumors of the pancreas.

A pituitary tumor was manifest in 17 of the 56 patients and a tissue diagnosis of parathyroid adenoma was recorded in well over one-half of the total. A clinical diag-

## SITE OF ULCERS AT FIRST OPERATION

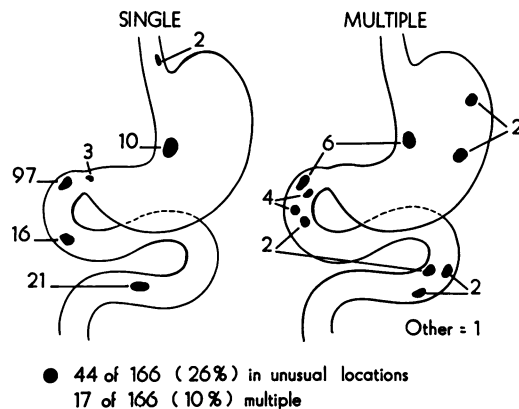


FIG. 6. Note that 74 per cent of the primary ulcerations occurred at the usual site of the average duodenal ulcer. In addition, gastric ulcer occurred in only 18 patients and six of these had an associated duodenal ulcer.

nosis of hyperparathyroidism had been made in 15. This group also included ten beta cell islet adenomas and three of the 24 were reported as having had functioning adrenocortical tumors with Cushing's Syndrome.

The association of functioning endocrine tumors calls for extreme care in the preparation and management of these patients. This is particularly true when more than one endocrine organ is involved and it is of interest that 15 or 26 per cent of those with associated endocrine disease had two and 11 or 19 per cent had three or more tumors over and above the islet cell adenoma.

### Family History

As indicated previously, multiple endocrine adenomatosis was noted in only eight or 3 per cent of the cases studied. Single functioning endocrine tumors without ulceration had occurred in the families of 14 or 5 per cent of the 260 cases. These included the sister of one of the first two reported patients who had died of an insuloma. The familial incidence of acid peptic disease was slightly higher than that usually reported, i.e., 22 or 8 per cent. The

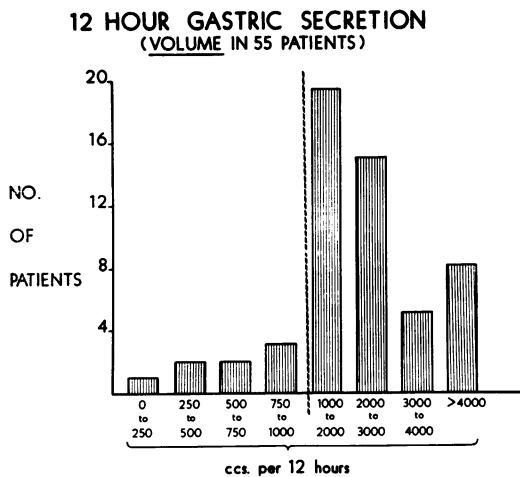


FIG. 7. The volume of the 12-hour night secretion exceeded 1 liter in 47 of 55 patients.

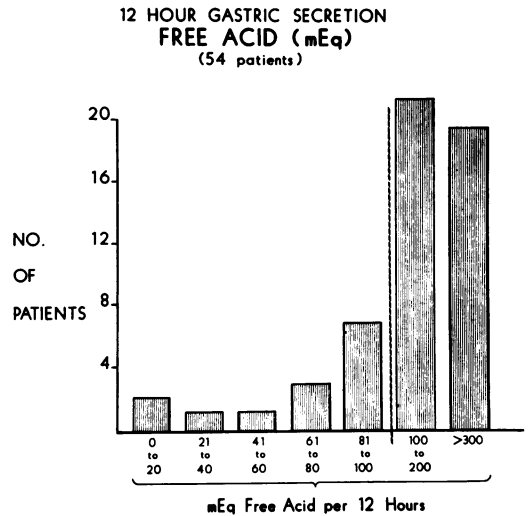


FIG. 8. Free acid in the 12-hour night secretions exceeded 100 mEq. in 40 of the 54 patients studied.

Zollinger-Ellison Syndrome as we know it occurred in 12 instances (5%) and in most cases involved siblings. These findings indicate the importance of further study of the familial incidence of this syndrome.

### Gastric Secretion

One hundred fifty-five or 94 per cent of 164 cases with sufficient data reported hyperacidity as a factor of major importance in these patients. Low acidity was reported in seven or 4.5 per cent and achlorhydria was noted in two or 1.5 per cent. Hypoacidity and achlorhydria were most common in those patients with severe diarrhea. The volumes recorded for 12-hour night secretions varied from less than 250 cc. in one patient to over 4,000 cc. in eight patients (Fig. 7). Forty-seven or 85 per cent exceeded 1,000 cc. which is the most obvious cut-off point in determining the value of the 12-hour gastric secretion. Forty-nine per cent made more than two liters; 22 per cent over three liters, and 14 per cent made over four liters of gastric juice. It should be noted, however, that eight patients had volumes of less than one liter; three had volumes of over 750 cc. but less

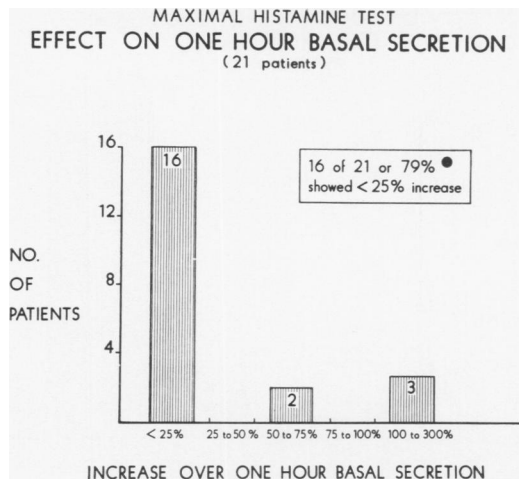


FIG. 9. The effect of histamine on the one-hour basal secretion recorded in 21 patients showed that the majority already were producing the maximum amount of acid gastric juice. The 5 exceptions may be related to the fact that endocrine function occasionally is cyclic in nature.

than 1,000 cc. and four recorded from 250 to 750 cc.

The 12-hour night secretion was reported as mEq. of free acid in 54 patients and the most obvious diagnostic cut-off point was again at 100 mEq. as shown in Figure 8. Seventy-four per cent exceeded this value and 35 per cent were over 300 mEq. On the other hand, 26 per cent were less than 100 mEq.

The *one-hour basal secretion* in 25 patients varied from 11 to over 80 mEq. of free acid. The augmented histamine test in 21 patients showed an increase of the one-hour secretion of less than 25 per cent in 16 or 79 per cent and has proven to be very helpful as a confirmatory test (Fig. 9). On the other hand, two patients showed an increase of from 50 per cent to 75 per cent and three demonstrated an increase of from 100 per cent to 300 per cent.

### X-ray Findings

The x-ray findings are most characteristic (Fig. 10). Thirty-five made mention of the hypertrophy of the gastric mucosa.

Duodenal ileus occurred frequently. An abnormal feather-like small bowel pattern was seen in 57 and rapid transit in 28. In our experience, an alert radiologist can make the diagnosis.

Let us now turn our attention to several *Variants Influencing Survival*. The first of these and in our opinion a very important factor, is the high incidence of acute complications requiring emergency surgery as the first abdominal operation for ulcer and/or diarrhea resulting from a non-beta islet cell tumor. All told, 76 or one-third of the total operated cases fall in this category. Forty-three had perforated and there were 21 survivors. Eleven of the 14 operated as a semi-emergency for obstruction are dead indicating the extreme importance of fluid loss in these patients. The remaining deaths include six of the 12 requiring emergency operation for hemorrhage and five of seven explored for diarrhea. Volvulus and gangrene of the small bowel were the cause of death in four of the five patients dead with diarrhea.

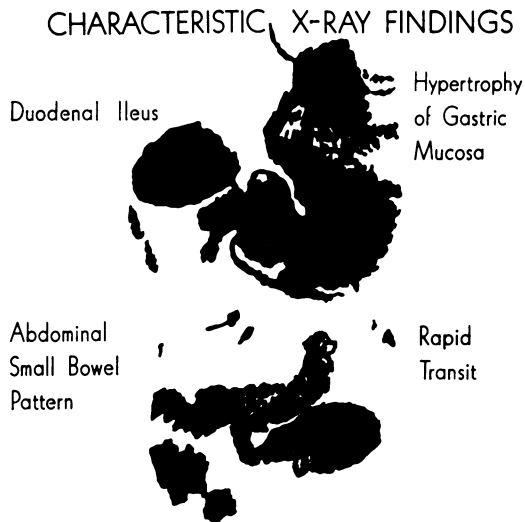


FIG. 10. X-ray findings are so characteristic that an alert radiologist can make the diagnosis if acquainted with the clinical history. The last three patients diagnosed at Marquette University were diagnosed in this fashion.

**Influence of Initial Operation and Resection of Tumor on Survival**

Eighteen of 39 patients whose initial surgical procedure included resection of tumor are living. Twenty-two patients had no definitive operation for ulcer at that time and 12 are still living and well with no evidence of gastric hypersecretion or recurrent tumor. Nine of these have had no additional operation for ulcer. Sixteen patients had a simultaneous gastrectomy. Eight are living, four with subsequent total gastrectomy. One of the other survivors has re-bled suggesting recurrent or residual tumor. All except one of those patients in this group dead of their disease had residual tumor which suggests the difficulties in determining resection for cure. The one patient surviving resection of tumor plus total gastrectomy at the initial operation is living and well.

The over-all survival of 75 tumor resected patients with sub-total gastrectomy is 39 or 52 per cent. The best results occurred in 22 patients whose current status includes total gastrectomy and resection of tumor. Nineteen or 86 per cent of these are living.

A study of the influence of gastric resection on survival points out the beneficial in-

**INFLUENCE OF GASTRIC RESECTION ON SURVIVAL**

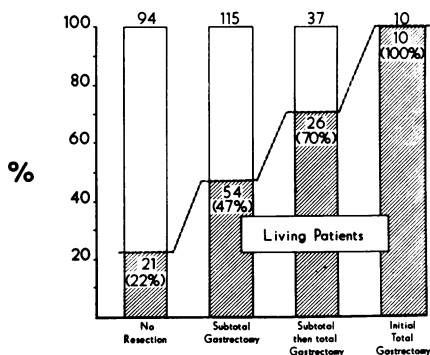
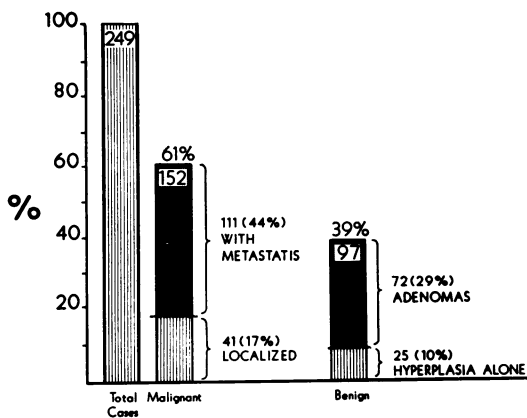


FIG. 11. The influence of sub-total and total gastrectomy on survival is summarized in this chart. 36 of the 47 patients with total gastrectomy are living and it is of interest that only a few of these have had nutritional problems as a result of the total removal of the stomach.

**BENIGN VS. MALIGNANT TUMORS**



● Diffuse microadenomas in 48 or 19%.

FIG. 12. Localized malignant tumors and identifiable and resectable adenomas occurred in 46 per cent of the patients. The association of microadenomata reduced this percentage to 38 per cent.

fluence of total gastrectomy (Fig. 11). Only one-fifth of the 94 patients with no resection of the stomach are surviving. Fifty-four or 47 per cent of 115 with sub-total gastrectomy are living. Twenty-six or 70 per cent of the 37 patients coming to total gastrectomy after subtotal resection are included as survivals and this percentage rises to 100 per cent for those ten patients who had a total gastrectomy as their first definitive ulcer procedure. It is important to remember that the survival was 86 per cent in 22 patients with resection of tumor plus total gastrectomy.

Acceptance of total gastrectomy as a means of controlling the gastric hyperacidity increased with each additional operation and included only four of 64 at the first abdominal procedure and 12 of 71 or 17 per cent at the second. Six of these had no prior definitive procedure for ulcer since the first operation was limited to closure of a perforation. Use of total gastrectomy remained approximately the same at the third operation but increased to 25 per cent at the fourth and to 52 per cent at the fifth procedure.

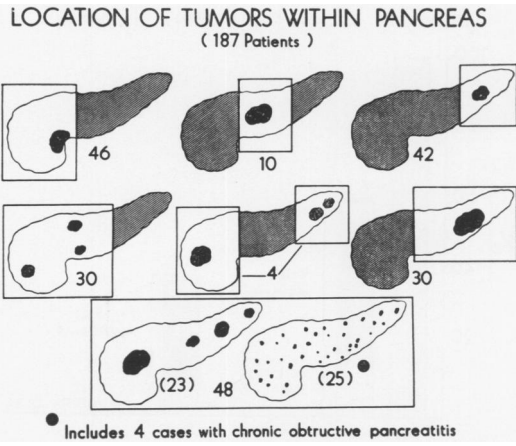


FIG. 13. The tumors either single or multiple involved two anatomical areas of the pancreas in 29 per cent and included the entire gland in 19 per cent. In the opinion of the authors, total pancreatectomy is never indicated when treating a Zollinger-Ellison syndrome. The chronic obstructive pancreatitis could be either primary or secondary in origin.

**Type and Location of Tumor**

As shown in Figure 12, three-fifths of the tumors were malignant and 44 per cent of the total patients had metastatic lesions when first diagnosed. Identifiable and resectable benign adenomas were seen in less than 30 per cent and diffuse hyperplasia or microadenomatosis alone was present in one out of ten patients. Actually, the over-all incidence of microadenomata is 19 per cent since it does occur along with benign or malignant adenomata. Here again this finding limits the value of hemipancreatectomy for both benign adenomata and localized malignant tumor.

Solitary lesions limited to one anatomical area of the gland occurred in only one-half of the patients and with a head-body-tail ratio of 4:1:4 (Fig. 13). The lesions were multiple and involved two anatomical areas in 29 per cent and included the entire gland in 19 per cent.

Eighty of the patients with malignant disease had positive lymph nodes. Sixteen of these were paraduodenal, 28 were pancreatic or buried in the substance of

the pancreas (Fig. 14). The super gastric lymph nodes were involved in three, the subpyloric nodes in 15, and the inferior gastrics in four. Lymph nodes were present in the hilus of the spleen in two instances and in the abdominal mesentery in seven. Removal of tumor containing lymph nodes along the gastric curvatures as part of a subtotal gastrectomy may account for the slightly increased protection when combined with tumor resection.

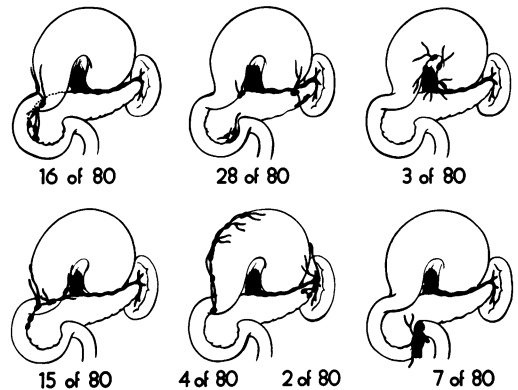
In addition to lymph node metastasis, 67 per cent of the tumors had spread locally and 48 per cent showed lesions in the liver. Only two of the 111 non-localized malignant tumors involved the lung.

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

**Methods of Absolute Diagnosis**

The methods of absolute diagnosis shown in Fig. 15 include biopsy of an abdominal

**LOCATION OF POSITIVE LYMPH NODES**  
( 56 of 80 patients )



● Location not known in 24 of 80 cases

FIG. 14. Common sites of lymph node metastasis. Resection of positive nodes along the curvatures of the stomach as part of a sub-total or total gastrectomy may account for some of the protective action of these procedures when combined with tumor resection.

mass in 40, excision biopsy of a pancreatic tumor in 41, removal of a duodenal lesion in nine, lymph node biopsy in 15, and hemipancreatectomy for palpable lesions in 46. The tissue diagnosis was made in 16 patients by means of a blind resection of the body and tail of the pancreas. In eight patients the primary lesion was aberrant and located in the stomach or in the duodenum and the diagnosis, therefore, was made postoperative. Ninety-three patients were not diagnosed until autopsy.

It is of interest that the percentage of correct diagnosis made at each of several consecutive operations showed no improvement until the 6th procedure and average about 50 per cent at each operation. For example, 21 of 53 patients were diagnosed correctly at the third operation and nine of 17 at the fifth.

### Summary and Conclusions

The ulcerogenic tumor of the pancreas has occurred in 12 children under 15 years of age and may be an important cause of ulcer in childhood. If so, it will be important to study the effect of total gastrectomy upon the growth of the child.

Although frequently the cause of fulminating ulcer disease, one out of four patients with the Zollinger-Ellison syndrome have been ill for five years or longer and one in ten for ten years.

Diarrhea is an important manifestation of the syndrome and may occur without ulceration.

Although the major cause of abnormally located primary peptic ulceration, 75 per cent of those studied were suffering from gastro-intestinal ulceration at the usual sites.

Associated endocrine disease has occurred in about one out of every five patients and although complicating the overall management, this finding can be helpful in suggesting the diagnosis.

### METHOD OF ABSOLUTE DIAGNOSIS

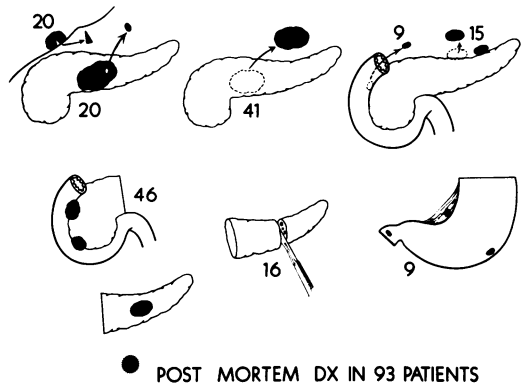


FIG. 15. Lymph node biopsy alone afforded a tissue diagnosis in 15 patients and multiple node biopsies should be employed more frequently when the syndrome is strongly suspected.

The Zollinger-Ellison syndrome per se is familial in some instances and has occurred in at least 12 families. Multiple endocrine adenomatosis accounts for only 3 per cent of the total patients studied.

Hypersecretion of acid gastric juice is common and histamine fails to stimulate further secretion in the majority of patients.

The end results following resection of tumor alone are not sufficiently good to justify recommendation of this form of treatment. Furthermore, sub-total gastrectomy does not give sufficient protection if there has been inadequate removal of tumor tissue.

The collected data indicates that total gastrectomy as the initial definitive ulcer procedure has given the best survival and if resection of tumor is feasible short of total pancreatectomy, then it should be combined with tumor resection. Total gastrectomy does not seem advisable without a definitive tissue diagnosis.

### Acknowledgments

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## DISCUSSION

DR. ROBERT M. ZOLLINGER (Columbus, Ohio): I wonder if Dr. Ellison reviewed the literature to prove to himself once again that there is really something to this syndrome? His review has tended to convince me that perhaps there are causes for ulcer outside the stomach.

He reviewed the literature about eight years ago and since that time has added another 250 cases. I think we can expect that if these ulcerogenic tumors arise from the alpha cells, they should occur at the same frequency as the reported Beta cell tumors. His report tends to prove this point.

Furthermore, at all times the literature shows that about 25 per cent are associated with other glands of internal secretion, and his fingers tend to substantiate this finding.

We have attempted on occasion to associate islet cell hyperplasia with the syndrome, but as we review the literature and our own slides with the pathologists, they point out there are so many causes for islet cell hyperplasia that we have come to drop this as a definite possibility.

I had hoped that Dr. Ellison might be able to ferret out a specific diagnostic sign. Personally, I believe that the only one that is pretty certain is the ulcer which occurs in the region of the ligament of Treitz, and once again, as Dr. Ellison pointed out, about 20 to 25 per cent do occur in that area.

We agree that the operation of choice is total gastrectomy, although in the original presentation Dr. Ellison did refer to a case we operated on in which we removed a solitary tumor in the tail of the pancreas and the patient survived for five years without recurrence.

You may be interested to know that one of the original patients who we presented before this Association in 1955 is still living. She has a Roux-en-Y type of pouch. Her weight is more than 140 pounds, and ten days ago she was delivered of her second daughter. We were hoping for a boy and had planned to name him Eddie-Robert.

We hope that further studies will make available early chemical identification of that unknown substance which has been talked about so much this morning—namely, gastrin. Several of my associates, namely, Drs. Elliott and Endahl, are pursuing these studies with considerable vigor.

DR. LESTER R. DRAGSTEDT (Gainesville, Florida): Dr. Ellison came to see me shortly after he had his first patient, and I was, of course, enormously interested, and especially so when Dr. Harry Oberhelman, one of my associates, discovered seven of these tumors among our vagotomy failures.

It took the clear eyes of Dr. Ellison and Dr. Zollinger to see the relation between the tumor and the hypersecretion. I simply attributed this hypersecretion that persisted after the vagotomy to our failure to get all of the vagus nerves.

I have given some thought to this problem in the intervening years and have become increasingly doubtful that these tumors are really of pancreatic islet origin. I believe rather that they develop from the cells that manufacture gastrin. It is true that the functioning gastrin-producing cells are located chiefly in the antrum of the stomach but it is not improbable that many may be widely scattered throughout the upper gastrointestinal tract. At all events, the physiological activity of a cell is a better criterion of its origin than is its anatomical appearance. These tumors secrete gastrin or a humoral agent very like gastrin in its physiological activity. The analogy with parathyroid adenomas that secrete the parathyroid hormone is a close one. The occurrence of these Zollinger-Ellison tumors in association with tumors of other endocrine glands such as the parathyroids, adrenal cortex, gonads, or hypophysis has been cited as evidence that they too are of endocrine origin, that is, that they arise from islet tissue. This concept arises because of the difficulty many have in appreciating the fact that the antrum of the stomach is an endocrine origin quite as much as the parathyroid glands or the pancreatic islets.