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Zollinger-Ellison syndrome : a review of the literature and report of suspected cases

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THE ZOLLINGER-ELLISON SYNDROME
A REVIEW OF THE LITERATURE AND REPORT OF A SUSPECTED CASE

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I. INTRODUCTION

The association between noninsulin-producing islet-cell adenomas, fulminating peptic ulceration, and gastric hypersecretion was first characterized as a syndrome by Zollinger and Ellison in 1955[1]. They originally reported two cases of jejunal ulceration with extremely high gastric acidity and islet cell adenomas of the pancreas, and added four collected cases from the literature. Eiseman and Maynard in 1955 first proposed the term "Zollinger-Ellison syndrome" because "prior case reports merely record the bizarre coincidental occurrence of the two conditions.[2]" In 1956 Ellison[3] presented an excellent analysis of 24 cases, including five new cases and 17 from the literature. Recently Zollinger and McPherson[4] mentioned a total of 48 cases, and since then there have been at least eight new cases reported,[5,6,7,8] making a total of approximately 56, the exact number of cases depending upon the criteria used for inclusion in the syndrome.

In this paper, a case is not accepted as Zollinger-Ellison syndrome unless there is reasonable evidence of: (1) moderate to severe ulcer diathesis, and (2) pancreatic islet-cell adenoma, non-insulin producing. Those excluded are considered separately.

Donaldson, vomEigen and Dwight[9] surveyed the literature in November, 1957, and found only 21 cases acceptable to them of the approximately 30 reported to that date. They were unable to accept five of Ellison's[3] cases, although they did not state their reasons for exclusion. These cases meet the criteria given above and are included in the following analysis. However, the two cases of Verner and Morrison[6] and the one of Priest and Alexander[10] are not acceptable as true Zollinger-Ellison syndrome, because there was no evidence of peptic ulceration; and case two of Waddell, et.al.[7], is not acceptable because of failure to demonstrate a pancreatic adenoma.

The pancreatic islet cells are derived from ductal epithelium, and perform the endocrine function of the gland. Cell types are designated as alpha, beta and delta; beta cells producing insulin and alpha cells producing glucagon, the "hypoglycemic-glycogenolytic factor."

The islet cell tumors of the Zollinger-Ellison syndrome are rarely insulin producing. The working explanation of the syndrome assumes that islet-cell tumors produce a substance responsible for the ulcer diathesis.

CASE REPORT

Interest in the Zollinger-Ellison syndrome stemmed from observation of the following patient while on the surgery service at Lincoln General Hospital.

Mrs. A.N., a 40-year-old, white female, first noticed intermittent "gnawing" pain in the epigastrium in February, 1955. During cholecystectomy in October, 1955, a "small area of inflammation" was discovered in the duodenum. A medical regimen was recommended post-operatively, but was only observed when distress was marked.

She was hospitalized at Lincoln General Hospital on December 4, 1958, with complaints of severe, persistent, epigastric distress of four days' duration, not relieved by antacids and milk. Systemic review revealed recent, mild constipation, "bloating," consumption of large quantities of aspirin for pain relief, but no diarrhea. The abdomen was tender to firm pressure in the left mid-epigastrium. A "superficially infiltrating, squamous-cell carcinoma of the cervix" had been treated with radium and x-ray in February, 1957, with no evidence of recurrence. Laboratory studies are reported in Table A.

The abdomen was opened on December 12, 1958. The entire duodenum was markedly dilated, thought due

to compression by the superior mesenteric vessels. There was an ulcer just distal to the pyloric ring. A hard, ovoid, lymph node, about eight millimeters in diameter was discovered in the mesentery of the jejunum in the region of the ligament of Treitz. A 75% subtotal gastric resection, Polya type, and bilateral oophorectomy were performed.

On section, the node was gray-white to tan in color and smooth in consistency and contour. Microscopic examination showed almost complete replacement by neoplastic tissue. The cytoplasm was faintly eosinophilic, and the nuclei moderately prominent. There were numerous, oval, calcific densities, resembling the Psammomal bodies seen in tumors of ovary and thyroid. Extension into the perinodal fat was noted. A diagnosis of low-grade, metastatic, adenocarcinoma of probable pancreatic islet-cell origin was made. The ovaries showed fibrous atrophy, with no evidence of carcinoma.

Post-operatively, the patient demonstrated a tachycardia of unexplained origin. On December 7, 1958, an electrocardiogram showed supraventricular tachycardia, but no other abnormalities. She was treated with digitalis and quinidine. The pulse rate returned to normal several days later. Gastric analysis on March 5, 1959,

showed no free acid with histamine stimulation.

Marked peptic ulceration was present, but pre-operative gastric analysis was not performed. A low-grade, metastatic carcinoma was found in a lymph node, which could have drained the pancreas. However, the origin of the primary lesion is unknown. The histopathology is consistent with islet-cell or carcinoid origin, except for the well-delineated, multiple, ovoid, calcific densities. No other case with these bodies has been reported.

Since the last admission, the patient has lost 18 pounds. Complaints are mild and consistent with a routine post-gastrectomy course. She was achlorhydric three months after operation. This is compatable with the Zollinger-Ellison syndrome, but is not the typical event. MacKenzie[5] reported a similar case, but gastrectomy was combined with vagotomy.

It is concluded that:

1. Sufficient evidence is not yet available to classify this case as Zollinger-Ellison syndrome, and that:
2. On the basis of histopathology and post-operative gastric analysis, it is tentatively not thought to be Zollinger-Ellison syndrome.

TABLE A
LABORATORY STUDIES - MRS. A.N.

	12/5/58	12/6/58	12/7/58	12/8/58	12/9/58	12/15/58	3/5/59
Hb. (gm)	14.6	G	16.4				
WBC (mm^3)	5,050	A S T R I C					
U.A.	Normal						
Serum sodium (mEq/l)		R E		142			
Potassium (mEq/l)		C T I		2.48	4.5		
Serum amylase		O N		32 units			
Phosphorus (mg%)					2.6	3.3	
Calcium (mg%)					8.5	8.8	
Alkaline phosphatase (Bodanski)					6.60	5.3	

Gastric analysis:	cc.	Free	Total
Fasting:			
Specimen 1	18	0	10
Specimen 2	15	0	6
Histamine			
Specimen 1	16	0	-
" 2	8	0	-
" 3	12	0	-

II. THE PATIENT

The sex distribution in reported cases has been about equal. Ages have ranged from 19 to 78, but it is rarely seen under 30. Onset usually occurs in the fourth and fifth decades. The interval from the onset of symptoms until the initial operation for ulcer has varied from months to thirty years, the average duration being about six years. The mortality rate is greater than 80 percent. Of those whose death is attributable to the syndrome, 75 percent were due to complications of peptic ulcer, whereas tumor was the cause of death in about 20 percent. Of the remaining, the cause of death is unknown or not attributable to the syndrome. The average life expectancy from the first demonstration of peptic ulcer has been sixteen months in those in whom islet cell tumors were not discovered until autopsy. The average duration of life in patients whose pancreatic tumors were resected during life was eight years. No psychological evaluation has been reported to determine whether these patients exhibit the "ulcer personality." This would seem to be of some importance if Waddell's[7] theory is correct (q.v.).

III. PEPTIC ULCERATION

The large majority of patients are first seen because of symptoms of peptic ulcer or one of its complications. The ulcer pain is frequently atypical. At the time of the initial operation or upper gastrointestinal examination by radiography, about 75 percent of cases show single ulcers, while 25 percent have multiple involvement. About one-half of the original ulcers are found in the first portion of the duodenum, a relatively low incidence compared with ulcers uncomplicated by adenomas. The remaining ulcers are widely distributed, sites including jejunum, esophagus, fundus, pre-pylorus, and the terminal two-thirds of the duodenum. Recurrent ulcers may be found at any of these locations, but most frequently are stomal, and may continue to appear as long as any acid-secreting cells remain.

Complications include those of typical peptic ulcer but are more severe and frequent. Gross and microscopic characteristics of the ulcer are not distinctive.

IV. GASTRIC SECRETORY STUDIES

Some mention of the nature of the gastric secretions has been reported in over half of the cases, (see table 1 for partial compilation). The 12-hour overnight volume ranged from 910 cc. to 3170 cc. in seven cases. Free HCl was 106 mEq/l and 136 mEq/l in two patients, while chloride varied from 136 to 160 mEq/l in two.

Waddell, et.al.[6], presented detailed laboratory studies on two patients, but due to absence of a pancreatic adenoma in case two, the results cannot be included here. In 16 patients without ulcer the volume of gastric secretions averaged 61 ml. per hour; the average pH was 2.26 and the average free HCl was 2.22 mEq/l. In 75 patients with duodenal ulcer (uncomplicated) the basal values were as follows: volume 95 ml. per hour, average pH 1.8, free HCl 4.3 mEq/l. In case one of their two the basal values were as follows: volume 467 ml per hour, average pH 0.99 and free HCl 49.2 mEq/l.

Their case one showed an increase in volume of secretions with peptone and histamine stimulation, as in the normal controls, but a decrease with insulin stimulation. The latter is a deviation from the normal, but only one patient was involved, and the authors do

not state clearly whether the test was repeated for confirmation. The same three stimulants were again administered during continuous nor-epinephrine infusion, and a reduction in volume was noted in each instance, but there was no control for this particular procedure. A curve was plotted as a function of neutral chloride production per hour and free acid per hour. The pitch of the resulting curve was found to be the same for both cases one and two and for control groups with and without ulcer. They concluded that the abnormality of gastric secretion was quantitative rather than qualitative. This does not satisfactorily explain the marked variation in chloride secretion.

TABLE 1
GASTRIC SECRETORY STUDIES

AUTHOR	VOLUME	FREE HCl	CHLORIDE	pH
Ellison[3] 24 cases	12-hour volume: 910 - 3170 cc. in 7 >1000 cc. in 6 of 7 >2000 cc. in 4 of 7	Total: 66-308 mEq. in 6 >100 in 4 of 6		
MacKenzie[5]				
Case I		Fasting-120 mEq/l Ewald - 136 mEq/l		
Case II	No report			
Donaldson[9]				
Case I	24-h volume: 3000-11,800 cc.	54-150 clinical units	136-160 (mEq/l)	
Waddell[7]				
Case I	467 ml/hr.	106 mEq/l (av)	141 (av)	0.99
Controls without ulcer	61 ml/hr.	29 mEq/l (av)	105 (av)	2.26
Controls with ulcer	96 ml/hr.	41 mEq/l (av)	108 (av)	1.8

. DIARRHEA

Diarrhea as a major component of the syndrome has received increasing attention in the literature. The first case, described in the original article by Zollinger and Ellison[1], presented with chief complaints of abdominal pain and diarrhea of eight years' duration, while severe, intermittent diarrhea was present in one of the four collected cases reviewed in the same article. In 1958, Verner and Morrison[6] collected seven cases from the literature with diarrhea as a major component and added two of their own. Of the nine cases, only four are acceptable under the above criteria, having recurrent ulcer and islet-cell adenoma. Of the remaining five cases, four are not included because of the absence of severe or recurrent peptic ulceration. Case number three does not seem to be at all like the syndrome, nor a sound modification thereof.

Since the above review was published, there have been several cases with diarrhea as a prominent symptom:

Thistlethwaite and Horwitz[8]: Case 1: Diarrhea of ten years' duration with ulcer and pancreatic adenomata.

MacKenzie, et.al.[5]: Case 1: Diarrhea, duodenal ulcer, islet cell carcinoma. Case 2: Three-year history of recurrent attacks of diarrhea, hyperchlorhydria, jejunal ulceration, and islet cell carcinoma.

Waddell, et.al.[7]: Case 1: Diarrhea of three years' duration, gastric hyperacidity, jejunal ulcers, islet cell carcinoma.

Donaldson, et.al.[9]: Case 1: Very similar to above, but 10 months' duration of diarrhea before admission.

The addition of these five cases makes a total of nine in which diarrhea was a major component of the syndrome. Although Verner and Morrison[6] indicate that death from renal failure is not an atypical clinical course, they include several cases having minimal or no ulceration. The nine cases above show a less malignant type of diarrhea, death being attributable directly to this mechanism in only Donaldson's[9] case, so far as is known.

The four cases listed below do not meet the criteria of the Zollinger-Ellison syndrome, but present similar characteristics: (1) All are associated with non-insulin producing islet-cell tumors, (2) Histologically they resemble the tumors seen in the syndrome, and (3) All

had severe diarrhea which was primarily responsible for morbidity and mortality. In three of the four cases, other endocrine abnormalities were found.

Verner and Morrison[6]: Case 1: Severe diarrhea, hypokalemia and renal failure with noninsulin-producing islet-cell adenoma and chromophobe adenoma of the anterior pituitary. Case 2: Severe diarrhea as above, islet cell adenoma without beta cell granules, minimal parathyroid hyperplasia.

Priest and Alexander[10]: Severe diarrhea as above, with gastric hypersecretion (presumed) but with non-recurrent, shallow ulcer on the lesser curvature.

Moldawer, et.al.[11]: Severe diarrhea as above with noninsulin-producing islet-cell tumor, parathyroid adenoma and thyroid adenoma.

If the above may be temporarily included in the syndrome, it will be seen that the severity of the diarrhea is inversely proportional to the severity of the ulcer. On one end of the spectrum a large group of cases is found having severe ulceration, but no diarrhea. In the mid-spectrum, a smaller group of cases is found with both ulcer and diarrhea. The third group, smallest

of the three, is characterized by severe diarrhea with minimal, if any ulcer diathesis. Verner and Morrison[6] advance the hypothesis that two different tumors of the islets may arise, one composed of alpha cells and the other of delta cells, each producing a different clinical course: In the former ulcer diathesis is more in evidence, while in the later diarrhea predominates. In the intermediate group ulceration usually appears after onset of diarrhea.

It has generally been postulated in the literature that the voluminous gastrointestinal secretions are responsible for the diarrhea, rather than their malabsorption. The potassium deficiency seen in the four cases above and in Donaldson's case is thought to be secondary to the prolonged diarrhea.

VI. PANCREATIC ADENOMAS

In the majority of cases multiple primary tumors or those with metastases are present. Multiple adenomas may occur simultaneously even when they are histologically benign[5]. In about 75 percent of cases the tumors are histologically malignant, and in 50 percent spread beyond the confines of the pancreas has been demonstrated. Metastases occur to liver, regional lymph nodes and duodenum most frequently and about equally, although several instances have been reported with diffuse peritoneal carcinomatosis. Clinically and microscopically the primary and metastatic tumors are usually of low-grade malignancy. The second case presented by MacKenzie, et.al.[5], had liver metastases which did not increase in number or appreciably in size over a 30 month period. Gross description of the adenomas and their metastatic secondaries is infrequently reported.

Frequent photomicrographs have accompanied case reports in the literature. In general the tumors are fairly well circumscribed with a thin, fibrous capsule. They are composed of trabeculae and solid clumps of cells with nuclei located in the basal portions. The cytoplasm tends to be faintly eosinophilic, finely granular and

abundant. There is fairly uniform agreement that beta cells occur infrequently, and when present, as a minority element. The presence of alpha cells is difficult to evaluate, since methods used for the differentiation of islet cells are frequently subject to unreliable results. The time between death and tissue fixation is critical. In several tumors reported in the literature a small proportion of cells have contained clusters of granules varying up to one micron in diameter which stained bright red with several specific stains. These were thought to be alpha cell granules. Although Priest and Alexander[10] report such findings, it is noted that the autopsy was performed 48 hours after death.

Although alpha cell granules have been reported in other cases[5,6,12], the tissue preparation may be subject to the same criticism. It is significant that Gomori, who had the opportunity to examine the tissue removed in Ellison's cases, found no specific granulations when using his own methods.

In an occasional case, the tissue has been analyzed for suspected compounds. In MacKenzie's case two, a metastatic specimen contained less than 0.1 unit of insulin per gram. "The normal non-diabetic pancreas,

extracted by the same methods yields 2.3 plus or minus 0.2 units per gram.[5]" In their case two, Thistlethwaite and Horwitz[8] reported a negative analysis for serotonin, insulin and glucagon.

Although diffuse calcification has been reported in a few instances[8], nothing resembling the ovoid calcific densities so prominate in the adenomatous lymph node removed from the patient reported in this paper has been previously mentioned.

VII. OTHER ENDOCRINE ADENOMAS ASSOCIATED WITH THE ZOLLINGER-ELLISON SYNDROME

Adenoma, carcinoma or hyperplasia in one or more endocrine glands other than the pancreas have been found in about one-fifth of the cases of the syndrome, as reported in table two, while in many of the remainder, a search for other endocrine involvement has not been made. Of the eight cases in table two, the pituitary was involved in six, the adrenal in five, the parathyroid in four, and the pancreas once, as a beta cell adenoma.

Peptic ulceration associated with endocrine abnormalities other than noninsulin-producing islet-cell tumors has been reported in the cases listed in table three. These are not acceptable cases of the Zollinger-Ellison syndrome. In this series, peptic ulcer was observed with pituitary involvement in eight of the nine cases, while clinical evidence of endocrine abnormality was seen in cases one through eight, manifest as hypoglycemia. Cases of hypoglycemia associated with peptic ulcer have been found only in patients with multiple endocrine abnormalities[9]. H. M. Rhoades[13] reviewed almost 400 patients with functioning islet-cell tumors and found no case of peptic ulcer with hyperinsulinism. In general, this indicates that beta-cell tumors of the pancreas cannot be linked with peptic ulcer.

TABLE II
CASES OF ZOLLINGER-ELLISON SYNDROME WITH
MULTIPLE ENDOCRINE INVOLVEMENT

AUTHOR	GLANDS INVOLVED			
	PITUITARY	PARATHYROID	ADRENAL	PANCREAS
Gerstel[14]	Acidophilic adenoma (Achromegaly)	Chief cell adenoma	Nodular adenomatosis	
Gordon & Olivetti[15]			Multiple adrenal cortical adenomas Diffuse cortical hyperplasia	
Underdahl, et.al.[16]	Chromophobe adenoma	Adenoma	Adenoma	
Ellison[3]	Basophilic adenoma			
Eiseman & Maynard[2]	"Evidence of tumor"	Adenoma Hyperparathyroidism		
Cunningham et.al.[17]			Cortical adenoma Medulary hyperplasia	Cystic beta cell adenoma
Wermer[18]	Mixed eosinophilic & chromophobe adenomas Achromegaly	Adenomatous hyperplasia	Cortical tumor	
Ellison[3] (Case 21)	Basophilic adenoma			

TABLE III
PEPTIC ULCERATION ASSOCIATED WITH ENDOCRINE
ABNORMALITIES OTHER THAN NONINSULIN
PRODUCING ISLET CELL TUMORS

AUTHOR	PITUITARY TUMOR	PARATHYROID	PANCREAS	ADRENAL	EVIDENCE OF FUNCTION
Underdahl, et. al.(16)					
Case 1	X-ray evidence	Adenomas	?	----	Hypoglycemia
Case 2	"Evidence of"	Adenomas	?	----	Hypoglycemia
Shelburne & McLaughlin(19)	Tumor	Adenoma	Islet cell adenoma	----	Hypoglycemia Hyperparathyroidism
Furbetta & Santucci(20)					
Case 1	X-ray evidence	----	?	----	Achromegaly & Hypoglycemia
Case 2	X-ray evidence	----	?	----	Achromegaly & Hypoglycemia
Cunningham, Hawe, & Evans (17)	----	----	Islet cell adenomas	Cortical adenomas Hyperplasia cortex & medulla	Hypoglycemia
Wermer (18)					
Case 1	X-ray evidence	?	?	----	Hypoglycemia & Hyperparathyroidism
Case 2	Mixed adenoma	----	Diffuse islet-cell adenomatosis	Cortical adenomas & hyperplasia	Hypoglycemia
Waddell,et.al.(7)	"Abnormality of"	----	----	Adenoma	----

VIII. THEORIES AS TO ETIOLOGY

Zollinger and Ellison originally hypothesized that the islet cell tumors secreta a substance responsible for the ulcer diathesis. Insulin cannot be indicted since no case of peptic ulcer associated with hypoglycemia has been reported except when multiple endocrine abnormalities were present.

Earlier experiments[21,22] led Poth and From[23] (1950) to suggest that alpha cell secretion of glucagon may play a part in the production of peptic ulcer. These investigators diverted the external pancreatic secretions from the duodenum by an external pancreatic fistula. Most of these animals developed severe ulceration. However, removal of the external secretions by total pancreactomy was seldom associated with the development of peptic ulceration. It was assumed that removal of the pancreas eliminated an ulcerogenic factor in the external secretions.

Hypoglycemia produced by commercial insulin on prolonged administration will produce typical peptic ulceration in animals. Since commercial insulin contains glucagon, it was thought that it might be an ulcerogenic factor. Zollinger and Ellison found in one of

their cases that the patient's serum contained a substance with a paper electrophoretic pattern identical to that of glucagon. They were unable to reduplicate this finding on the same patient or on any other. No other such finding has been reported until a recent case[8] in which a similar unconfirmed finding was reported. Eiseman and Maynard performed experiments on dogs by giving a continuous infusion of glucagon, which failed to demonstrate any effect on gastric secretion or motility.[2]

Several authors have suggested that humoral factors other thon those of the pancreas may be operational in the etiology of the syndrome, since multiple adenomas affecting several endocrine glands have been found in a large proportion of patients with the Zollinger-Ellison syndrome, and since ulcer diathesis has been associated with endocrine adenomas other than those of the pancreas.

It has recently been postulated by Thistlethwaite and Horwitz[8] that serotonin is the "ulcerogenic hormone." The histo-pathology of non-beta cell tumors of the pancreatic islets and of carcinoids have quite similar appearances in many instances. Thistlethwaite and Horwitz have suggested that some tumors thought to be of islet cell origin may be metastatic carcinoids. However, the administration of serotonin apparently inhibits,

rather than stimulates, gastric secretion.

Waddell, et.al[7], present the interesting hypothesis that hypothalamic disfunction might produce both abnormal autonomic activity leading to the production of peptic ulceration and multiple endocrine adenomas through its influence upon the pituitary.

Verner and Morrison[6] present the hypothesis that two different tumors of the islets may arise, one composed of alpha cells and the other of delta cells, each producing a different clinical course. In the former peptic ulcer predominates and in the later, diarrhea is more in evidence.

MacKenzie[5] (1958) questioned whether the islet cell tumor plays any part in the production of the peptic ulcer. A survey of the literature has not demonstrated a case in which total removal of the islet cell tumor has resulted in complete relief of ulcer symptoms, as the sole operative procedure.

IX. MANAGEMENT

Zollinger proposed radical treatment for this condition at present. In patients who fit the syndrome clincially, but in whom no tumors can be found at operation, he suggests total gastrectomy with resection of the body and tail of the pancreas. If a pancreatic tumor is found, he recommends excision with total gastrectomy. Although this may seem radical, there is a continuing recurrent, severe, peptic ulceration found in a large majority of those who have undergone subtotal gastrectomy.

MacKenzie recommends exploration of the pancreas in all cases in which the abdomen is opened for the treatment of peptic ulcer. He also recommends excision of any islet cell tumors if found. He advocates "fairly radical gastrectomy, possibly combined with vagotomy, in an effort to render the patient achlorhydiric," but thinks that total gastrectomy is too crippling to be used in the primary operation.

X. SUMMARY

The association between noninsulin-producing islet-cell adenomas, fulminating peptic ulceration, and gastric hypersecretion was first characterized as a syndrome by Zollinger and Ellison in 1955. To date, approximately 56 cases have been reported, depending on the criteria used for inclusion in the syndrome.

The sex distribution has been about equal, and onset usually occurs in the fourth and fifth decades. In the typical case, the peptic ulceration runs a fulminating and lethal course over a period averaging sixteen months. There is a high incidence of atypically located ulcers and recurrent ulcers. There has been a marked increase in both acidity and volume of gastric secretion in most of the cases subjected to gastric analysis.

In the majority of cases multiple primary tumors of the pancreas or those with metastases are present, the tumors exhibiting a low-grade malignancy both clinically and histologically. Specific granulations are infrequent and those reported are difficult to evaluate since methods used for the differentiation of islet cells are frequently subject to unreliable results.

Diarrhea as a major component of the syndrome has received increasing attention in the literature. Noninsulin

producing islet cell tumors have been reported with severe diarrhea, leading to hypolalemia and death due to renal failure, but other endocrine abnormalities were usually found. In these cases, the ulcer diathesis seems to be inversely proportional to the intesnity of the diarrhea. A large percentage of cases meeting the criteria for inclusion in the Zollinger-Ellison syndrome have had neoplastic involvement of other endocrine glands.

Peptic ulceration associated with endocrine abnormalities other than noninsulin-producing islet-cell tumors has been reported in a series listed above. Peptic ulcer is frequently associated with hyperparathyroidism and carcinoids of the gastrointestinal tract.

Zollinger and Ellison originally hypothesized that islet cell tumors secrete a substance reponsible for the ulcer diathesis. Several authors have suggested that humoral factors other than those of the pancreas may be operational in the etiology of the syndrome,since (1) multiple adenomas affecting several endocrine glands have been found in a large proportion of patients with the syndrome, and (2) since ulcer diathesis has been associated with endocrine adenomas other than those of the pancreas. MacKenzie has questioned any relationship between islet-cell tumor and peptic ulceration.

Management consists of resection of the pancreatic adenoma combined with either subtotal gastrectomy in

which a large percentage of stomach is removed, or total gastrectomy.

XI. CONCLUSIONS

1. A sever ulcer diathesis associated with endocrine neoplasia has been noted in a number of instances in the literature. The tumor found most frequently is noninsulin-producing islet-cell adenoma of the pancreas. More than one endocrine gland is often involved. Severe diarrhea has also been noted in association with endocrine neoplasia, most frequently with noninsulin-producing islet-cell adenoma.
2. There is experimental evidence that the secretions of the pancreas are in some way related to peptic ulceration.
3. To date no conclusive evidence has been offered to show that the pancreatic adenomas are capable of producing any hormone, ulcerogenic or not.
4. Positive identification of cell type in the non-beta cell adenomas has not been accomplished.
5. There is no evidence that insulin is involved.
6. There is no convlusive evidence to suggest that glucagon is produced by these adenomas. There is evidence to suggest that glucagon has no effect on gastric secretions and motility.

7. There is no experimental evidence to support the involvement of serotonin.

8. There is no experimental evidence that the hypothalamus is responsible for either ulcer or adenoma.

9. A case of sever peptic ulcer associated with metastatic adenocarcinoma is reported. It is concluded that:

    1. Sufficient evidence is not yet available to classify this case as Zollinger-Ellison syndrome, and
    2. On the basis of histopathology and post-operative gastric analysis, it is tentatively not thought to be Zollinger-Ellison Syndrome.

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