Ectopic Apudocarcinomas and Associated Endocrine Hyperplasias of the Foregut

STANLEY R. FRIESEN, M.D.,* JAMES E. McGUIGAN, M.D.†

Foregut endocrine polypeptide-secreting APUD cells (Amine-Precursor-Uptake and Decarboxylation), in their embryologic migration from neural crest to foregut may become "arrested" in the mesoderm or in other ectopic locations. They may become hyperplastic, adenomatous or malignant. Eight illustrative patients are reported. One patient had "pancreatic hyperparathyroidism" with hypercalcemic crises, pancreatic apudocarcinoma, normal parathyroids, biologically active parathormone, but inert immunochemically to the usual parathyroid antisera. Two had gastrin-secreting malignancies in the mesoderm. Remission after excision, but eventual recurrence of the syndrome due to islet cell hyperplasia required total gastrectomy. One patient had a gastric corpus apudocarcinoma found prospectively with hypergastrinemia which required excision of the tumor. One patient had acromegaly with hypergastrinemia and antral gastrinosis treated by pituitary irradiation, One patient had the antral or intermediary type of the Zollinger-Ellison syndrome with moderate hypergastrinemia, duodenal ulcer and antral gastrinosis, treated by vagotomy and antrectomy. One patient had hyperparathyroidism with antral gastrinosis, treated by parathyroidectomy. One patient had malignant Zollinger-Ellison syndrome and developed associated thyroid parafollicular cell hyperplasia and parathyroid chief cell hyperplasia, treated by total gastrectomy and multiple endocrine excisions. These investigative observations demonstrate ectopic loci and associated hyperplasias which support the concept of migration and bizarre potentiality of polypeptide-secreting cells of the foregut.

Presented at the Annual Meeting of the American Surgical Association, Quebec City, Quebec, May 7-9, 1975.

*Department of Surgery, University of Kansas Medical Center, Kansas City, Kansas 66103.

†Division of Gastroenterology, Department of Medicine, University of Florida College of Medicine, Gainesville, Florida 32610.

Supported in part by NIH Grants #RR828, AM13711, and CA15332, the Agustin Morales Fund, and American Cancer Society Grant #DT-17.

From the Division of Gastroenterology, Department of Medicine, University of Florida College of Medicine, Gainesville, Florida and the Department of Surgery, University of Kansas Medical Center, Kansas City, Kansas

THERE ARE ENDOCRINOPATHIES, particularly in the foregut region, in which the functioning tumor is situated in an unexpected, ectopic location;[11,17,21,28,29,40,41] there are also tumors which are situated entopically, as expected, but which appear to function ectopically, i.e. by the elaboration of humoral substances which would have been expected to arise from another location.[12,13,22,30,31,40,45,48] Such observations suggest that there may be several mechanisms of development of foregut endocrine syndromes. The prevailing concept in which normally situated endocrine cells spontaneously become adenomatous or malignant and autonomously secrete their humoral substance in excess is best exemplified by insulinomas which often present a relatively "pure" syndrome. However, aberrations from that general understanding are being described for insulinomas, which include observations of mesodermal insulin-containing tumors,[5,28] hyperinsulinism due to hyperplasia without tumor,[18,19,42,44] and clinical associations suggestive of other endocrinopathies.[24] In the instance of gastrinomas a greater variability of clinical pictures emerges which raises questions as to their genesis and development (Fig. 1).[10]

In order to understand the many aberrations and the ectopic phenomena which are sometimes seen in foregut endocrinopathies of all types, including pulmonary

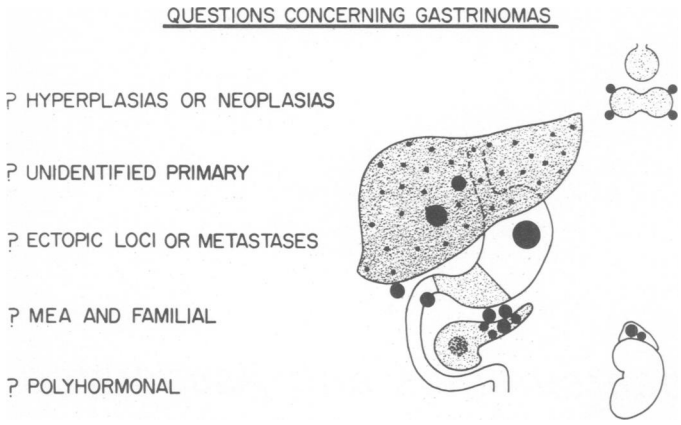

FIG. 1. Diagram illustrating aberrations in the clinical pictures observed in the Zollinger-Ellison syndrome. Questions concerning the genesis of gastrinomas are prompted by the occasional failures to identify a primary lesion in the pancreas or to differentiate metastases from ectopic loci, or hyperplasia from neoplasia, or islet cell from carcinoid tumors; also, in comparison with insulinomas, there is a higher incidence of malignancies, of metastases, of multiple endocrine involvement, of familial associations and polyhormonal elaborations. In addition, there are unique instances of inappropriate ectopic elaboration of gastrin from parathyroid adenoma and thyroid medullary carcinoma. There are also unexplained objective observations of tumor regressions, such as the disappearance of military-type metastases in the liver and lungs.

tumors which may "inappropriately" elaborate humoral substances,[30,48] it is relevant to review briefly the embryologic and cytochemical characteristics of the endocrine secretory cells. Pearse and others have demonstrated that most of the peptide-secreting endocrine cells of the foregut have common cytochemical characteristics in which the cells take up precursor amines and decarboxylate them to form polypeptides, hence the term APUD cells (Amine Precursor Uptake, Decarboxylation).[32] The APUD series of cells appears to be one of four groups generally termed neurolophomas which by definition have their origin in the neural crest.[33] Moreover, Polak and Pearse have demonstrated experimentally the migration of these fluorogenic APUD cells from their ectodermal neural crest origin through the mesoderm to the foregut entoderm[34] where normally these cells function in homeostasis with one another. It is conceivable that arrests of such migrations in embryologic development could result in ectopic mesodermal locations of endocrine cells and subsequent tumors. The ectopic elaboration of a hormone (from an unexpected site) conceivably could occur if there had been errant migrations of cells to inappropriate sites). Also, it has been suggested that the migrating cell, being a precursor cell, may have multipotentiality for humoral elaboration.[10,48]

Ectopia thus may be the result of errors in embryologic migration and secretory potentiality. The development of hyperplasia, and neoplasia of APUD cells may not be as simply stated. Conceptually, such cellular changes may be genetically instigated, as is evident in the familial multiple endocrine adenomatosis (MEA) syndromes,[49] or hyperplasia may occur as "neo-budding" of ductile cells into islet cells,[8] or as nesidioblastosis[47] resulting in a "domino phenomenon" of successive histologic and functional changes. On the other hand, as has been suggested within the concept of nesidioblastosis, cellular hyperplasia may occur also as a secondary manifestation in response to the environment of the cells. For instance, the hypoglycemia resulting from hyperinsulinism may stimulate glucagon release and a hyperplasia of glucagon-secreting cells. The antral gastrin cell hyperplasia associated with gastric acid hypersecretory states[15,43] may be a compensatory response to the chronic acid environment which inhibits gastrin release. Antithetically, the antral G-cell hyperplasia which has been reported to be associated with pernicious anemia,[4] could be explained as an adaptive response to an environment of chronic achlorhydria in which the G-cells may be chronically stimulated. In the acid hypersecretory states (exclusive of the Zollinger-Ellison syndrome) the serum gastrin levels are within the normal range,[27] while in achlorhydric states the gastrin concentrations in the serum are usually elevated;[14,26] in any case, the release of the peptide from the cells appears to be influenced by the environment of the cells, at least until the abnormal cells secrete their hormonal substance autonomously.

Whether endocrine cell hyperplasias are the result of genetic abnormalities or of compensatory, adaptive responses to their environment in the entero-insular axis, it is relevant to use suppression and stimulation tests to determine the autonomy of the secretory capacity of the cells[3] and to differentiate, if possible, between hyperplasia and neoplasia. Progressive changes in either direction from hyperplasia to adenomatous and malignant neoplasia have not been proven.

The purpose of this report is to document some observations derived prospectively in patients which exemplify ectopic and mesodermal loci of peptide-secreting APUD cell malignancies (4 patients) and to describe examples of associated hyperplasias of APUD cells in 8 patients. These observations support concepts of embryologic errors in development of the endocrine foregut during cell migration, as well as possible environmental instigation of endocrine cell hyperplasias.

Clinical Observations

The essential manifestations observed in 8 patients are summarized in Table 1. More detailed descriptions of the pertinent clinical and laboratory studies are presented in the text for each patient and the unique features of each case are discussed in the Comments. Cases 1 through 4 illustrate ectopic locations of endocrine malignancies and ectopic sources of polypeptide elaboration and all 8 cases

TABLE 1. *Ectopic Apudocarcinomas and Associated Hyperplasias of the Endocrine Foregut.*

Patient, Age	Tumor Site	Clinical Picture	Endocrine Manifestation	Exocrine Manifestation	Associated Hyperplasia	Treatment	Comments
R.W.,8	Pancreas-liver	"Hyperparathyroidism"	? Parathormone Gastrin	Hypercalcemia	Islets Antrum	Subtotal Pancreatectomy	Death
A.T.,66	Mesodermal (Paragastric)	Zollinger-Ellison Syndrome	Gastrin	Hyperacidity	Islets Antrum	1) Excision tumors Vagotomy & antrectomy 2) Total Gastrectomy Pancreas biopsy	Well
R.L.,47	Mesodermal (parapancreatic)	Diabetes Zollinger-Ellison Syndrome	Gastrin	Hyperacidity	Islets	1) Excision tumor 2) Distal pancreatectomy 3) Total gastrectomy	Well
B.McC.,74	Antral leiomyomata Gastric fundus Apudocarcinoma	Vomiting Melena	Gastrin	Achlorhydria	Antral Gastrinosis	1) Excision antral tumors 2) Excision fundal tumor	Well
H.C.,67	Pituitary	Acromegaly	Growth Hormone Gastrin	Achlorhydria	Antral Gastrinosis	Telecobalt pituitary Irradiation	Well
R.T.,38	None	Duodenal ulcer Zollinger-Ellison Syndrome (antral type)	Gastrin	Hyperacidity	Antral Gastrinosis	Vagotomy-antrectomy	Well
J.L.,46	Parathyroid Adenoma	Hyperparathyroidism	Parathormone	Hypercalcemia Hyperacidity	Antral Gastrinosis	Excision parathyroid Adenoma	Well
L.R.,36	Adrenocortical adenoma Pancreatic apudocarcinoma (metastatic)	Cushing's syndrome Zollinger-Ellison Syndrome	Cortisol Gastrin	Hyperacidity	Islets Parathyroid Parafollicular Adrenocortical	1) Adrenalectomy 2) Total gastrectomy 3) Hypophysectomy 4) Partial parathyroidectomy	Death

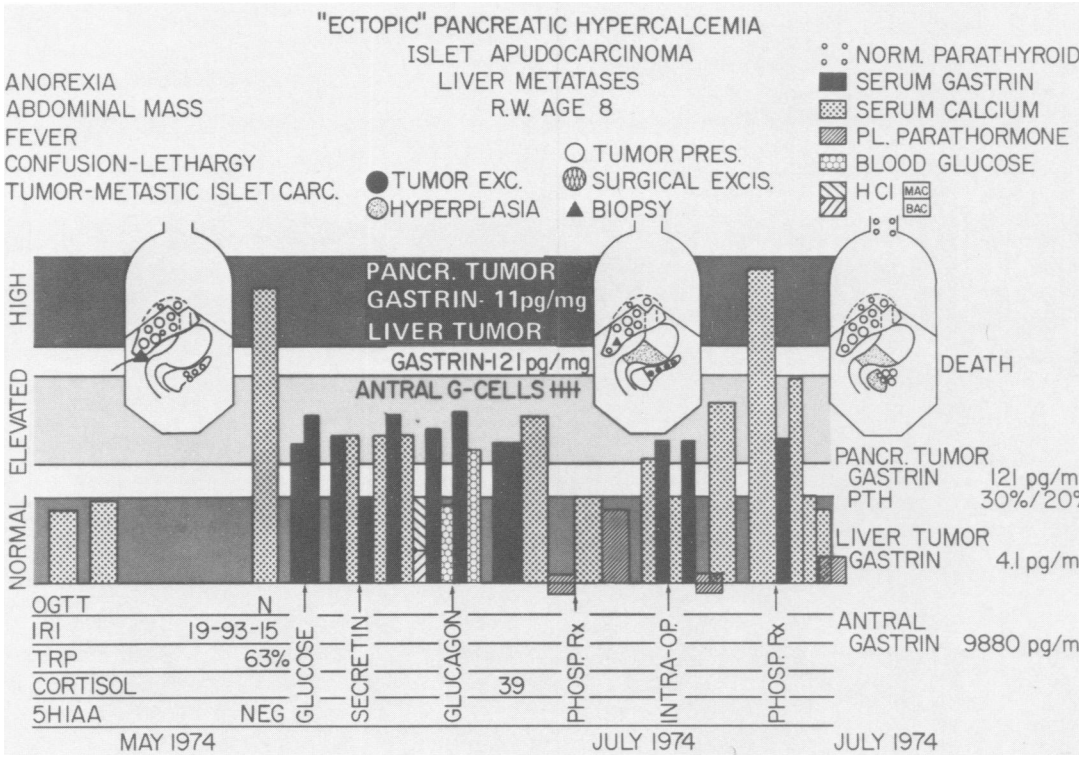

FIG. 2. Diagrammatic representation of the clinical course of patient R. W., in whom hypercalcemic crises appeared to be attributable to an ectopic source of parathormone-like activity in an apudocarcinoma of the pancreas, metastatic to the liver. The parathyroid glands were normal. The moderate elevations of serum gastrin are attributable to the antral G-cell hyperplasia.

illustrate unexpected endocrine hyperplasias which were present in association with known clinical syndromes.

Case 1. Diagnosis: "Pancreatic ectopic hyperparathyroidism"—apudocarcinoma of the pancreas with liver metastases; hypercalcemic crises associated with immunochemically inert, and suppressed levels of plasma parathormone; normal parathyroid glands, bones and kidneys; hypergastrinemia, without ulcer, associated with islet cell and antral G-cell hyperplasia.

Patient R.W. (Fig. 2) an eight-year-old boy, developed symptoms of anorexia, abdominal fullness and a low-grade fever. A palpable abdominal mass led to an exploratory operation at the patient's community hospital. A biopsy of a metastasis in the liver disclosed an islet cell carcinoma composed of APUD cells. He was transferred to the University of Kansas Medical Center where studies revealed serum calcium and phosphorus values of 14.4 and 2.9 mg%, respectively. These had been normal one week previously. Total proteins were 5.8 gm%, the total reabsorption of phosphate (TRP) ratio was 63%, and there were two determinations of undetectable levels of immunoassayable parathormone, using guinea pig antiserum to bovine parathyroid antigen. Radiologic survey of the skeletal system, as well as bone scan and bone marrow biopsy, revealed no evidence of lesions in the bones. X-rays of the chest, sella turcica, upper gastrointestinal tract and intravenous pyelography were normal; isotopic scans of the liver and pancreas were consistent with metastatic disease. A gastric analysis revealed a basal acid output (BAO) of 0.4 mEq/hr which rose to 5.3 mEq/hr on histalog stimulation; serum gastrin levels ranged between 400 and 600 pg/ml, irrespective of normal or elevated levels of serum calcium and without significant elevations when stimulated by oral glucose or intravenous secretion or glucagon. Blood glucose values were normal, with normal oral glucose tolerance. A glucagon provocative test (1 mg I.V.) produced normal peaked glucose and insulin responses. Plasma cortisol, blood serotonin levels and 5 hydroxy indole acetic acid (5HIAA) output in the urine were normal. After the hypercalcemia was corrected by means of phosphate enemas, the previously undetectable PTH, using guinea pig antibody to bovine PTH, assumed normal levels, at which time a distal subtotal pancreatectomy was done in an attempt to reduce the stimulus for hypercalcemia. Metastases in both lobes of the liver were confirmed. During operation, determinations of calcium, parathormone and gastrin levels in the venous blood from the pancreas and from the right atrium showed no significant differences in PTH or gastrin concentrations at the two loci before and after pancreatectomy. A slight but transient reduction in serum calcium occurred after resection. After 24 hours the serum calcium values gradually increased without a concomitant increase in serum gastrin values, but there was a decrease of PTH values to undetectable levels. On the fifth postoperative day, extreme weakness and obtundation associated with serum calcium values of 14 and 15 mg% necessitated treatment with phosphates with a response again to normal calcium values. The development of

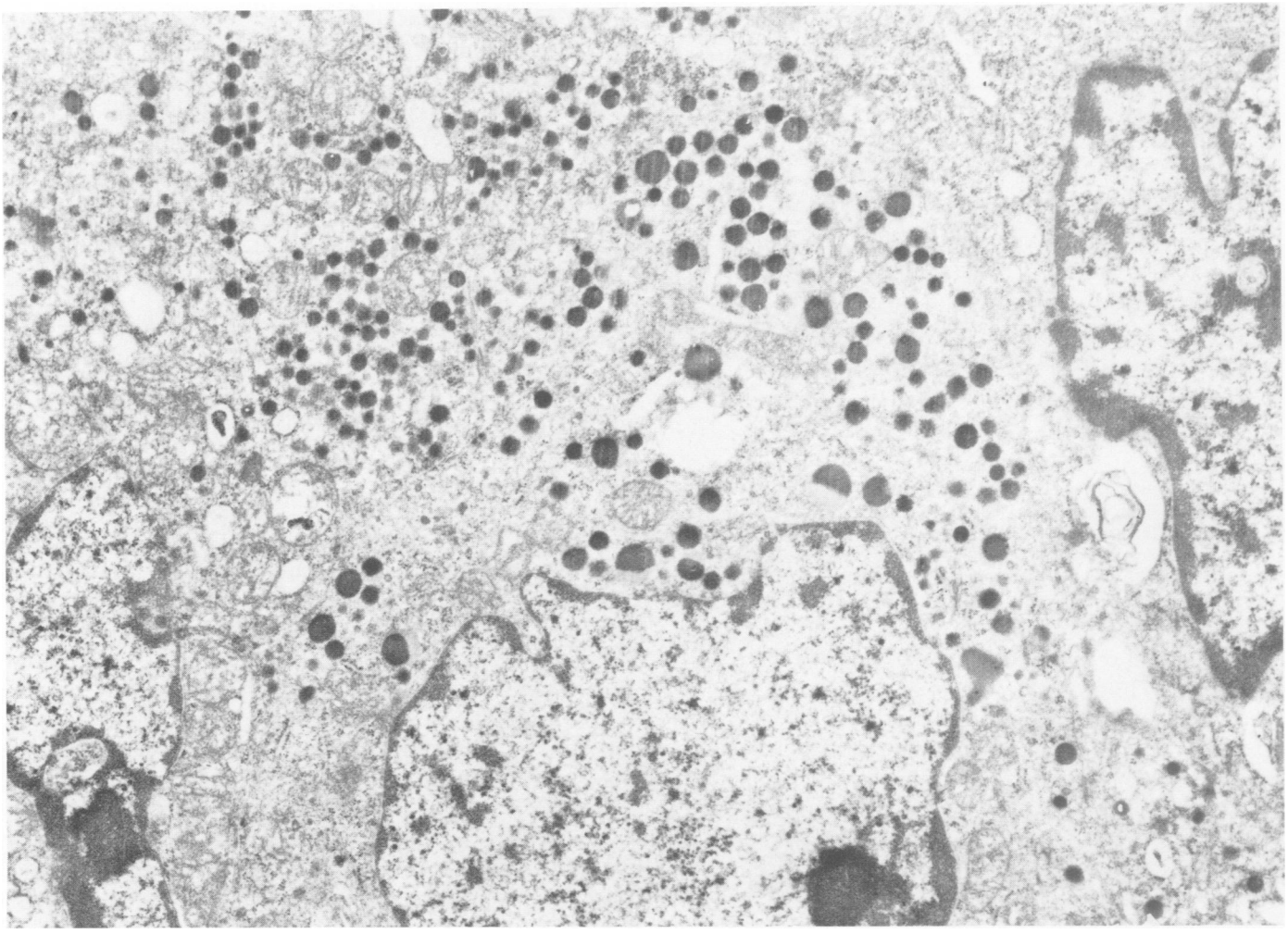

FIG. 3. Electronmicroscopic photomicrograph of portions of tumor cells from the malignant apudocarcinoma of the pancreatic islets from patient R. W. Numerous pleomorphic secretory granules are present in the cytoplasm which confirms the endocrine nature of the tumor. These granules are surrounded by a single limiting membrane and are moderately electron-dense. (Original magnification ×15,800.)

hypercalcemic nephropathy precluded the use of streptozotocin treatment. The patient developed marked ascites with ventilatory failure and died on the ninth postoperative day. At autopsy the remaining tumor was localized to the liver; the parathyroid glands were small and histologically normal; the pancreatic islets were hyperplastic; there was adrenocortical nodular hyperplasia and nephrocalcinosis; and the antral G-cells were hyperplastic (8 to 12 per acinus, the normal population is 0 to 2 cells per acinus).* Immunoassayable gastrin in the pancreatic tumor and hepatic tumor was no greater than in the hyperplastic pancreas (121 pg/mg) but the gastrin content of the antral mucosa was high (9,880 pg/mg). Immunochemical assay of the serum for PTH, during hypercalcemia, using another assay system, (guinea pig antiserum (GPI M) to porcine parathyroid antigen), yielded a just detectable value of 11 μlEq/ml of parathormone. Radioimmunoassay of the pancreatic tumor, extracted with acetic acid—acetone, using the same assay system, demonstrated nonspecific effects in the absence of antibody ("damage") with a 10% increment increase of free parathormone over bound parathormone. Immunofluorescent studies, using antiserum G.P. 012, did not demonstrate cellular localization of immunoreactive PTH in the tumor. These results are interpreted to indicate that the PTH molecule from ectopic sources may in some way be aberrant, such that it is not recognized by any of the antisera used in these studies. Electronmicroscopy of the pancreatic and hepatic tumor cells, however, revealed abundant secretory granules, confirming the endocrine nature of the tumor (Fig. 3). The granules are strikingly different from alpha, beta or delta cell granules of the islets of Langerhans. The

*Antral mucosal biopsy specimens were prepared for light microscopy by toluidine blue staining of glutaraldehyde-fixed, resin-imbedded sections. It is cautioned that the G-cell population estimations are gross counts of cells located specifically in the juncture of the middle and deep thirds of the antral mucosa, which have the morphologic appearance of G-cells (large, round, oval, "clear" cells with a large nucleus) and which can be further identified by immunofluorescence as gastrin cells. For more accurate quantitation, more specific preparations are advisable.[25]

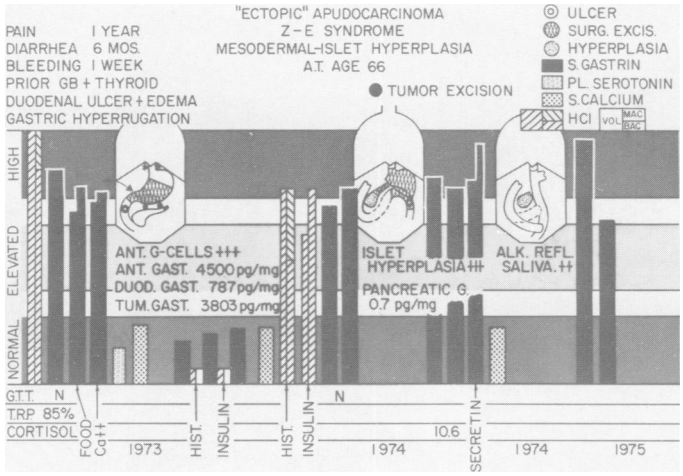

FIG. 4. Diagrammatic representation of the clinical course of patient A. T., in whom excision of two ectopic mesodermal gastrin-secreting "apudocarcinomas" plus antrectomy, only temporarily altered the course of the Zollinger-Ellison syndrome. The redevelopment of acid hypersecretion, hypergastrinemia and stomal ulceration secondary to islet cell hyperplasia required total gastrectomy. The elevated serum gastrin is decreasing.

possibility that this tumor may have arisen from a "fourth cell type" is likely.

Comment: The clinical findings in this patient suggest an ectopic locus for an unidentified parathormone-like substance from the apudocarcinoma of the pancreatic islets and the liver tumor. The hypercalcemia, hypophosphatemia and reduced tubular reabsorption of phosphate are consistent with other reported examples of ectopic elaboration of a PTH-like substance.[1,7,23,30,31,37,39] The identification of secretory granules in this case distinguishes this tumor from non-endocrine malignances with hypercalcemia (pseudohyperparathyroidism).[1,16] The immunochemical studies of the sera and tumor, and the immunofluorescent studies of the tumor indicate that the aberrant PTH-like molecule is of different antigenicity than the parathormones elaborated by parathyroid glands.[2,31] It is possible that the hypercalcemic agent is yet another substance, such as a prostaglandin.[38] It is less likely that the parathyroid glands are the source of the humoral substance because of their small, histologically normal appearance, and the lack of higher levels of plasma PTH in the jugular veins than in the pancreatic-portal veins. Furthermore, secondary parathyroid gland secretion of PTH which could be stimulated by glucagon elaboration from the tumor is unlikely in this patient because there was no fasting hyperglycemia, and there were normal glucose and insulin responses to both oral glucose and intravenous glucagon. It is interesting to note that the serum calcium and PTH levels in this patient correlated inversely, which suggests that the hypercalcemia suppressed the PTH elaboration from his own normal parathyroid glands. It is reasonable to assume that the moderate hypergastrinemia without ulcerogenic consequences may have resulted from antral G-cell hyperplasia, rather than as a consequence of pancreatic elaboration of gastrin. Endocrine screening of this patient's family has yielded a paternal grandfather with sellar enlargement consistent with a benign pituitary adenoma, and a father with gastric acid hypersecretion.

Case 2. Diagnosis: Two ectopic mesodermal malignant paragastric gastrinomas, antral G-cell hyperplasia; Zollinger-Ellison syndrome with remission after excision of the tumors and the antrum, but subsequent recurrence due to ulcerogenic islet cell hyperplasia which required total gastrectomy.

Patient A.T., (Fig. 4), a 66-year-old woman, related a one-year history of upper abdominal pain, initially relieved by food intake. She developed diarrhea 6 months prior to study and had two episodes of "tarry stools." An upper gastrointestinal x-ray series demonstrated a duodenal ulcer, duodenal spiculation and jejunal flocculation. A celiac angiogram demonstrated no tumor blush and liver scan was normal. Gastric acid secretory studies revealed a 12-hour overnight volume of 4510 ml; basal acid secretion was 370 mEq/12 hr. Repeat studies showed a basal acid output of 20 mEq/hr which on histalog stimulation increased to 38 mEq/hr, a ratio of 0.5. Serum gastrin determination by immunochemical assay was 2850 pg/ml; additional values ranged between 768 and 1200 pg/ml. Feeding and intravenous infusion of calcium (5 mg/Kg/hr) produced only a 10% increase in serum gastrin values. Serotonin and parathormone assays of plasma were within normal range. A 2-hour postprandial blood glucose was at the upper limit of normal (116 mg%), 5HIAA in the urine was qualitatively negative, and the TRP ratio was 85%. An antral mucosal biopsy at endoscopy revealed moderate hyperplasia of G-cells (2 to 5 G-cells per mucous acinus). With a diagnosis of Zollinger-Ellison syndrome, an operation revealed a duodenal ulcer, a grossly and microscopically normal-appearing pancreas, no tumor of the duodenum, no evidence of metastatic disease in lymph nodes or liver, and a thickened stomach without tumor; on close inspection, however, two soft nodules, approximately 6 x 15 mm each, were found in peritoneal planes of the lesser omental sac adjacent and posterior to the stomach (Fig. 5). Frozen and permanent sections of these excised nodules were reported as APUD cell tumors, having malignant endocrine characteristics consistent with islet cell tumors. There was a lack of argentophilia and no evidence of lymph nodal tissue. It was thought, based on prior experience, that excision of the two mesodermal "rests" might not control the hypergastrinemia and, because of the known antral G-cell hyperplasia, an antrectomy with vagotomy was added to the operative treatment. Postoperatively the acid secretory patterns revealed no acid basally, after either stimulation by histolog

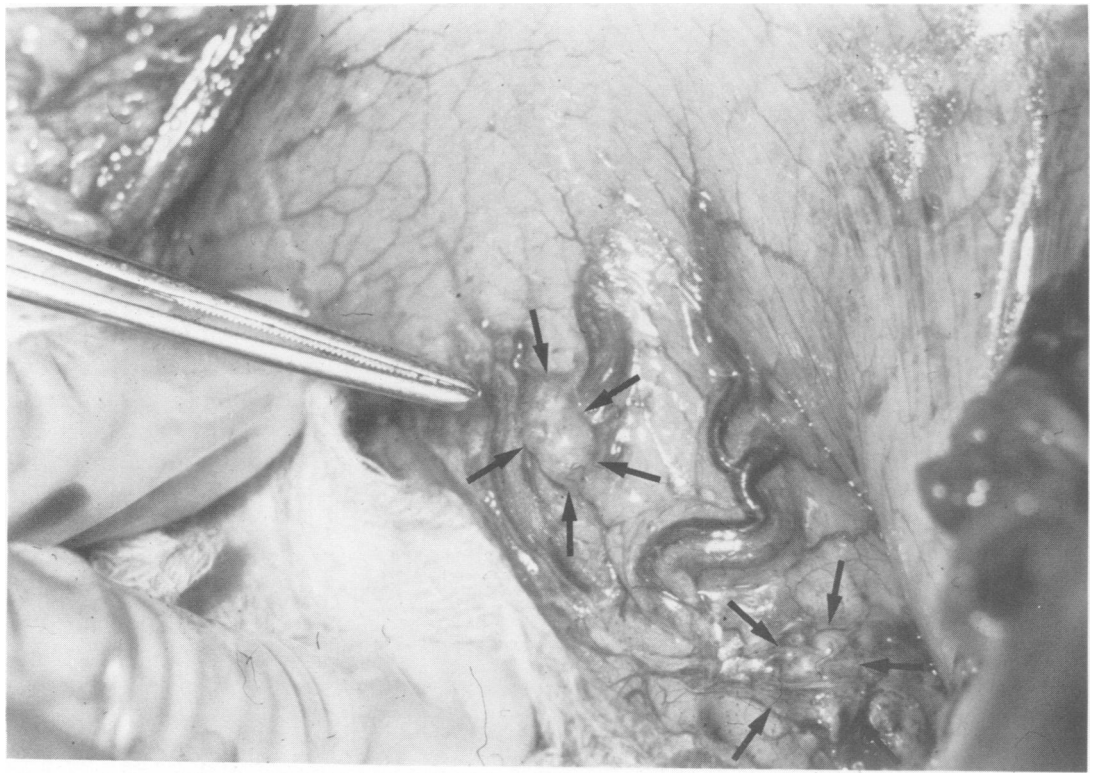

FIG. 5. Photograph taken during operative exploration of patient A. T., which illustrates two ectopic, mesodermal, retrogastric nodules (marked by arrows) in the lesser omental sac. These nodules, which were devoid of any lymph node characteristics histologically, contained gastrin (3800 pg/mg) by immunochemical assay.

or after insulin hypoglycemia. Serum gastrin values fell to 181, 209, and 253 pg/ml immediately. The mesodermal tumors contained gastrin (3800 pg/mg) comparable to that in the antral mucosa (4500 pg/mg) as determined by immunochemical assay. The patient was asymptomatic for a period of 4 months, after which she developed pain in the left upper abdomen which radiated to the back. She also described the onset of watery bowel movements. Upper gastrointestinal x-ray examination demonstrated two large stomal ulcers at the gastrojejunostomy. A 12-hour gastric volume now was 1600 ml, containing 126 mEq/12 hr. The ratio of the basal acid output to maximal acid output on histalog stimulation was 0.6. A Hollander test which produced an hypoglycemia of 35 mg%, stimulated acid secretion from 68 mEq/L basally to 118 mEq/L. The serum gastrin values were elevated to levels between 800 and 1000 pg/ml.

With a diagnosis of recurrent Zollinger-Ellison syndrome, thorough exploration at operation disclosed stomal ulceration but no further tumors or evidence of metastases. A distal (5 cm) amputation of the tail of the pancreas revealed an increase in the size and number of islets on frozen section. (Permanent sections revealed islet cell hyperplasia with evidence of nesidioblastosis.) Based on the clinical findings of stomal ulcer, recurrent acid hypersecretion, elevated serum gastrin values, and islet cell hyperplasia on frozen section, a total gastrectomy was done. The pancreas contained very little gastrin (0.7 pg/mg). The abdominal pain disappeared but the patient began to experience "heart burn," and "excessive" salivation (apparent but not quantitatively increased) and the serum gastrin two months postgastrectomy was over 1000 pg/ml, rising to 1400 pg/ml in three months and to 1900 pg/ml in five months. Mechanical dilatation of the esophagojejunostomy failed to relieve the "alkaline reflux and salivation." Secretin (96 Jorpes units I.V.) stimulation slightly elevated the serum gastrin levels (1962 pg/ml base to 2333 pg/ml at one hour) without alterations in calcium, glucose, immunoreactive insulin or human growth hormone levels. Surgical revision of the Roux en Y from a 14 inch to a 30 inch limb failed to effect relief of the patient's symptoms. At the present time, 9 months after total gastrectomy, the symptoms are spontaneously relenting and the serum gastrin content is decreasing (946 pg/ml). The submaxillary salivary glands have been prominent, but not enlarged.

Comment: This patient illustrates the Zollinger-Ellison syndrome which can be associated with ectopic mesodermal APUD cell tumors, containing gastrin by immunochemical assay. Temporary remission of symptoms, acid values, and serum gastrin values occurred after excision of these tumors, together with antrectomy and vagotomy (because of the associated antral G-cell hyperplasia). Recurrence of symptoms due to stomal ulceration after 4 months, with recrudescence of acid hypersecretion and increased serum gastrin values required total gastrectomy, at which time the only APUD cell abnormality which could be found was islet cell

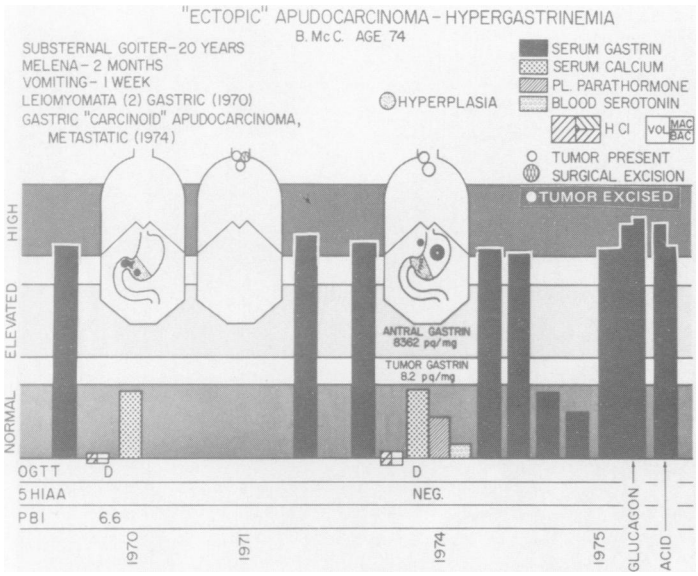

FIG. 6. Diagrammatic representation of the clinical course of patient B. McC., in whom a malignant, ectopic apudocarcinoma of the body of the stomach developed 4 years after excision of two leiomyomata of the antrum, during prospective studies of her hypergastrinemia, achlorhydria, antral gastrinosis and diabetes melitus.

hyperplasia. Protracted elevations of serum gastrin levels with symptoms of reflux and salivation call to mind a report of salivary gland and duodenal Brunner's gland hyperplasia in a Zollinger-Ellison patient.[20] It remains to be seen whether further difficulties relative to her islet cell hyperplasia or other potential tumors will occur in the future.

Case 3. Diagnosis: Ectopic mesodermal malignant parapancreatic gastrinoma, with persistence of the Zollinger-Ellison syndrome after excision of the tumor and the distal pancreas; associated ulcerogenic islet cell hyperplasia which eventually required total gastrectomy; amelioration of the diabetes mellitus. (This case has been reported in part previously[12] but is included here to illustrate the mesodermal nature of the tumor, a fact not fully appreciated, except in retrospective study.)

R. L., a 47-year-old man with longstanding diabetes mellitus, was operated upon for an umbilical hernia, during which operation a mass anterior to the pancreas was palpated and removed. The parapancreatic tumor proved to be malignant histologically. A subsequent distal pancreatectomy and a second-look procedure failed to demonstrate persistent neoplasia (only islet cell hyperplasia was found); these procedures did not alleviate the progressive nature of the ulcerogenic syndrome. A total gastrectomy eliminated the syndrome and significantly reduced the patient's insulin requirements. At the present time, 8 years after total gastrectomy, the patient is clinically well with normal serum gastrin values but is requiring insulin treatment again. There is intolerance to oral glucose; also there is a relatively flat response of glucose levels to exogenous glucagon (1 mg I.V.) (glucose levels rising from 312 mg% to 339 mg% in 15 minutes). Levels of immunoreactive insulin have been unmeasurable because of the excessively high circulating insulin antibodies. Assays for glucagon have not been done. At the present time the determinations of calcium, parathormone, serotonin, human growth hormone are normal, as are serum gastrin values.

Comment: Upon review of the operative findings and of the histology of the parapancreatic islet cell carcinoma, it is apparent now that the tumor was not situated in pancreatic or lymph node tissues; for these reasons an ectopic mesodermal locus is ascribed to it. The associated islet hyperplasia proved to be progressively ulcerogenic. It is interesting to note that one of the two patients in the original report of the syndrome by Zollinger and Ellison demonstrated two nodules, one "islet cell tumor on the surface of the pancreas, with metastases in an adjacent lymph node."[50] The development of

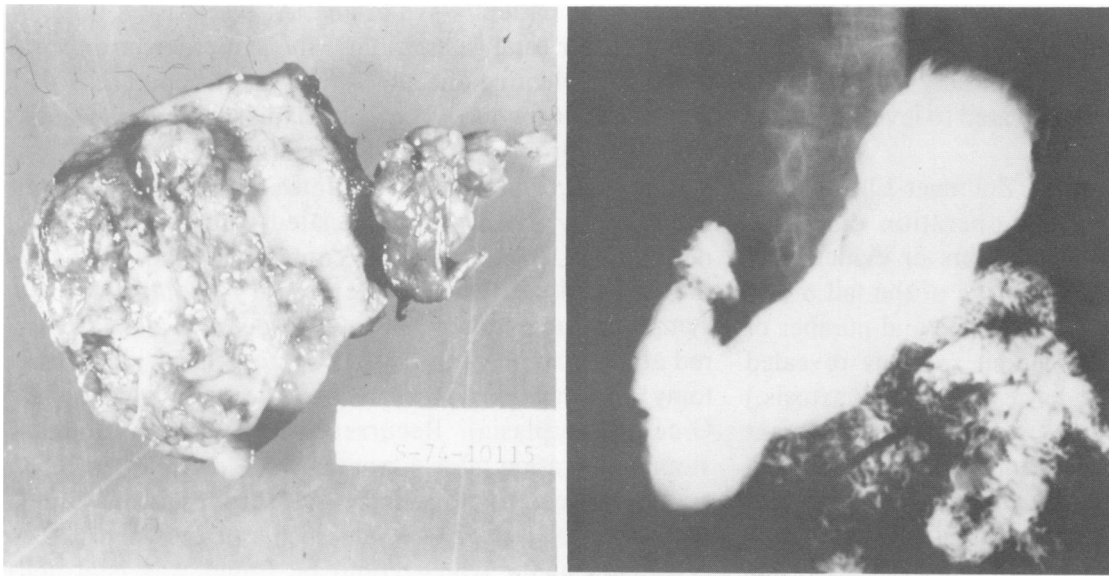

FIG. 7. Photograph (left) of the ulcerating apudocarcinoma and lymph node metastases which were removed from the gastric corpus in patient B. McC. The ectopic location high on the lesser curvature is seen on the x-ray on the right.

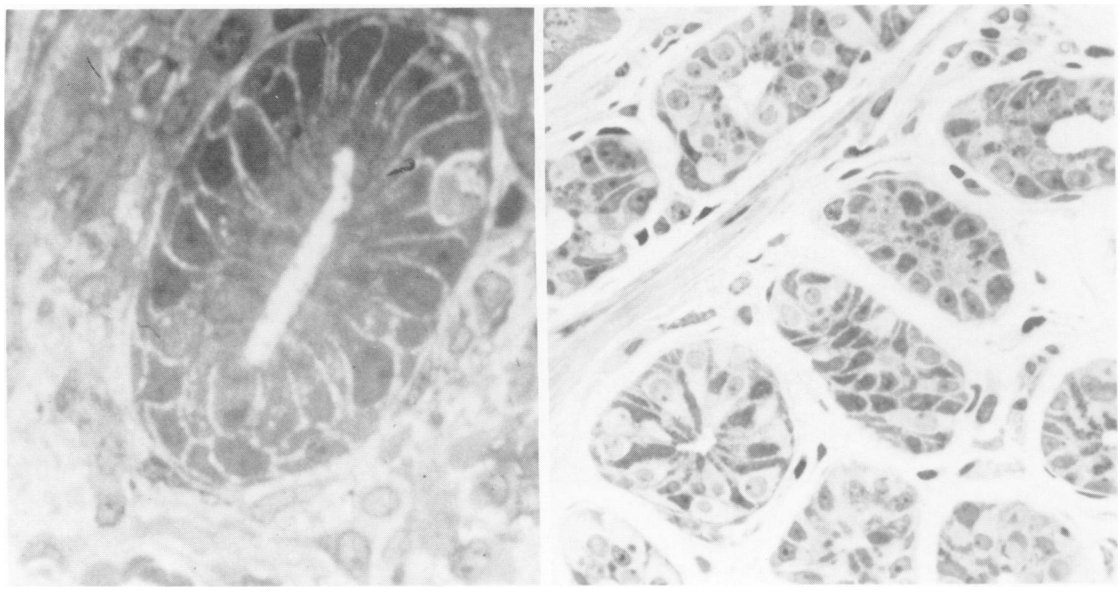

FIG. 8. Photomicrographs illustrating, on the right the increased antral G-cell population (8-12/acinus) (clear, round, oval cells) in patient H. C., as compared to the normal (0-2 cells/acinus) picture seen on the left. The antral G-cell hyperplasia in this patient is associated with achlorhydria, without anemia, hypergastrinemia, and acromegaly. (Original magnification ×480 and ×440.)

the syndrome in R. L., superimposed on diabetes mellitus with amelioration of the insulin requirements after total gastrectomy, and the more recent return to a diabetic picture, only mildly responsive to exogenous glucagon, all suggest that environmental influences may affect polypeptide homeostasis within the entero-insular axis.[46]

Case 4. Diagnosis: Ectopic apudocarcinoma located in the body of the stomach which was found prospectively in a patient with hypergastrinemia, antral gastrinosis, achlorhydria without anemia, and diabetes mellitus.

B. McC., (Fig. 6), a 74-year-old woman with diabetes mellitus, gave a history of a "goiter" which had been present for 20 years. Two months prior to her first hospital admission there was an episode of melena and vomiting of one week's duration. Appropriate studies demonstrated pedunculated tumors of the antrum with prolapse into the duodenal lumen, achlorhydria to histamine, and cholecystolithiasis; an excision of two leiomyomata of the antrum, a cholecystectomy and an incidental appendectomy were performed in 1970 without sequellae. A serum gastrin determination obtained during that hospitalization was reported as 1110 pg/ml; this was confirmed on several occasions and was considered to be compatible with histamine-fast achlorhydria. In 1971 a partial thyroidectomy for colloid goiter was done in a hospital in her community. In 1974 the patient complained of chest pain, belching and vomiting of one week's duration. Upper gastrointestinal x-rays demonstrated a large ulcer crater located high on the posterior wall of the stomach, having the appearance of malignancy (Fig. 7). There was continued achlorhydria to histalog stimulation; serum gastrin determinations ranged from 1103 to 1292 pg/ml. Other laboratory determinations were within normal limits, including a blood serotonin level. At operation a large, localized, ulcerated apudocarcinoma having some cytologic characteristics of a carcinoid tumor, with lymph node metastases, was excised; the liver appeared normal. The tumor contained a very small amount of gastrin by immunochemical assay (8.2 and 10.4 pg/mg); the antral mucosa, however, contained 8360 pg/mg. There was hyperplasia of the G-cells in the antrum (6 to 10/acinus); no gastrin cells and very few parietal cells were discernible histologically in the mucosa of the body of the stomach. By 15 days after operation the serum gastrin level decreased to normal levels of 68 and 125 pg/ml. Re-evaluation 3 months later disclosed that the serum gastrin levels were again elevated to levels of 1008 to 2386 pg/ml: there was persistent achlorhydria and the G-cell population of the antral mucosa was still increased. Intragastric administration of 0.1 N hydrochloric acid (pH=1.6) over a period of 60 minutes (120 drops/min) produced a slight decrease in serum gastrin levels from 2341 to 1752 pg/ml over 75 minutes. An isotopic scan of the liver was compatible with a diagnosis of hepatic metastases; a needle biopsy did not confirm that diagnosis. The patient is being prospectively observed.

Comment: It seems reasonable to assume that the ectopic APUD cell malignancy of the body of the stomach is related in some unknown way to the hypergastrinemia, achlorhydria and antral G-cell hyperplasia, each of which apparently preceded the development of the metastasizing tumor. Although gastrin-containing tumors of the stomach have been reported previously,[17,21,41] the development of one in the non-antral portion of the stomach while under observation of hypergastrinemia has not been described previously. The failure of intra-gastric acidification to significantly suppress serum gastrin levels suggests that the probable metastatic apudocarcinoma in the liver autonomously releases gastrin and that the re-

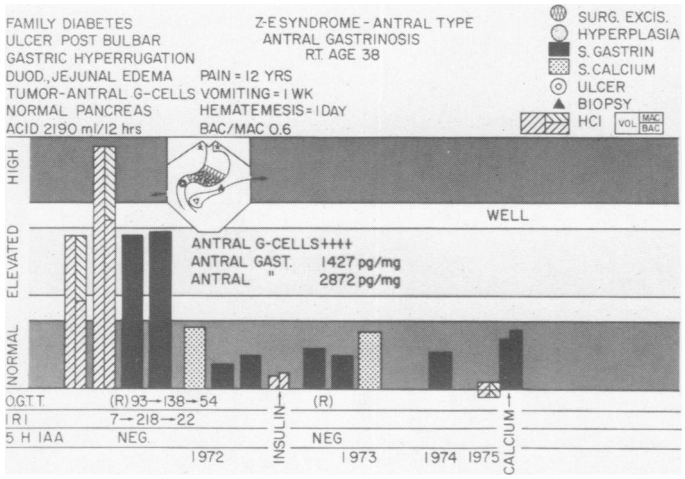

FIG 9. Diagrammatic representation of the clinical course of patient R. T. in whom the clinical findings suggested the diagnosis of the Zollinger-Ellison syndrome. The moderate elevation of the serum gastrin (400-1000 pg/ml), however, was attributable to antral G-cell hyperplasia without other APUD cell abnormalities. An antrectomy with vagotomy promptly reversed the antral or intermediary type of the "Zollinger-Ellison" syndrome.

current hypergastrinemia is not secondary to antral release of gastrin.

Case 5. Diagnosis: Pituitary acromegaly, elevated human growth hormone levels with associated antral G-cell hyperplasia, hypergastrinemia, and histamine-fast achlorhydria, treated by telecobalt irradiation of the pituitary.

H. C., a 67-year-old woman, first noted enlarging hands and feet 15 years prior to these studies; for one year she had also noted abdominal cramping pains, occasional melena, fatigue and polyuria with polydipsia. Physical examination demonstrated prognathism, macroglossia, prominant orbits and frontal bossing, enlarged hands and feet, and moderate hypertension (180/100 mm Hg). Human growth hormone values were elevated 28 to 49 ng/ml during an oral glucose tolerance test with diabetic glucose intolerance and persistently moderately elevated levels of serum gastrin between 400 and 500 pg/ml. Gastric aspiration yielded 215 ml in 12 hours with a pH of 7.1 and an achlorhydria refractory to histalog stimulation. The level of vitamin B_{12} in the blood was normal (546 pg/ml) and serum parietal cell antibodies were present. The patient was treated by telecobalt irradiation (4608 r/3 weeks). In 6 months, during re-evaluation, there was symptomatic improvement and diminution of growth hormone levels to 18 ng/ml. At 9 months following treatment the growth hormone levels returned to their high levels and the serum gastrin values increased to 1104 pg/ml fasting, with no increased response to intravenous exogenous glucagon (1 mg). There were normal, peaked glucose and insulin responses to glucagon. The patient was still achlorhydric without anemia and the G-cell population of the antral mucosa was increased, (8 to 12/acinus), indicative of G-cell hyperplasia (Fig. 8).

Comment: This patient illustrates a combination of findings which are probably interrelated, though a cause and effect relationship is not evident at this time. Acromegaly, antral gastrinosis and hypergastrinemia in this patient are associated with gastric achlorhydria, rather than with acid hypersecretion, as has been reported previously.[4,43] Hypergastrinemia has been reported in association with achlorhydria with and without pernicious anemia and has been shown to decrease significantly during intragastric administration of 0.1 N hydrochloric acid.[14] The increased levels of serum gastrin after irradiation therapy to the pituitary gland in this patient have not been explained, but may be related to the G-cell hyperplasia in the antral mucosa.

Case 6. Diagnosis: Duodenal ulcer, postbulbar, Zollinger-Ellison syndrome (antral type); gastric hyperacidity; moderate hypergastrinemia associated with antral gastrinosis and normal pancreatic islets, treated satisfactorily by antrectomy and vagotomy.

R. T. (Fig. 9), a 38-year-old man, presented a history of abdominal pain of 12 years' duration with radiologically documented duodenal ulcer for 10 years. Increasing severity of the ulcer pain culminated in vomiting and hematemesis in spite of regulated out-patient medical management. X-ray examinations demonstrated, in addition to a post-bulbar ulceration, prominant duodenal folds, gastric hyperrugation, jejunal edema and a non-visualized gall bladder after double dosage. Endoscopy confirmed the ulceration. Gastric analysis demonstrated an overnight 12-hour volume of 2190 ml with an increase in basal acid output from 15 mEq/hr to 43 mEq/hr after histalog stimulation. The serum gastrin concentration was 558 pg/ml. The G-cell population of the antral mucosa was hyperplastic (10 to 12 G-cells/acinus). Calcium levels were normal. An oral glucose tolerance test showed only mild glucose intolerance but there was a marked insulin response to the hyperglycemia (from 7 to 218 μU/ml when the blood sugar was 238 mg%). At operation no islet cell abnormalities could be found histologically in the biopsies of the tail and head of the pancreas, or in adjacent lymph nodes or the duodenum. Accordingly, truncal vagotomy and antrectomy were done. There was an immediate resolution of the elevated serum gastrin levels to 126 pg/ml after vagotomy and to 67 pg/ml after antrectomy. During operation, but prior to vagotomy and antrectomy, a bicarbonate solution was instilled intragastrically (200 ml at pH 8.0) with little change in serum gastrin levels (from 430 to 480 pg/ml); the antral mucosal gastrin content decreased from 1427 to 1021 pg/ml. Postoperatively the insulin gastric analysis demonstrated no increase in a basal gastric acid concentration of 11 mEq/L during hypoglycemia of 27 mg%. A

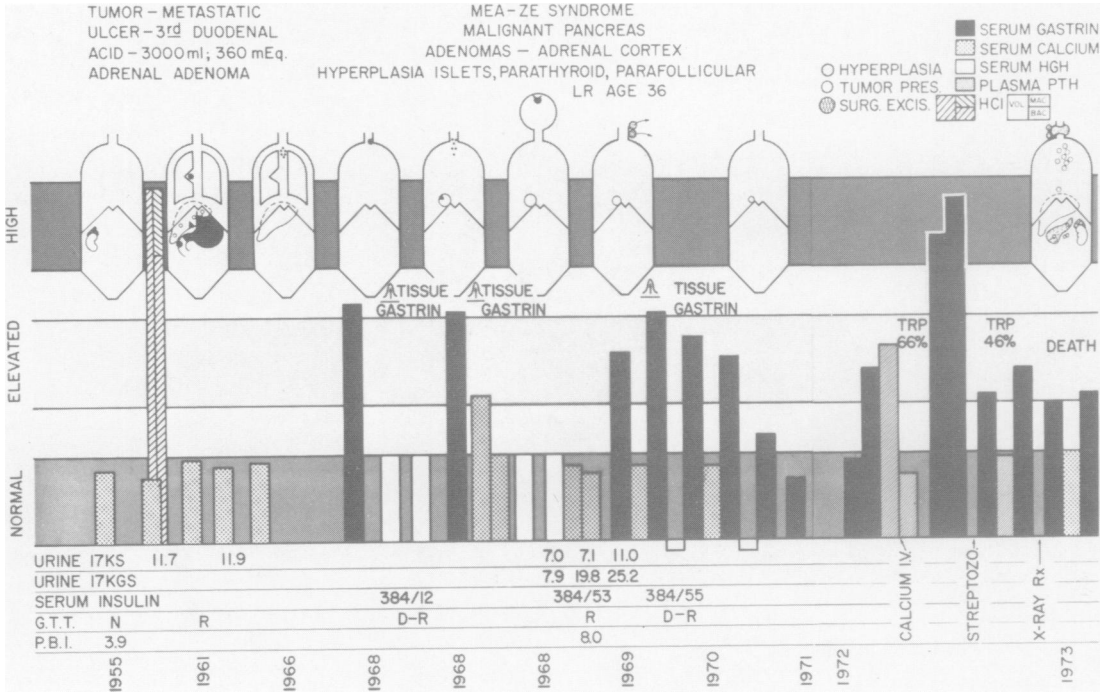

FIG. 10. Diagrammatic representation of the clinical course of patient L.R. in whom multiple endocrine adenomatosis ranged from APUD cell hyperplasias to benign and malignant APUD cell neoplasias. There were two significant periods of ulcerogenic tumor regression (7 years after total gastrectomy, and 5 years after hypophysectomy). Death 18 years after right adrenalectomy was relatively precipitous and was associated with cellular hyperplasia of the two remaining parathyroid glands, the thyroid parafollicular cells, the opposite adrenal cortex, and the pancreatic islets.

three-year follow-up revealed normal fasting gastrin levels in the serum, with a response from 95 to 209 pg/ml on induced hypercalcemia. There was basal gastric achlorhydria with no acid response to insulin hypoglycemia or histalog administration, and there was no evidence of recurrent ulcer nor endocrinopathies.

Comment: The clinical and radiologic findings which are strongly suggestive of the Zollinger-Ellison syndrome, but which are accompanied by only moderate elevations of serum gastrin levels (400 to 1000 pg/ml) deserve careful scrutiny. If, as shown in this patient, there is antral G-cell hyperplasia, without pancreatic islet cell or duodenal mucosal abnormalities, an antrectomy with vagotomy should suffice as adequate treatment and should be clearly confirmed by observing the reduced gastric acid secretion in the postoperative course. Polak et al. have described a Zollinger-Ellison syndrome, type I, with antral gastrinoma,[35] as being differentiated from the original type described by Zollinger and Ellison based primarily on an antral rather than a pancreatic source of gastrin elaboration. It has also been postulated that the antral variety described here may represent a transitional stage or intermediate type between the duodenal ulcer diathesis and the classical pancreatic islet cell ulcerogenic syndrome.[13] A "borderline ulcerogenic tumor syndrome" has also been described by Zollinger which has not been attributed to antral dysfunction.[51] It is possible that other gastrin cell tumors of the antrum reported previously probably represent a further stage of evolution from hyperplasia to neoplasia.

Case 7. Diagnosis: Non-familial parathyroid adenoma with hyperparathyroidism associated with antral gastrinosis, gastric hyperacidity and normal levels of serum gastrin.

J. L., a 46-year-old man, complained of fatigue and sexual impotence for one year. Physical examination was normal except for hypertension (160/105). Serum calcium values ranged between 11.6 and 12.5 mg% and serum phosphorus values ranged between 1.3 and 2.3 mg%. Plasma parathormone levels were repeatedly elevated with higher levels in the left jugular venous samples than in the right (left 460 ng/ml; right 280 ng/ml). TRP ratios were 52, 36, and 50%. There was gastric acid hypersecretion (13 mEq/hr basally and 26 mEq/hr after histalog stimulation); the G-cell population of the antral mucosa was markedly increased (10 to 12 G-cells/acinus). Basal serum gastrin values (56 to 85 pg/ml) were not significantly altered in response to feeding or administration of glucose, arginine or insulin. Other studies revealed mild glucose intolerance, a Type IV hyperlipoproteinemia, and normal thyroid and adrenocortical parameters. Radiologic examinations of the chest, sella, hands, kidneys, gallbladder were normal; upper gastrointestinal radiologic examination demonstrated a thickened wall in the second portion of the duodenum without ulceration.

A left parathyroid adenoma and a right normal parathyroid gland were surgically removed, following which serum calcium and phosphorus levels and TRP ratios returned to within normal ranges. The plasma parathromone determinations indicated undetectable values immediately postoperatively and have remained so. Three years following parathyroidectomy gastric acid

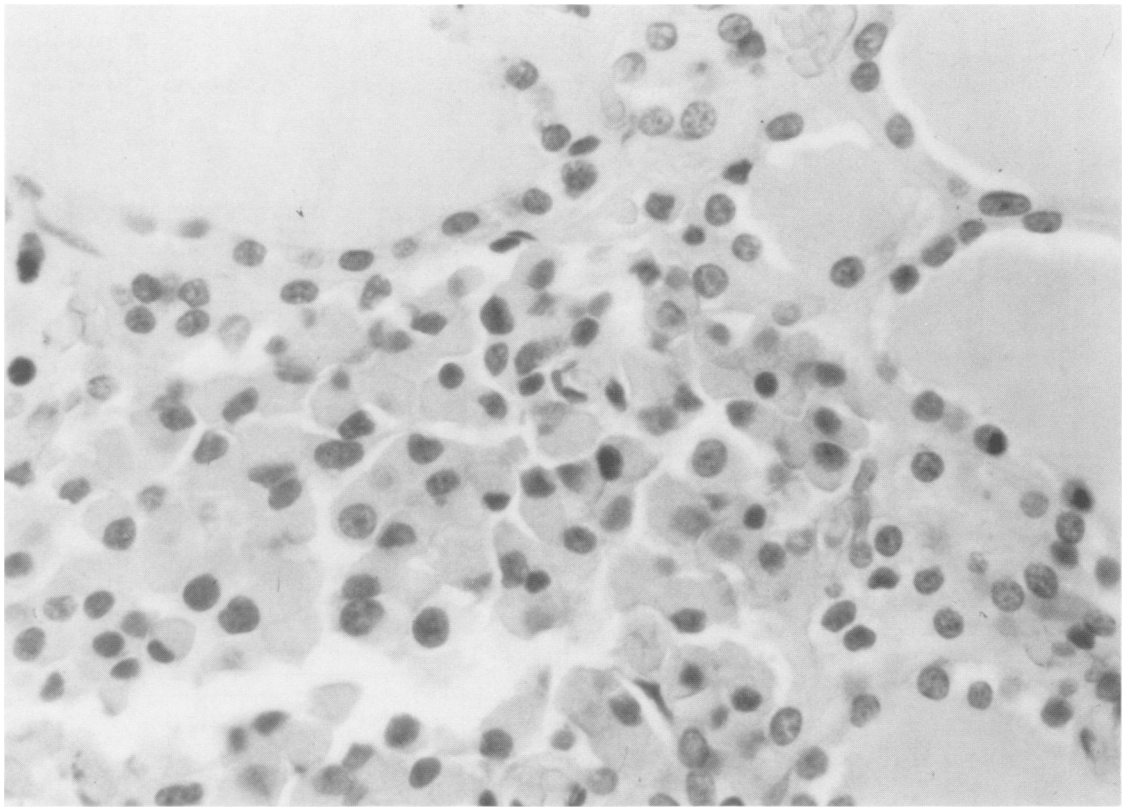

FIG. 11. Photomicrograph illustrating the hyperplasia of calcitonin-secreting, parafollicular (C) cell tissue of the thyroid gland found at the time of autopsy in patient L. R.

secretion has returned to normal values and the serum gastrin values ranged from 43 to 83 pg/ml and were not responsive to intravenous secretin. Antral G-cell hyperplasia persists in this patient after parathyroidectomy and correction of hypercalcemia.

Comment: Antral gastrin cell hyperplasia may be the reason for the relatively high incidence (15 to 20%) of acid-peptic duodenal ulceration and acid hypersecretion in primary hyperparathyroidism although, to date, this finding has been implicated only by association.[4,36] The consistently low normal serum gastrin levels are comparable to those observed in patients with duodenal ulcer. The persistence of the antral G-cell hyperplasia after the reversal of the hypercalcemia and gastric hyperacidity suggests that the hyperplasia may be developmental, rather than adaptive to its environment. Certainly many more patients such as have been reported[6] with various types of hyperparathyroidism need to be studied prospectively, before and after parathyroidectomy, to clarify the association of antral and parathyroid abnormalities. An exceptional instance of a gastrin-containing parathyroid adenoma with hypergastrinemia causing the Zollinger-Ellison syndrome has been described.[45]

Case 8. Diagnosis: Familial multiple endocrine adenomatosis syndrome, adenomatous Cushing's syndrome, malignant Zollinger-Ellison syndrome; temporary tumor regressions after total gastrectomy and hypophysectomy; clinically unsuspected associations of APUD cell hyperplasias of the pancreatic islets, parathyroid glands, thyroid parafollicular cells, and the opposite adrenocortical gland. This patient has been reported in part previously,[12] but is included here to add the findings of the developed hyperplasias before his death, 19 years after his first endocrine symptoms.

Patient L. R., (Fig. 10), a 36-year-old male, presented first with duodenal ulceration and Cushing's syndrome, for which a right adrenocortical adenoma was excised (1955). A metastatic, non-Beta islet cell carcinoma with Zollinger-Ellison syndrome required total gastrectomy (1961). This was followed by apparent regression of metastatic tumor, as observed by an abdominal second-look procedure and low bio-assay values of serum gastrin. Six years later cervical and mediastinal metastases were excised. Seven years after total gastrectomy, at a time when all of the biopsied mediastinal tumor could not be completely removed, a surgical hypophysectomy (histologically normal) was done (1968). There was a second period of visible tumor regression over a 5-year period, associated with a fall in immunoassayable gastrin from approximately 1500 pg/ml to 700 pg/ml in the first 2 years. In 1969 an excision of a cervical mass revealed parathyroid hyperplasia; there had been no clinical evidence of hyperparathyroidism nor hypercalcemia. There were no further problems until in 1973, within a month of his death, (18 years after his first endocrine operation), he showed signs of acute hypopituitarism, hypoglycemia, weakness, and sudden massive mediastinal spread of metastases which did not respond clinically to streptozotocin or x-radiation. A fall in the immunoassayable serum gastrin from 3676 to 450 pg/ml occurred while on

streptozotocin therapy, at which level the serum gastrin remained until his death. Post-mortem examination revealed islet cell hyperplasia (nesidioblastosis), metastatic islet cell carcinoma to the periaortic mediastinal and cervical lymph nodes, (none remained in the liver), chief cell hyperplasia of two remaining parathyroid glands, parafollicular (C) cell hyperplasia of the thyroid gland (Fig. 11), subtotal absence of the pituitary gland, and nodular hyperplasia of the remaining adrenocortical tissue. The mediastinal tumor contained no gastrin on immunochemical assay. Familial involvements in this patient have been reported previously.[13]

Comment: This complicated clinical course illustrates the protracted and metachronous involvement of the foregut endocrine abnormalities ranging from hyperplastic to neoplastic changes over at least a 19-year period. Regressions of tumor and clinical remissions seemed to be associated with treatment, including total gastrectomy and hypophysectomy, while recurrences appeared to be associated with subsequent development of further pluroglandular hyperplasias. After total gastrectomy, at which time a liver metastasis had been excised for biopsy, liver involvement was never again seen, a phenomenon still unexplained. For the most part of the 19 years of studies and operations, the patient led a useful and happy life as a postman in his community.

Discussion

The clinical and laboratory observations in these patients were made in a prospective fashion for the most part, except where retrospective review of tissues was indicated. The purpose of reporting the findings as they are observed is to document them, even though the precise interpretation of the observations may not be possible or even correct. Surely further observations by clinicians and investigators will require re-evaluations and assessments with the passage of time. The information gained to date seems to suggest that embryologic errors in development can explain many of the bizarre features of foregut endocrinopathies; modifications of known syndromes are possibly related to associated endocrine cell hyperplasias which may attend alterations in environmental homeostasis. Treatment of the Zollinger-Ellison syndrome, especially by total gastrectomy, may reverse imbalances in feedback systems so that remissions of the syndrome, and even tumor regressions, are occasionally observed. Hypophysectomy, employed on only one occasion, resulted in only a temporary 5-year remission and regression, before a sudden and fulminating growth of a non-gastrin-containing mediastinal tumor occurred in this familial, genetic type of multiple endocrine adenomatosis syndrome in Case 8. Whether the ulcerogenic tumor is located entopically or ectopically in the Zollinger-Ellison syndrome, the treatment by total gastrectomy continues to yield beneficial results in terms of control of the ulcerogenic potential, of tumor suppression, and of ultimate survival for most patients.[9]

Acknowledgments

The authors gratefully acknowledge the assistance of the following: Dr. Robert Bolinger and Dr. Barbara Lukert for their assays of serum for gastrin, parathormone, insulin, cortisol and growth hormone; Dr. Janardan Reddy, Dr. William Gourley and Dr. Frank Mantz for the electron and light microscopic studies in some of these patients; Dr. Arthur Klotz, Dr. James Rhodes, Dr. Constantine Arvanitakis and their house staff for the gastroscopic antral mucosal biopsies; Dr. Robert Nordquist and Dr. Genaro Palmieri for the immunofluorescent studies for PTH in tumor; and Dr. Claude Arnaud and Dr. James Flueck for the special studies for identification of parathormone-like substance in serum and tissues.

References

1. Ackerman, N. B. and Winer, N.: The Differentiation of Primary Hyperparathyroidism from the Hypercalcemia of Malignancy. Ann. Surg., 181:226, 1975.
2. Arnaud, C. D.: Parathyroid Hormone: Coming of Age in Clinical Medicine, Am. J. Med., 55:577, 1973.
3. Creutzfeldt, W., Arnold, R., Creutzfeldt, C. and Track, N.: Pathomorphologic, Biochemical, and Diagnostic Aspects of Gastrinomas (Zollinger-Ellison Syndrome). Human Pathol., 6:47, 1975.
4. Creutzfeldt, W., Arnold, R., Creutzfeldt, C., et al.: Gastrin and G-cells in the Antral Mucosa of Patients with Pernicious Anaemia, Acromegaly and Hyperparathyroidism and in a Zollinger-Ellison Tumour of the Pancreas. Europ. J. Clin. Invest., 1:461, 1971.
5. Crocker, D. W. and Veith, F. J.: Mesodermal Tumors Associated with Hypoglycemia: Review of Literature and Report of a Case. Ann. Surg., 161:418, 1965.
6. Dent, R. I., James, J. H., Wang, C.-A., et al.: Hyperparathyroidism: Gastric Acid Secretion and Gastrin. Ann. Surg., 176:360, 1972.
7. DeWys, W. D., Stoll, R., Au, W. Y. and Salisnjak, M. M.: Effects of Streptozotocin on an Islet Cell Carcinoma with Hypercalcemia. Am. J. Med., 55:671, 1973.
8. Feyerter, F.: Uber die Patholigie peripherer vegetativer Regulationen am Beispiel des Karzinoids und des Karzinoidsyndrom, in *Handbuch der Allgemeinen Pathologie,* Berlin: Springer-Verlag, 1966, Vol. 8, pt. 2.
9. Fox, P. S., Hofmann, J. W., Decosse, J. J., and Wilson, S. D.: The Influence of Total Gastrectomy on Survival in Malignant Zollinger-Ellison Tumors, Ann. Surg., 180:558, 1974.
10. Friesen, S. R.: Zollinger-Ellison Syndrome. Current Problems in Surgery, Year Book Publ., Inc., Chicago, April 1972.
11. Friesen, S. R., Hermreck, A. S. and Mantz, F. A. Jr.: Glucagon, Gastrin, and Carcinoid Tumors of the Duodenum, Pancreas, and Stomach: Polypeptide "Apudomas" of the Foregut. Am. J. Surg., 127:90, 1974.
12. Friesen, S. R., Bolinger, R. E., Pearse, A. G. E. and McGuigan, J. E.: Serum Gastrin Levels in Malignant Zollinger-Ellison Syndrome After Total Gastrectomy and Hypophysectomy. Ann. Surg., 172:504, 1970.
13. Friesen, S. R., Schimke, R. N. and Pearse, A. G. E.: Genetic Aspects of the Z-E Syndrome: Prospective Studies in Two Kindred; Antral Gastrin Cell Hyperplasia. Ann. Surg., 176:370, 1972.
14. Ganguli, P. C., Cullen, D. R. and Irvine, W. J.: Radioimmunoassay of Plasma-Gastrin in Pernicious Anaemia, Achlorhydria Without Pernicious Anaemia, Hypochlorhydria, and in Controls. Lancet, 1:155, 1971.
15. Ganguli, P., Polak, J., Pearse, A. G. E., et al.: Antral-Gastrin-Cell Hyperplasia in Peptic Ulcer Disease. Lancet, 1:583, 1974.

16. Goldberg, M. F., Tashjian, A. H. Jr., Order, S. E. and Dammin, G. J.: Renal Adenocarcinoma Containing a Parathyroid Hormone-like Substance and Associated with Marked Hypercalcemia. Am. J. Med., 36:805, 1964.
17. Goodrick, W. I. M. and Dockerty, M. D.: Zollinger-Ellison Syndrome Associated Gastric Tumor Showing Islet-cell Features, Minnesota Med., 46:634, 1963.
18. Harrison, T. S., Child, C. G. III, Fry, W. J., et al.: Current Surgical Management of Functioning Islet Cell Tumors of the Pancreas. Ann. Surg., 178:485, 1973.
19. Howard, J. M., Moss, N. H. and Rhoads, J. E.: Collective Review: Hyperinsulinism and Islet Cell Tumors of the Pancreas, with 398 Recorded Tumors: Surg., Gynecol., Obstet., 90:1417, 1950.
20. Jones, B. S., O'Hagan, J. J., Phear, D. N. and Sheville, E.: A Case of the Zollinger-Ellison Syndrome Associated with Hyperplasia of Salivary and Brunner's Glands. Gut, 11:837, 1970.
21. Larsson, L. I., Ljungberg, O., Sundler, F., et al.: Antro-Pyloric Gastrinoma Associated with Pancreatic Nesidioblastosis and Proliferation of Islets. Virchows Arch. (Pathol. Anat.), 360:305, 1973.
22. Law, D. H., Liddle, G. W., Scott, H. W., Jr. and Tauber, S. D.: Ectopic Production of Multiple Hormones (ACTH, MSH and Gastrin) by a Single Malignant Tumor. N. Engl. J. Med., 273:292, 1965.
23. Lukert, B. P.: Calcium and Cancer: Hypercalcemia in Malignancy Simulating Hyperparathyroidism. J. Kansas Med. Soc., 67:305, 1966.
24. Markowitz, A. M., Slanetz, C. A., Jr. and Frantz, V. K.: Functioning Islet Cell Tumors of the Pancreas: 25-Year Follow Up. Ann. Surg., 154:877, 1961.
25. McGuigan, J. E. and Greider, M. H.: Correlative Immunochemical and Light Microscopic Studies of the Gastrin Cell of the Antral Mucosa. Gastroenterology, 60:223, 1971.
26. McGuigan, J. E. and Trudeau, W. L.: Serum Gastrin Concentrations in Pernicious Anemia. N. Engl. J. Med., 282:358, 1970.
27. McGuigan, J. E. and Trudeau, W. L.: Serum Gastrin Levels Before and After Vagotomy and Pyloroplasty or Vagotomy and Antrectomy. N. Engl. J. Med., 286:184, 1972.
28. Miller, D. R., Bolinger, R. E., Janigan, D., et al.: Hypoglycemia due to Nonpancreatic Mesodermal Tumors: Report of Two Cases. Ann. Surg., 150:684, 1959.
29. Oberhelman, H. A., Nelson, T. S., Johnson, A. N. and Dragsted, L. R.: Ulcerogenic Tumors of the Duodenum. Ann. Surg., 153:214, 1961.
30. O'Neal, L. W., Kipnis, D. M., Luse, S. A., et al.: Secretion of Various Endocrine Substances by ACTH-Secreting Tumors—Gastrin, Melanotropin, Norepinephrine, Serotonin, Parathormone, Vasopressin, Glucagon. Cancer 21:1219, 1968.
31. Palmieri, G. M. A., Nordquist, R. E. and Omenn, G. S.: Immunochemical Localization of Parathyroid Hormone in Cancer Tissue From Patients With Ectopic Hyperparathyroidism. J. Clin. Invest., 53:1726, 1974.
32. Pearse, A. G. E.: Common Cytochemical and Ultrastructural Characteristics of Cells Producing Polypeptide Hormones (the APUD Series) and Their Relevance to Thyroid Ultimobranchial C-cells and Calcitonin. Proc. Roy. Soc., London., 170:71, 1968.
33. Pearse, A. G. E. and Polak, J. M.: Endocrine Tumours of Neural Crest Origin: Neurolophomas, Apudomas and the APUD Concept. Med. Biol., 52:3, 1974.
34. Pearse, A. G. E. and Polak, J. M.: Neural Crest Origin of the Endocrine Polypeptide (APUD) Cells of the Gastrointestinal Tract and Pancreas. Gut, 12:783, 1971.
35. Polak, J. M., Stagg, B. and Pearse, A. G. E.: Two Types of Zollinger-Ellison Syndrome: Immunofluorescent, Cytochemical and Ultrastructural Studies of the Antral and Pancreatic Gastrin Cells in Different Clinical States. Gut, 13:501, 1972.
36. Polak, J. M., Bussolati, G. and Pearse, A. G. E.: Cytochemical, Immunofluorescence and Ultrastructural Investigations on the Antral G Cells in Hyperparathyroidism. Virchows Arch. (Zellpathol.), 9:187, 1971.
37. Powell, D., Singer, F. R., Murray, T. M., et al.: Non-parathyroid Humoral Hypercalcemia in Patients With Neoplastic Diseases. N. Engl. J. Med., 289:176, 1973.
38. Raisz, L. G.: Prostaglandins and the Hypercalcemia of Cancer. N. Engl. J. Med., 289:214, 1973.
39. Riggs, B. L., Arnaud, C. D., Reynolds, J. C. and Smith, L. H.: Immunologic Differentiation of Primary Hyperparathyroidism from Hyperparathyroidism due to Nonparathyroid Cancer. J. Clin. Invest., 50:2079, 1971.
40. Rosen, S. W. and Weintraub, B. D.: Ectopic Production of the Isolated Alpha Subunit of the Glycoprotein Hormones—A Quantitative Marker in Certain Cases of Cancer. N. Engl. J. Med., 290:1441, 1974.
41. Royston, C. M. S., Brew, D. St. J., Garnham, J. R., et al.: The Zollinger-Ellison Syndrome due to an Infiltrating Tumour of the Stomach. Gut, 13:638, 1972.
42. Schein, P. S., DeLellis, R. A., Kahn, C. R., et al.: Islet Cell Tumors: Current Concepts and Management. Ann. Intern. Med., 79:239, 1973.
43. Solcia, E., Capella, C. and Vassallo, G.: Endocrine Cells of the Stomach and Pancreas in States of Gastric Hypersecretion. Rendic. R. Gastroenterol., 2:147, 1970.
44. Stefanini, P., Carboni, M., Patrassi, N. and Basoli, A.: Hypoglycemia and Insular Hyperplasia. Ann. Surg., 180:130, 1974.
45. Stremple, J. F. and Watson, C. G.: Serum Calcium, Serum Gastrin, and Gastric Acid Secretion Before and After Parathyroidectomy for Hyperparathyroidism. Surgery, 75:841, 1974.
46. Unger, R. H. and Eisentraut, A. M.: Enteroinsular Axis. Arch. Intern. Med., 123:261, 1969.
47. Vance, J. E., Stoll, R. W., Kitabchi, A. E., et al.: Nesidioblastosis in Familial Endocrine Adenomatosis. JAMA, 207:1679, 1969.
48. Weichert, R., Reed, R. and Creech, O.: Carcinoid-Islet Cell Tumors of the Duodenum. Ann. Surg., 165:660, 1967.
49. Wermer, F.: Genetic Aspects of Adenomatosis of Endocrine Glands. Am. J. Med., 16:363, 1954.
50. Zollinger, R. M. and Ellison, E. H.: Primary Peptic Ulceration of the Jejunum Associated with Islet Cell Tumors of the Pancreas. Ann. Surg., 142:709, 1955.
51. Zollinger, R. M.: Islet Cell Tumors of the Pancreas and the Alimentary Tract. Am. J. Surg., 129:102, 1975.

Discussion

Dr. Robert C. Hickey (Houston): Dr. Friesen and Dr. McGuigan have put together a very thoughtful presentation. These authors have described eight patients with varying endocrine excesses, some overtly polyglandular, and having in common foregut APUD cell proliferation.

In the disorders of the polyendocrine excess it's difficult at times to put it all together. There are probably three main groupings, Dr. Wells has referred to one, MEA II, and Dr. Zollinger is very familiar with the MEA I; and further, there's ectopic hormone production, usually of incomplete hormones, by malignant non-endocrine tissues and even at times by endocrine tissues.

Orderly thought can become very confusing. When a tumor of neuroectodermal origin as the parafollicular thyroid cells of Nonidez (1932) or the APUD cells of Pearse (as has been discussed here) produces also another peptide, as a hormone-like ACTH substance, the result is a florid corticoid excess over-production of a steroid. Dr. Friesen might comment upon his patient that potentially had this type of disorder.

In this polypeptide hormonal disease array, I wish to present another syndrome, published recently from the Anderson that should probably be grouped with the MEA I: a syndrome of an identified carcinoid tumor of the foregut, with a parathyroid adenoma, and circulating calcitonin excess.