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Discussion

Dr. John H. Mulholland (New York): It is a pleasure to discuss this paper and to have read the manuscript beforehand, even though I am at a disadvantage following the usual professional presentation we have come to expect of Dr. Zollinger.

This is one more item of knowledge chipped from our mountain of ignorance about ulceration of the gastro-intestinal tract. Dr. Zollinger presented a great deal of material in a short time. He included, as you noted, material on the biochemistry of most complex gastro-intestinal hormones; on internal secretions of that enormous endocrinologic structure, the gastro-intestinal tract; and on human genetics.

Of particular interest was his reference to the atrophic pancreas as a source of the secretagogue which initiated a vicious cycle resulting in uleration. The precise source of the acid stimulating material was not clear to me. When pancreatic acinar cells are destroyed many potent enzymes are released, some of which have the property of denaturing of lysing proteins. Such cellular destruction ends in the atrophy which was evident in the photomicrograph he showed. I would like to ask Dr. Zollinger, does he attribute the source of secretagogue to deteriorating acinar cells or to relatively well preserved islet cells?

Dr. Edgar J. Poth (Galveston): I wish only to draw your attention to one situation which I have observed in conjunction with this over-all study, and that is, if you remove the entire pancreas and then give histamine in beeswax, you can develop fulminating peptic ulcer disease, which I think we did in 1948. This does not fit in completely with a lot of these observations and I wonder if Dr. Zollinger can comment on this observation.

Dr. Edwin H. Ellison (Milwaukee): Once again we are indebted to Dr. Zollinger and his associates for their observations on the mechanism of ulceration in the Zollinger-Ellison Syndrome and the choice of operation when faced with this problem.

I, too, agree that total gastrectomy with removal of the resectable tumor, but short of total pancreatectomy, continues to be the surgical treatment of choice, even when the presenting complaint is prolonged, persistent disabling diarrhea.

A recent personal experience will serve to emphasize our feeling that total gastrectomy still remains the treatment of choice. I. B., a 49-year-old white woman was referred to Marquette for evaluation in March of this year with a nine-year history of severe diarrhea and weighing only 81 pounds. At operation in 1956 a lesion thought to be a metastatic carcinoid of the pancreas had been removed. Two years later the slides were reviewed and the diagnosis was changed to islet cell carcinoma.

During her illness the average number of loose stools per day varied from three in 1953 to as many as 15 or more in 1962. Following excision of what later proved to be an islet cell carcinoma from the pancreas the patient had a relief of her symptoms for a period of three months. The diarrhea then recurred requiring two to three hospitalizations per year up until March of this year. Therapy had included a glutein free diet, cortisone, and pancreatin by medical consultants all to no avail.

In 1958, excision of an islet cell cancer of the liver presumably in the passages resulted in temporary improvement probably related to constant Levin suction for a considerable time after the operation. In January of this year, that is, 1962, during an admission for massive hemorrhage, a duodenal ulcer was diagnosed for the first time.

Here, again, our patient had relief from the persistent diarrhea following this admission but only while gastric suction was continued.

During the last hospital admission, the diarrhea would decrease for two or three days following measurement of a 12-hour secretion and then recur. The daily pattern of diarrhea is of interest. One to three liquid stools occurred daily during the daylight hours but from midnight until 7:00 a.m. diarrhea stools was the usual occurrence. In general this corresponded to the time that nothing in the way of food or medication was being taken by mouth. The hyperperistalsis manifest by the patient on physical examination of the abdomen was quite marked.

With this background, and these findings and I believe for a first time a total gastrectomy was advocated in an attempt to control diarrhea thought to be due to the excessive production of acids secondary to an ulcerogenic tumor of the pancreas. The stomach specimen showed the marked and very characteristic hypertrophy of the gastric mucosa seen so commonly in patients with the Zollinger-Ellison Syndrome. The initial estimate of acid producing cells that I. B. had indicated 16 times as many parietal cells as usually seen in the normal individual.

I am happy to report that she is now four weeks following operation and the patient has been gaining approximately a half a pound of weight per day on hourly feedings, and she has had no further diarrhea. This result supports strongly the suggestion that the excess acid production in the stomach of these patients is the basic cause of the diarrhea.

One other point comes to mind: In recent months, through cooperation with the surgical faculty at the University of Michigan in Ann Arbor and the surgical staff at St. Luke's Presbyterian Hospital in Chicago, our group has been able to obtain fresh tumor tissue and have attempted transplanting these tissues both into animals and growing it in tissue culture. One of my associates, Dr. Stewart Wilson, using a technic learned while working with Dr. Warren Cole as a medical student, has carried out these experiments. Presently we have two tumors, i.e., the Ann Arbor tumor and the St. Luke's Presbyterian tumor growing both in guinea pigs receiving cortisone and in tissue culture. This project was undertaken in an attempt to obtain more tissue to extract by Gregory's method, so as to increase the likelihood of identifying responsible hormone *per se*.

More recently we have begun to study cells from the tissue culture by electron microscopy. These pure cultures of tumor cells show large nucleus, typical mitichondria, and perhaps most important, hyalin bodies scattered throughout the cells. This finding seen in tissue cultures of both tumors, suggests the presence of secretory granules. Plans are underway to, perhaps, further identify these highland bodies by more specific stains.

DR. STANLEY R. FRIESEN (Kansas City): I never fail to be stimulated by Dr. Zollinger's ideas. He has stimulated me to ask two questions. One, I notice in his presentation he referred to a cycle in chronic pancreatitis in which secretin was mentioned as being stimulated by acid, this in turn stimulating islet cells. Perhaps I am revealing my ignorance, but I really thought that secretin had to do with the stimulation of acinar cells. I would like him to clarify this point for me.

The other question I would like to ask is whether he perhaps can explain a problem that we have seen recently. This is a patient who had all the classical findings of the Zollinger-Ellison syndrome. I carried out a total gastrectomy, from which he has recovered nicely. The tumor was metastatic to lymph nodes and liver and mediastinum and I sent generous pieces of this tissue to both Gregory and to Code, both of whom failed to find this gastrin-like substance in this tumor.

It is an islet cell tumor, not hypoglycemic, not beta cell. The only other thing about this particular patient is that five years prior to this time an adrenocortical adenoma was removed by Dr. Kittle; this patient had Cushing's syndrome at that time from which he has recovered nicely in the five-year span. Perhaps Dr. Zollinger has an explanation for me as to the findings in this case.

DR. CHARLES B. PUESTOW (Chicago): Just before I came to this meeting I received a copy of this paper and a letter from Dr. Zollinger stating that he thought I might be interested because of our work on pancreatitis. I did not realize it was being presented at this meeting, but it gave us considerable material for thought.

The Zollinger-Allison syndrome and the recognition of the stimulation of non-beta cell tumors of the pancreas on gastric secretion and the production of extensive ulcers has been a monumental contribution. We are not familiar with the possibility that an increase in islet cells might possibly cause the same kind of stimulation. If this is true, it might be an indication to perform more radical resections of the pancreas for pancreatitis. On the other hand, we have been trying to preserve as much of the pancreas as possible in order to allow a maximum amount of pancreatic regeneration or restoration of pancreatic function. In our series of between 40 and 50 operations in which the pancreas and its ducts are widely opened to permit free drainage and the pancreas anastomosed to a defunctionalized loop of jejunum, no massive ulcers have developed. In only one case did a duodenal ulcer develop which became obstructive. In this case the pancreas had been implanted into the posterior wall of the stomach and at the subsequent operation we found that all intra-gastric pancreas had been digested away and thus, presumably, had destroyed all islet cells in that portion of the gland. During a five-year period, 216 patients were admitted to the hospital with a diagnosis of pancreatitis. Of this group,

only 13 (6.0%) had associated duodenal ulcers and no gastric ulcers were reported. I believe this percentage of peptic ulcer is lower than the average percentage found in all hospitalized patients. Might not the tremendous hyperplasia of islet tissue noted by Dr. Zollinger be more apparent than real and due to loss of parenchyma of the gland? This is a very stimulating paper and should give added impetus to many investigators in the field of pancreatic disease.

DR. LESTER DRAGSTEDT (Gainesville): I would like to raise two points. Many years ago when Dr. R. R. Bensley of Chicago claimed that ligation of the pancreatic ducts in animals caused hyperplasia of the islets, Drs. DeTakats and Wilder tried this operation in the treatment of human diabetes mellitus. It was a complete failure; subsequently we have learned in our laboratory that tying off the ducts of the pancreas causes not only atrophy of the parenchyma of the pancreas but also reduces the functional capacity of the islets by at least 50 per cent. The glucose tolerance of animals whose ducts are ligated and whose pancreases are degenerated is profoundly reduced—as much as is secured by taking out at least half of the pancreas.

I would like to raise the question, how good is the evidence that these ulcero-genic tumors are of islet cell origin? My associates, Drs. Harry Oberhelman, Nelsen, Rigler and I have encountered nine of these tumors in our experience. Five of them were in the duodenum and five of them were in the pancreas. One was in the duodenum beneath the mucosa about a centimeter distal to the pylorus. Is it not possible that these tumors arise from the cell, at present unknown, that manufactures gastrin? The isolation by Prof. Gregory and his associates, and now by Dr. Zollinger, of an agent which is indistinguishable in its physiologic action from gastrin seems to support this theory. An objection, of course, is the fact that so far as I know, no one has found one of these tumors in the antrum of the stomach.

Another question: Is it possible that the degenerated pancreas from which Dr. Zollinger got an active extract actually contained one of these tumors? It is difficult to show that in the dog any of the mechanisms of gastric secretion are dependent on the pancreas.

DR. DAN W. ELLIOTT (closing): Dr. Mulholland inquired about the presence of islets and whether the gastric secretogogue comes from islets or acinar tissue. We must presume from the pathologic sections, from the absence of acinar tissue, and from the overgrowth of islets, that this secretogogue does actually come from the islets, althought the islet cell of origin cannot be pinned down.

Dr. Poth has posed an important question with regard to the role of the pancreas in ulcer. We have been very much stimulated by his observations in 1948 and later. It is true that an ulcer may be stimulated in the total absence of the pancreas. In the work to which he referred, the ulcerogenic stimulus was histamine. Since this substance acts directly on the parietal cells to produce acid, it is not surprising that it can produce an ulcer whether or not the pancreas is present.

In our work with pancreatic ductal ligation, producing gastric acid hypersecretion, we have found that the hypersecretion is not abated by the removal of the pancreas. Therefore, in stimulating the stomach, the pancreas is acting through more than one anatomical site. We have also found that once hypersecretion is induced by ligation of the pancreatic ducts, removal of the gastric antrum does abate this hypersecretion somewhat. Therefore, we can say that although the pancreatic islets make a gastric secretogogue, they also cause ulcers through stimulation of endocrine tissue outside the pancreas as well.

We, too, have been interested in electron microscopy, like that which Dr. Ellison showed you. His pictures are typical of islet alpha cells. In some of our material, there is evidence of alpha cell granules and in other tumor sections these granules cannot be seen quite so readily.

Dr. Friesen has asked an interesting question with respect to secretin and the vicious circle of physiologic activity by which chronic pancreatitis patients are made worse. We have postulated that if chronic pancreatitis is accompanied by islet hyperplasia, and the production of a gastric secretogogue, this substance will act directly upon the parietal cells to make excessive acid. If more acid is made, more secretin should be produced in the duodenum.

This substance acts, of course, upon the acinar cells of the pancreas. If we believe—and we do—that the evidence is irrefutable that ductal obstruction plays a role in chronic pancreatitis, then this increased secretin stimulation of acinar cells against obstruction may be of definite importance in provoking further pancreatic inflammation.

The tumor that Dr. Freisen removed, and in which he was unable to find a gastric stimulant, is unique. We have been able to find this stimulant in all of our tumors except one, which weighed only 170 mg. However, we have noticed that if an ulcerogenic tumor also contains glucagon-like activity, it is more difficult to assay the gastric stimulant, and the reaction of the test animal to this stimulant seems to be reduced. It may be that glucagon present in his tumor extract inhibited the acid response that he otherwise might have obtained; or it may be simply that no gastric stimulant was there at all.

We would like to thank Dr. Dragstedt as well for his observations. We do not really know for sure that ulcerogenic tumors actually arise from the pancreatic islets, but our best histologic evidence so far indicates this origin.