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Discussion

Dr. James Charles Thompson (Galveston): We have studied the antral mucosal gastrin levels in patients with the Zollinger-Ellison syndrome—only three such patients—and found them to be normal. They were patients who had pancreatic tumors. I would like to ask Dr. Friesen if he has measured antral gastric mucosal levels in patients with the Zollinger-Ellison syndrome, with and without pancreatic tumors, and specifically to ask what the tissue gastrin levels are in patients who have this hyperplasia, or gastrinoma; and secondly, to ask what happens after antrectomy to the serum gastrin levels in patients who have antral gastrinomas and no pancreatic tumors.

Dr. Robert M. Zollinger (Columbus): I am really sorry I brought it up, it is causing so much trouble.

Dr. Friesen always comes up with new and stimulating concepts about these gastrin producing islet cell tumors. Sometimes I believe him, and sometimes I do not. This morning I am not quite sure, but I would like to believe him.

It is perfectly true, as he points out, that many of these instances do occur in families. In our experience, I think we have eight families of approximately 30 cases that we have studied rather intensively.

In addition, we have reviewed the records of about 800 reported cases through 1970, and we feel that the Wermer syndrome is involved in about one in 20, or 5%, and that multiple endocrine involvement is present in 20 to 25% of the cases.

However, I would point out that when you review the literature, there has been no mention of any endocrine survey in at least one half of the cases, so right off the bat we have about 400 cases in which we could not be sure about the true incidence of endocrine involvement. And furthermore, recent studies have demonstrated the islet cell tumors are associated with an increase in thyrocalcitonin, which in turn may result in hyperplasia of the parathyroid glands. So, when you begin to realize that the parathyroids are involved, in perhaps 20% of the cases, this may be a secondary effect, and not a true endocrine involvement, as we, at least, tend to regard it.

Dr. Friesen presents a very interesting concept concerning the antrum and gastrin cell hyperplasia, which he believes may be of sufficient magnitude to be consistent with the term "gastrin cytoma." The origin of the gastrin cell, I think, is still a little bit debatable. We heard Dr. Greider from Washington University talk to us the other day about this. She has been studying this problem for many, many years, and I am not sure that the light microscopists or the electron microscopists are really certain where, or to what extent these cells really occur.

I hope, however, that he is correct in this assumption and that biopsy of the antrum may assist the clinician. This may be particularly helpful in the borderline cases that we have heard about this morning, when the gastrin level tends to be low.

I would say just a word about low gastrin levels. When they are low, I mistrust the immunoassay rather than the patient. Of course, all tumors have to start small, and it is true that some of them are borderline, and here we would have an example of biopsy of the antral mucosa, which might help in these borderline cases.

President Moore: I would like to ask Dr. Friesen a question. If this is a single gene, why does it involve so many different organs? Could it be that the pituitary is basic to most of the cases? I noticed you had, I think, one or two with enlarged sellae.

Dr. S. R. Friesen (closing): I will answer Dr. Thompson's questions first, if I may. Did we measure the tissue antral gastrin content in Zollinger-Ellison patients? The answer is no. We have measured tissue gastrin values in the antrum in dogs, but not in these patients.

What happens to the serum gastrin after an antrectomy in which there is antral gastrinosis? I do not know exactly, except in the instance of one patient, particularly. This patient had very high gastric acid values, over 2000 ml. in 12 hours, over 100 mEq easily in that 12 hours of output of acid, and who had a serum gastrin value of 558, right in between the values for duodenal ulcer and the Zollinger-Ellison syndrome. At operation there was a nodular pancreas, and I biopsied the pancreas and a lymph node and found normal pancreas and no tumor in the

lymph node. I felt that, since I had no histologic proof of the Zollinger-Ellison syndrome, I would just do a vagotomy and antrectomy, which was done.

Postoperatively, his serum gastrin values have come down to 100 or less—even during operation—and the gastric acid secretion is zero.

I consider that there is an intermediary stage between the duodenal ulcer diathesis and the Zollinger-Ellison syndrome. This is in contrast to one of my co-authors, Professor Pearse, from London, who feels that there might be two Zollinger-Ellison syndromes in stages, one with a pancreatic islet cell adenomatosis, and one with an antral gastrinosis.

More likely, there is antral gastrinosis first, with an intermediary development into the full-blown Zollinger-Ellison syndrome with pancreatic involvement. Certainly, we need to do more correlative studies between the antrum and the pancreas. All we are doing is reporting what we have seen so far.

Dr. Zollinger rightly suggested that we really do not know what the familial incidence is in most patients with the Zollinger-Ellison syndrome until endocrine screening is done. This is the way we have found these patients. If we follow them long enough they will become symptomatic.

I have often wondered why hyperparathyroidism is so common in multiple endocrine adenomatosis, common in these patients, and common just in the survey of endocrine disease, particularly when we think that the parathyroid changes are a secondary phenomenon. We must consider them secondary, I believe, because even though these parathyroid cells secrete long-chain polypeptides, they have not yet been proven to derive from the neural crest, and they do not have some of the cytological characteristics that the other polypeptide secreting cells do.

So far, the parathyroid cell is the "odd man out." It has not really been explained. It is the only endocrine abnormality that is present in both multiple endocrine adenomatosis Type I and multiple endocrine adenomatosis Type II, in which there is a medullary carcinoma of the thyroid and pheochromocytoma.

Certainly, parathyroid disease so far must be considered as secondary to some other influence, such as Dr. Moore has suggested. Perhaps there is a pituitary influence in all of these situations; I think it occurs often enough to indirectly say that there probably is a primary pituitary influence. Of course, no trophic hormone to the antrum, pancreas or parathyroids from the pituitary has yet been described, to my knowledge.

The adrenal cortex secretes steroids, not polypeptides, and that certainly is secondary to pituitary ACTH stimulation.

Our electron microscopy studies show full secretory granulations in these biopsies, in these acid hypersecretory states at least. In pernicious anemia, in which there is no acid in the stomach, for instance, and in which there is no acid inhibition of gastrin release, the antral G cells are practically empty of granules.