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Discussion

PROFESSOR IVAN D. A. JOHNSTON (Newcastle upon Tyne, England): Andrew Kay in Glasgow first described a group of patients with duodenal ulcer who had recurrence after complete truncal vagotomy and whose gastric acid secretion was unaffected by the complete vagotomy. These patients required an antrectomy to reduce their acid secretion and heal their ulcers.

The demonstration of G-cell hyperplasia in the antrum of some patients with duodenal ulcers by immunofluorescent techniques was the next step in our understanding of this condition.

Interest in identifying these patients flagged mainly because the results of peptic ulcer operations were satisfactory. It did not, therefore, seem important, particularly when antrectomy was being added to vagotomy as routine in many centers, to try and identify this group of patients.

There are, however, several reasons for identifying those peptic ulcer patients who have this syndrome.

It is important to diagnose gastrinomas as early as possible in their development.

The introduction of H_2 blockade for the treatment of duodenal ulcer has reduced the number of gastric operations. Vagotomy alone is the operation chosen for many patients who have failed to respond to cimetidine or who have relapsed after a long course of H_2 blockers.

There is some evidence that the recurrence rate after vagotomy in these patients is high. The patients Dr. Friesen describes will be more numerous in the population of cimetidine failures coming to operation. Screening studies should produce a higher yield and allow the appropriate surgical treatment to be planned. The screening procedure must be simple, inexpensive and accurate.

Gastrin can be identified in gastric secretions. Was luminal gastrin measured, and is its measurement of value in identifying these patients? Does Dr. Friesen think that the increase in the levels of plasma gastrin following cimetidine treatment is of diagnostic importance because the gastrin level in patients with gastrinoma does not alter after cimetidine is given.

Should we be measuring serum gastrin, before and three hours after a standard meal as well as carrying out a secretin test, or can we omit the secretin test?

The objective in gastric surgery is to be both physiologic and offer the operation most suited to the patient's requirements. This

study encourages us to plan gastric operations more accurately. Dr. Friesen and his colleagues have clearly shown us how to identify this small but important group of patients with peptic ulcer disease.

DR. JOHN P. DELANEY (Minneapolis, Minnesota): This paper will prove to be the definition of a syndrome, and allow us to diagnose the syndrome clinically more accurately than in the past. As Dr. Friesen intimated, there has been doubt as to whether this syndrome really existed.

I would caution against the use of the endoscope to make the diagnosis. The tiny biopsy specimens obtained through the endoscope are inadequate to provide accurate quantification of G cells. My associates and I have compared endoscopic biopsy specimens with whole antrums, and the correlation is poor. The reason is that the distribution of the G cells is irregular. Some areas in normal antrums have many G cells, and others have few. So large specimens are needed to make a legitimate quantification. A group in Germany has demonstrated this point, and another in Japan has shown the same thing. So endoscopic biopsy specimens should not be depended upon to make the diagnosis of G cell hyperplasia.

In the laboratory, one of the phenomena we have observed is that a truncal vagotomy, or highly selective vagotomy, leads to antral G cell hyperplasia, each about doubling the number of antral G cells with a parallel increase in the resting and food-stimulated serum gastrin level.

In other words, vagotomy does induce the syndrome of antral G cell hyperplasia. This is one of my reservations about the presentation. Three of the patients had previous vagotomies. They would have been predicted to have hypergastrinemia and excessive numbers of G cells. The question is how to distinguish the patient who has had a vagotomy and has suspected primary G cell hyperplasia from all the other patients with vagotomy who have secondary G cell hyperplasia.

The answer may prove to be the secretin test. In normal persons it causes a reduction in serum gastrin level, as shown by Dr. Friesen, in patients with G cell hyperplasia; it causes no change in the serum gastrin level.

My question is whether Dr. Friesen has measured the serum gastrin reaction to a secretin infusion in individuals with vagotomy. What were the results in individuals with vagotomy, but not having the syndrome of G cell hyperplasia with acid hypersecretion and recurrent ulceration.

Finally, I would like to point out one thing that Dr. Friesen observed that has not been documented before. That is, patients with true Zollinger-Ellison syndrome of pancreatic tumor origin have normal numbers of G cells. This is in contrast to most endocrine feedback systems. The central G cells are seeing a high circulating serum gastrin level and a high luminal acid level. If they behaved like the adrenal glands or the thyroid, you would anticipate that the G cells would atrophy, and there would be fewer cells. In the Zollinger-Ellison syndrome, where there is a great deal of circulating gastrin, the cells do not atrophy, and therefore do not behave as a classic endocrine organ would.

DR. NORMAN W. THOMPSON (Ann Arbor, Michigan): Dr. Friesen has emphasized physiologic provocative testing to make the differential diagnosis between G-cell hyperplasia and the Z-E syndrome, and I would like to comment on another method for doing this.

During the last two years, we have studied all our patients suspected of having Z-E syndrome with percutaneous transhepatic venography and selective gastrin assays. One patient, a young man, had a positive secretin stimulation test, although not as marked as we would have expected in a typical instance of Z-E syndrome. He also had some degree of gastric outlet obstruction. For that reason we did venous localization studies, and found that his high gastrin level was from his right gastroepiploic vein. When the highest gastrin levels come from that vein, it means the gastrin is coming from the antrum. At operation, we found no pancreatic or ectopic islet cell tumor. An antrectomy and vagotomy were performed. Postoperatively the patient's serum gastrin levels returned to normal.

That is one way to confirm that the source of the gastrin in this syndrome is from the antrum and not the pancreas. I would not recommend it for every patient because it is usually not necessary. We were led to this study in this patient because of a false-positive increase in gastrin level after secretin stimulation. Has Dr. Friesen seen any patients with positive secretin stimulation tests who were proved not to have Zollinger-Ellison syndrome?

My associates and I have seen three such patients in the last year, all of whom had partial gastric outlet obstruction, whose gastrin stimulation test with secretin returned to normal after they were treated conservatively, allowing resolution of the outlet obstruction.

DR. EDWIN L. KAPLAN (Chicago, Illinois): One word of caution is appropriate. The diagnosis of pseudo-Zollinger-Ellison syndrome must be made preoperatively by provocative testing as Dr. Friesen outlined. It would be dangerous to reason that antral G cell hyperplasia were present just because no tumor can be found at operation. It is well known that many times the primary tumor which causes a true Z-E syndrome is very small and easily overlooked. This is especially true of the lesions found within the duodenal submucosa. In such cases, an antrectomy would not be helpful and would be inappropriate therapy.

DR. STANLEY R. FRIESEN (Closing discussion): Professor Johnston referred to the classic work by Sir Andrew Kay of Glasgow, who years ago made signal tests using gastric acidity as a measure of function of the stomach in relation to ulcer patients. It is still important to perform a gastric analysis, if only to ascertain that the patient does have hypersecretion of acid. However, it is not always possible to tell from the acid studies whether the patient has duodenal ulcer, Zollinger-Ellison syndrome, or pseudo-Zollinger-Ellison syndrome with much discrimination.

Professor Johnston talked about the failure of vagotomy and pyloroplasty, or vagotomy and drainage, and the failure after cimetidine therapy and asked whether or not we used luminal gastrin studies. We have not done that.

My patients with Zollinger-Ellison and pseudo-Zollinger-Ellison syndrome demonstrated an increase in serum gastrin values while taking cimetidine; I do not know whether that is a sign of progressive tumor growth, on the one hand, or progressive antral G cell hyperplasia on the other. This constitutes one of the cautions I would have about cimetidine therapy for any of these ulcerous conditions. When the gastrin level is elevated and increases while the patient is taking cimetidine one does not know when the patient's lesion is going to metastasize. Certainly cimetidine does not treat the abnormal physiology causing the hypergastrinemia.

Professor Johnston also talked about the meal stimulation results. The peak in serum gastrin level after a standard meal occurs within the first two or three hours, whereas the peak after secretion in patients with gastrinoma occurs within ten minutes after the intravenous push of two units of secretin per kilogram.

Professor Johnston also mentioned the possibility of tailoring the operation to the disease. This, of course, has been the desire of surgeons all along, to decide which patient gets a vagotomy and pyloroplasty, which one gets a vagotomy and antrectomy, and which one has a total gastrectomy. Now, by these physiologic tests, we do have a means of determining which operation the patient should have.

In other words, we are paying more attention preoperatively to the physiologic diagnosis than we are the pathologic diagnosis. The only other thing that supersedes that is the findings at the time of operation. One still has to operate on these patients to make doubly sure, or triply sure, that the patient does not have a tumor.

If a tumor has been overlooked and an antrectomy performed, the surgeon will know it within a week. The serum gastrin level is still going to be elevated; the acid level is still going to be increased.

Dr. Delaney cautioned against use of endoscopy for antral G cell biopsy. I have to concur. We do preoperative endoscopic biopsies for the antral G cells, if the middle layer of the mucosa is in the endoscopic biopsy specimen, one can make a preoperative diagnosis. When we compared the surgical antrectomy specimen with the endoscopic one, the most accurate was the surgical antrum fixed in Bouin's solution; in that situation one can count the G cells accurately.

It has been said that vagotomy leads to antral G cell hyperplasia, and experimentally it does; maybe it does in patients. Our three patients who had a prior vagotomy and drainage were operated elsewhere, and unfortunately the serum gastrin value was not known before the vagotomy.

I do not know whether the antral G cell hyperplasia is primary or secondary, Dr. Delaney. I have a feeling that the antral G cell hyperplasia is pathogenetically important as the primary abnormality in these patients, but it cannot be proved from the studies on these nine patients.

The question of atrophy of G cells is an interesting one. One would expect to find antral G cell atrophy in patients with hyperacidity, just as at first, when Zollinger and Ellison described tumors, we expected to find atrophic islet cells alongside the tumor. But early on it was recognized that the islets were not atrophic in patients who had pancreatic tumor, which led us to believe that the tumor might be multicentric or that there were multiple sources for the gastrin at least in patients with MEA and that a total gastrectomy had to be performed. Two of the patients in this series have islet cell hyperplasia as well, but it is not the cause of the hypergastrinemia, because the antrectomy brought the serum gastrin level down to normal.

Dr. Norman Thompson emphasized the functional and physiologic approach to the diagnosis, and I would also like to emphasize that. His finding of selectively elevated gastrin levels in the veins draining the antrum is important. It is the first and only demonstration that excess gastrin can come from the antrum by selective venous assay.

I have not seen any false-positive secretin tests, but I expect I will with time.

Dr. Kaplan, I have already responded to your excellent suggestion that we still have to explore the patient thoroughly and look for tumor. We have to make sure the patient does not have a tumor before we opt for antrectomy. I have never done a total gastrectomy in a patient with Zollinger-Ellison syndrome without there being absolute proof of tumor or islet cell hyperplasia. I have never done a blind total gastrectomy for elevated serum gastrin level alone. On the other hand, the addition of antrectomy to vagotomy when Ps-ZES is recognized will decrease the ulcer recurrence rate after vagotomy and pyloroplasty for duodenal ulcer by 10%.

Finally, now that we have cimetidine, we can be much more confident about doing an antrectomy in patients in whom we do not find a tumor.