In the presence of elevated serum calcium levels associated with hyperparathyroidism or in patients with advanced cardiac disorders, either the secretin or magnesium sulfate provocative infusion test, which has little or no hypercalcemic effect, should be substituted for the calcium gluceptate infusion.

A hepatic angiogram should be considered when either the fasting or stimulated gastrin levels exceed 1,000 Pgm. The incidence of hepatic metastases when the serum gastrin levels are elevated beyond this level is significant. Hepatic metastases were found in 8 patients (53%) of those having had hepatic angiography.

Chemotherapy should be considered when the postoperative gastrin levels are steadily increasing and exceed 1,000 Pgm/ml. Chemotherapy is routinely advised when hepatic metastases are proved at the time of operation, or by subsequent hepatic angiography.

Chemotherapy consisting of the triple-drug program of Tubercidin, Streptozotocin and 5-Fluorouracil, was given to 5 patients with extensive gastrinoma. These patients said they felt better and gained from 3 to 35 pounds in weight. One patient with a WDHA syndrome with metastases to the liver has remained symptom-free for almost one year on the chemotherapy program. Chemotherapy, regardless of the type, should be used more aggressively than it has been in the past in patients with extensive islet cell tumor involvement.

Since 60% of the patients in this series have died or exhibit definite evidence of tumor activity, it is assumed that the tumor is malignant and growth of the tumor has not been inhibited, although in many instances it is proceeding at a very slow rate. Approximately 40% of the patients seem to do well, despite modest elevations in gastrin levels, suggesting that the retained tumors could be considered benign.

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Discussion

DR. JAMES CHARLES THOMPSON (Galveston, Texas): If you had to choose among the gastrin challenges, I would think that secretin is still the better. I think that it allows one to make a differentiation within an hour or two hours. As far as I know, secretin releases gastrin only from gastrinoma tumors, whereas calcium releases gastrin from any kind of gastrin-bearing tissue.

As far as what is malignant, I think that really depends upon the definition. I would suggest that those patients who have high gastrin levels after excision of the primary tumor and after total gastrectomy have either multiple primary tumors or functioning metastases or both.

I would suggest that a model for these tumors is the carcinoid tumor. We all known that patients with carcinoid tumors will develop metatases and live in harmony with them for years, and then for some reason or other the metastases will begin to grow, because of changes in their own biologic potential, and will often kill the patient.

It's very important to treat these like malignant tumors, and extripate as much of the tumor as possible, and the patient will actually live longer.

It is distressing to us that many of our patients are now beginning to die. We have had two die in the last year, and others whom we tided along for a long time with intermittent doses of intrahepatic artery chemotherapy now seem to have escaped the ameliorative results of that, and are beginning to die.

It is encouraging to see the results that Dr. Zollinger and colleagues have achieved in the management of these metastatic tumors.

DR. STANLEY R. FRIESEN (Kansas City, Kansas): I think we're all very interested in this remarkable experience that Dr. Zollinger's group has had, and in their presentation today, and I think we better pay attention to it. The longer we see these patients, the more we're going to believe what he is saying about tumor being tumor, once and for all.

However, I don't think that I can be quite as pessimistic as his projections would indicate because our experience, which is different than his, is different because it's a smaller experience, and I think it is different also because we have a larger proportion, probably, of

familial patients who have multiple endocrinopathy, of which some of these have Zollinger-Ellison syndrome within it. And I think this does change our evaluation of gastrin levels and our evaluation of their future.

First of all, I would agree completely with the high levels of serum gastrin. If they are over 1000 picograms per mm, those patients have tumor.

What I'm concerned about are those patients who have a modest elevation of serum gastrin, somewhere between normal and 1000. And I think these levels can easily mean that they don't have a gastrinoma, but that they have another kind of tumor, maybe a serotonin-secreting tumor, or hyperplasia of any of the APUD cells of the whole endocrine system. At least, we have seen this happen. When they have a moderately elevated serum gastrin, they don't necessarily have a gastrinoma. They are likely to show up with something else, and they are very likely to be patients involved within a family of endocrinopathies.

Now, the authors have only one patient with a normal fasting serum gastrin, which surprises me, because in our small experience of about 15 patients we have 4 who have a normal fasting serum gastrin after having total gastrectomy. I have one patient with a modest elevation, up to 895, and he has no metastases that we could find by the routine tests—even exploration—but he has had a carcinoid tumor of the duodenum, and he probably still has one, and I think that is the cause of a moderately elevated serum gastrin.

There have been 5 deaths, one of which was a suicide, and all the deaths were associated with high serum gastrin levels, just as you have shown today. Four of these patients were sporadic. One was familial. And I think you have to divide them off, if you are going to make evaluations, and I couldn't tell, really, Dr. Zollinger, which of your patients have sporadic disease and which ones have familial or multiple endocrine adenopathy.

We have had three patients who have had objective evidence of regression of metastatic disease after total gastrectomy. One of these was a temporary regression, but he was apparently free of tumor for a period of 15 years. Then he escaped control, and had multiple hyperplasias and multiple tumors.

So you have to watch them, however, different our samplings are between our two experiences. These people must be repeatedly screened not only the patients themselves, but their families, because at the time you can't tell whether this is a familial situation or a sporadic situation.

As far as the chemotherapy is concerned, I have had very little experience. With the four deaths, two received intravenous Streptozotocin, and there was a reduction in serum gastrin levels, but the patients died. I think, if I had another patient who had hepatic metastases, I would certainly put him on an intra-arterial catheter and give him transhepatically, intra-arterial streptozotocin because of the good results that have been reported with metastases in liver from insulinomas and carcinoid cells, and from one or two patients with Z-E tumor in the liver.

One final remark, and a question. There have been a few reports of blackout spells, or seizures, in patients who had adudomas, specifically gastrin cell carcinomas, after total gastrectomy, even years later, and we have had two patients with blackout spells without hypoglycemia, without hypergastrinemia, but one of them had a slight elevation. In both of these patients the serotonin was elevated, and the serotonin was elevated in the patient who commited suicide.

I'm wondering if the association of hyperamines, or hyperserotoninemia, produces symptoms, a side we haven't described yet, and I wondered if they had ever seen patients with blackout spells, or seizures, postoperatively.

DR. RONALD K. TOMPKINS (Los Angeles, California): The contribution of the combination chemotherapy to the treatment of these malignant disease forms, of which there are two thirds of three quarters in that group, is a major one. We have not had any effective way to treat these patients prior to this, and we're all going to be very interested in seeing the followup of these initial few patients who have been treated. Although most of them had gastrinomas, there was one patient with watery diarrhea, hyperkalemia, and achlorhydria syndrome, or "pancreatic cholera" who was treated with this combination. And, of course, in this latter syndrome it's not possible to remove the target organ, as you do with a gastrinoma, since the target organ is the entire gastrointestinal tract.

In conclusion, I'd just like to ask Dr. Martin if he could tell us if they have had the opportunity to restimulate any of the patients after chemotherapy, to see if there is a change in the hormone levels from stimulation of calcium or secretin or magnesium after chemotherapy.

DR. BERNARD M. JAFFE (St. Louis, Missouri): I would like to ask one question. In the unique situation and ability you have to follow patients for fantastically long periods of time. Have you totally abandoned following changes in the basal gastrin as an important determinant in predicting survival? Do you get basal gastrin levels at prescribed periods? Have the levels changed? Have the changes echoed the changes that you have found with stimulation tests? Can you follow a patient with successive basal gastrin levels, or do you feel you need to have stimulation tests?

DR. EDWARD W. MARTIN JR. (Closing discussion): In addressing Dr. Tompkins' comments as far as secretin is concerned, we have found that, first of all, it's not available to everybody, and, secondly, it's more expensive. We agree that it does give you a nice quick response, but as Dr. Zollinger showed on some of the slides, we got a more dramatic response with the calcium. I think if somebody does have hypercalcemia or heart disease, it certainly could be used at that time.

Dr. Friesen, than you for your comments. One fourth of our cases are of the familial type, which we did not allude to in the manuscript. Half of these are doing very well, but another half not as well. Actually, Dr. Zollinger alluded to one such patient we just saw who had an angiogram. It is now one year since we started him on chemotherapy, and he has had a dramatic response to chemotherapy. Therefore, half of our familial endocrinopathies are in "trouble."

As far as deaths, we have had several deaths after the 5-year survival, so I think we have to look at the group that is less than 5 years with some skepticism, and wait for the final numbers to come in.

We're satisfied with the three-drug therapy. We have had absolutely no difficulty with it, no complaints. We don't have to beg the patients to tell us they feel better. They offer it. A lot of other types of chemotherapy have developed and the side effects are often much more severe and it has been an effort to get them to tell me they felt better because they were having a lot of nausea and vomiting, and side effects, but we have not had this difficulty. It's really a true good response, and they are having a better quality of life.

As far as intra-arterial Streptozotocin, I think that's pretty drastic, if you can have a report such as this, that we are having such good success; but that's just an individual situation.

We agree with Dr. Tompkins that this three-drug therapy is encouraging, and we encourage everybody here to take a long look at it, and if we have any unfavorable results, I'm sure Dr. Zollinger will be the first to admit it.

As far as Dr. Jaffe, we have followed the basal gastrin levels. We get them every time. But we do feel that the stimulation tests are a much better predictor of tumor activity.

Finally, Dr. Friesen, there have been no syncopal attacks that we know of. Nobody has had any blackout spells, or anything of this sort.