Observations on the Postoperative Tumor Growth Behavior of Certain Islet Cell Tumors

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Over a period of 21 years 39 patients with gastrinoma were surgically treated. Thirty-three patients had total gastrectomy with two postoperative deaths, and 6 patients had a lesser procedure. The postoperative fasting gastrin levels remained elevated and did not always indicate the extent of tumor involvement. Further mobilization of tumor gastrin by provocative infusion of calcium gluceptate, 15 mg/kg of body weight, should be carried out routinely. A hepatic angiogram should be considered when the gastrin levels exceed 1,000 picograms per ml. Chemotherapy consisting of Tubercidin, Streptozotocin and 5-Fluorouracil was given to 5 patients with extensive gastrinoma. All patients felt better and gained from three to 35 pounds in weight. Since 60% of the patients died or have definite evidence of tumor activity it is assumed that the tumor growth was not inhibited and that it is malignant. Approximately 40% of the patients seem to do well despite modest elevations in gastrin levels suggesting that the retained tumor could be considered benign.

IT HAS BEEN 21 years since certain islet cell tumors of the pancreas were accused of producing a potent gastric secretagogue responsible for a fulminating ulcer diathesis.[14] In the two decades since recognition of the syndrome, the secretagogue has been identified as gastrin, and total gastrectomy has been recognized as the best treatment in the majority of cases. It has been postulated that removal of the stomach may inhibit the growth of the retained tumor as well as hepatic metastases in some patients.[3] However, bizarre growth behavior of residual tumor with its effect on survival remains of considerable clinical interest. In an effort to evaluate the post-surgical growth behavior of these tumors, we undertook a study of 39 cases of gastrinoma.

Of 39 cases of gastrinoma treated, 33 had total gastrectomy with two postoperative deaths. Two of these patients committed suicide; one at three months and one at four and one-half years after total gastrectomy. For a variety of reasons 6 of the 39 patients had a lesser surgical procedure than total gastrectomy. These procedures included vagotomy and gastroenterostomy with left hemipancreatectomy; vagotomy and antrectomy; vagotomy and pyloroplasty; local excision of a small duodenal adenoma with vagotomy and pyloroplasty; local excision of a sizeable solitary adenoma; and left hemipancreatectomy, bilateral adrenalectomy, and ligation of the left gastric artery, and subsequent parathyroidectomy.

In all except three of the 39 patients microscopic proof of tumor was established by biopsy. Two of these three patients had total gastrectomy and the other had vagotomy and antrectomy. All three of these patients have had over the years persistent postoperative gastrin elevations ranging from 500 to 8900 picograms per ml (Pgm/ml) indicating presence of an active gastrin-producing tumor.

Study procedures included evaluation of the diagnostic value of fasting and stimulated gastrin levels, use of angiography, consideration of the effectiveness of chemotherapeutic agents and a study of survival in this group

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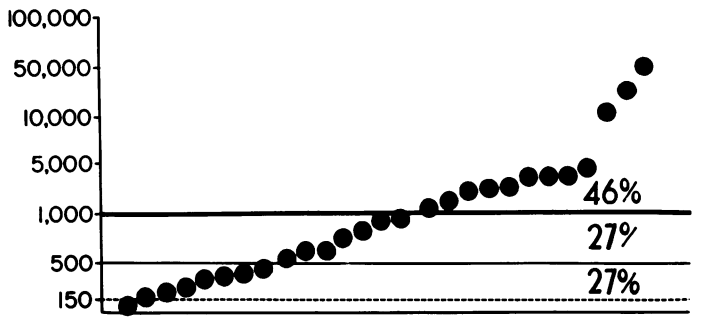

FIG. 1. All postoperative fasting gastrin levels except one, exceeded the normals of 150 pg/ml, as indicated by the dotted line.

of patients. Chemotherapy was initiated when liver metastases were proved or systemic symptoms of tumor activity were observed. Survival data were analyzed in an effort to substantiate the clinical impression that while some patients do well after total gastrectomy the majority eventually become worse. Patients were hospitalized in the Clinical Research Unit of the University Hospital, Ohio State University Medical Center. Time elapsed after operation varied, of course.

In the 26 patients studied since technic for measuring fasting gastrin levels became available, it was disturbing to find that in all but one patient the gastrin level was above our laboratory normal range of 150 Pgm/ml gastrin. These findings differed from observations on some of the same patients previously reported in 1973, undoubtedly due to improved technic in the performance of the gastrin radio-immunoassay.[9]

The patients fell into three groups differentiated by the range of their fasting gastrin levels (Fig. 1).

In 27% of the patients the fasting gastrin levels ranged between 100 and 500 Pgm/ml of gastrin. Another 27% had gastrin levels varying between 500 and 1,000 Pgm/ml of gastrin. The largest group, 46% of the patients, had gastrin levels from 1,000 Pgm/ml to much higher levels. These findings suggested the presence of active gastrin-producing tumors, even in many patients who appeared to have been perfectly well for many years following surgery. A gastrin level of 1,000 Pgm/ml or above was considered to be highly indicative of tumor activity and possible hepatic metastases.

In an effort to determine the most consistent and effective screening test for ferreting out postoperative tumor progression, 24 patients had infusions of calcium gluceptate as advocated by Passaro.[7] Fifteen of the patients who had had total gastrectomy had three provocative infusion tests including Jorpes secretin,[4,11] magnesium sulfate,[2,12] and calcium gluceptate. The average maximum response to these three provocative tests is shown in Fig. 2. One clinical unit of Jorpes secretin per kg of body weight given over a period of one hour produced prompt elevation of gastrin. Magnesium sulfate given in a dosage of 1.6 milliequivalents per kg of body weight over a period of 4 hours stimulated a higher gastrin level than secretin. Fifteen milliequivalents of calcium gluceptate per kg of body weight produced the most pronounced gastrin elevations in the majority of patients. The magnesium sulfate infusions tended to make the patients more uncomfortable than did the other infusion tests.

The fasting gastrin level was doubled by calcium gluceptate infusion in 86% of the patients, by magnesium sulfate in 50%, and by secretin in 21%, A gastrin response two and one-half times the fasting level occurred in 50% of patients following the calcium infusion, in 15% following magnesium sulfate, and only in 7% after secretin infusion. However, secretin did on occasion show a dramatic elevation in gastrin in the presence of proved hepatic metastases. In one patient with extensive hepatic metastases gastrin levels were singularly elevated to 40,000 Pgm/ml of gastrin following the secretin infusion and again a year later the secretin response remained much higher than that following infusion of magnesium sulfate or calcium gluceptate.

We agree with others that the calcium gluceptate infusion over a period of 4 hours with hourly determinations of serum calcium and gastrin levels produces the most consistent and dramatic elevations.[12] The only deterrant to its use might be in the presence of a fasting hypercalcemia associated with hyperparathyroidism or in cardiac patients when further elevations in serum calcium levels would be undesirable. Since the serum calcium levels were found to be minimally altered by secretin[2] and definitely depressed by magnesium sulfate, either of these two infusions should be substituted in the presence of hypercalcemia.

An interesting finding worthy of further speculation was elevation of the bone isoenzyme in 13 of 14 patients from fractionization of the alkaline phosphatase. In only 4 of these patients was the liver isoenzyme level also elevated.

The provocative calcium infusion studies in 24 patients proved the unreliability of fasting gastrin levels as an index of postoperative tumor activity, especially when such levels are below 500-Pgm/ml (Fig. 3). Six of the 7 patients with a fasting gastrin of less than 500 Pgm had levels above 500 Pgm following the calcium gluceptate infusion, suggesting persistent tumor activity. Only one (4%) did not exceed 500 Pgm following the calcium infusion challenge, but the fasting level of 100 Pgm/ml of gastrin was more than tripled. This patient had had only local excision of a 6 × 4 × 3 cm solitary tumor approximately 9 years previously. In 8 patients (30%) gastrin levels were between 500 and 1,000 Pgm/ml, and in 15 patients (66%) gastrin level was above 1,000 Pgm/ml. In the latter group, hepatic metastases should be strongly

suspected. Eight of these patients (53%) had proved hepatic metastases and three died. Hepatic angiogram was negative in the remaining 4 patients. Hepatic angiography is indicated when either the fasting or postprovocative infusion gastrin levels exceed 1,000 Pgm/ml.

During the past year chemotherapy has been given to all patients with hepatic metastases are verified or there is strong clinical evidence of increased tumor activity. Five of our patients on chemotherapy had had total gastrectomy, and one had had vagotomy and pyloroplasty.

Though many chemotherapeutic agents have been tried in the management of gastrin-producing islet cell tumors, only a few are effective. A combination of two toxic antibiotics, Tubercidin and Strpetozotocin, and the antimetabolite 5-Fluorouracil was selected.[1] Tubercidin (7-deazaadenosine), a molecule similar to adenosine, effectively alters RNA and DNA, stopping protein synthesis and DNA and RNA production and results in cell death. Pancreatic islet cells have been especially sensitive to this cytotoxic agent.

Murray-Lyon[6] reported in 1968 that the cytotoxic agent Streptozotocin (1-methyl-1-nitrosourea) was effective in the management of islet cell tumors. Previous animal studies had shown this agent to be diabetogenic. Tubercidin and Streptozotocin were combined with 5-Fluorouracil, which is the single most effective agent in the management of adenocarcinoma of the gastrointestinal tract, in a clinically safe dosage. No deaths or serious renal or liver toxicity resulted from this regimen. Transient bone marrow suppression does occur and an occasionally serious thrombophlebitis develops from Tubercidin if the rate of infusion is less than four hours.

On the first day Tubercidin was given in a dosage of 1.5 mg per kg of body weight mixed in 500 cc of the patient's own blood. The infusion is well tolerated if given slowly over a minimum of 4 hours. Twelve and one-half milligrams per kilogram of 5-Fluorouracil is given the same day and repeated for two additional days. After a 7-day rest period, a weekly dose of 12.5 mg per kg of Streptozotocin is given, alternating with a similar dose of 5-Fluorouracil for the next 6 weeks. After a rest period of 28 days the regimen is repeated, providing the hematologic picture is satisfactory and fasting glucose levels are within normal range.

Sardoff and Franklin[8] in 1972 reported a weight gain of 70 pounds in a patient with diffuse metastases to the liver associated with a gastrin-producing tumor. A total of 66 g of Streptozotocin was given to the patient in divided doses every two to three weeks for one year. The hepatic metastases regressed and he remained symptom-free for several years but his fasting serum gastrin eventually rose above 500 Pgm/ml. He had previously failed to respond to 5-Fluorouracil and

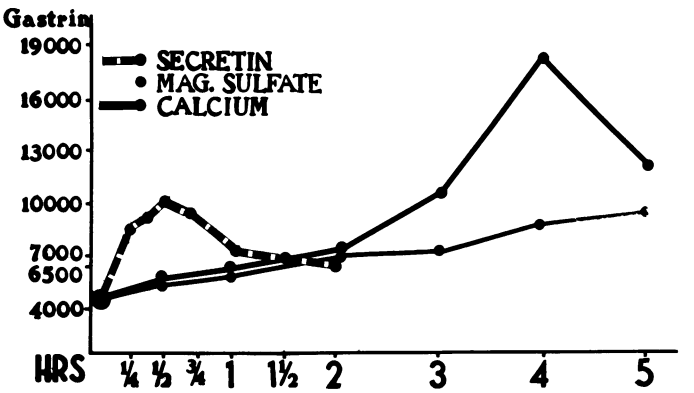

FIG. 2. The mean gastrin response in 12 post-total gastrectomy patients to each of three provocative infusion studies, demonstrated the superiority of calcium gluceptate.

cyclophosphamide therapy. In one patient a marked recession of the hepatic metastases was demonstrated by a second hepatic angiogram following chemotherapy for a period of 9 months. All 5 patients given chemotherapy volunteered that they felt better and each had a weight gain ranging from 3 to 35 pounds.

In one patient chemotherapy appeared to be quite effective in the control of the diarrhea associated with the islet cell tumor which produces pancreatic cholera.[5,10] The diarrhea had recurred two and one-half years after resection of the original tumor despite recent extirpation of a left hepatic lobe metastasis. The patient had normal stools within 30 days after treatment was started and has remained symptom-free for almost one year. His weight has remained stable and he is working every day.

It is acknowledged that different drugs have been used with varying success, and a much longer period of time will be required to evaluate the effectiveness of this particular triple drug chemotherapy program. Too often chemotherapy has been withheld because of the slow and uncertain course of the tumor until the patient's liver is filled with metastases.

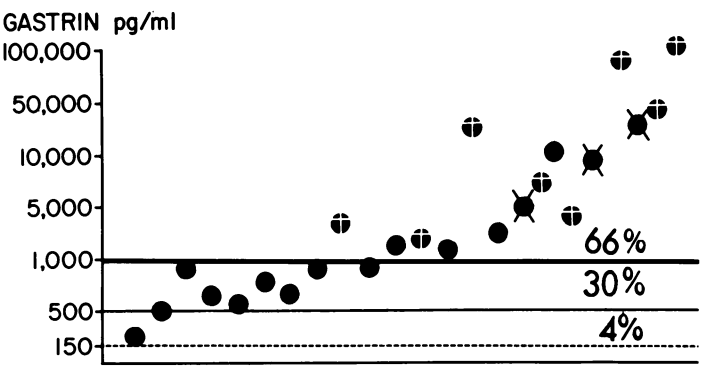

FIG. 3. The provocative infusion of calcium gluceptate provides more reliable postoperative information regarding tumor activity than fasting gastrin levels.

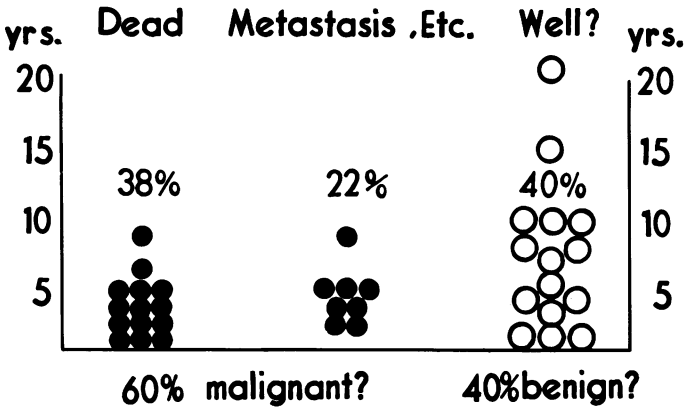

FIG. 4. The course of approximately 60% of the postoperative patients with gastrinoma are consistent with a malignant tumor.

An effort was made to analyze the survival pattern of the 37 patients with a gastrinoma (Fig. 4). Of 14 deaths, 38% of all patients, all but two occurred within 5 years after operation. One patient died of progressive tumor involvement 7 years and another 8 years following total gastrectomy, indicating a slow but sustained growth of the neoplasm.

Of 8 patients (22%) who had evidence of hepatic metastases or definite clinical evidence of tumor progression with gastrin levels above 1,000 Pgm/ml, 6 had had total gastrectomies, and two a lesser procedure. In 5 of the 6 total gastrectomy patients the liver metastases were visualized by angiogram and in one patient a solitary tumor nodule was excised from the undersurface of the left lobe.

In the two patients who had had procedures other than total gastrectomy, there was evidence of aggressive tumor activity. One of these patients had x-ray evidence of a deep ulcer crater in the second portion of the duodenum which accounted for several brisk upper gastrointestinal hemorrhages. She repeatedly refused total gastrectomy, so chemotherapy was started. Only time will tell whether or not the extensive tumor in the head of the pancreas can be controlled sufficiently to avoid further ulcer complications. The second patient had multiple endocrine gland involvement of the parathyroids, adrenals, and islets of the pancreas, and hypercalcemia and had been advised to have total gastrectomy because of ulcer symptoms. Seven of the 8 demonstrated metastatic involvement within 5 years after surgery.

Fifteen patients (40%) are presently living at intervals ranging from one to 22 years after operation. Of the 10 patients living longer than 5 years, one has angiographic evidence of extensive liver involvement with high gastrin levels so that only 9 (24%) are free of disease 5 years after operation. The advanced cases included early in this series may account for a lower survival rate than that reported in the literature.[13]

Survivors include one patient who had excision of a solitary pancreatic adenoma, a second with excision of a duodenal wall adenoma, and a third who had vagotomy and antrectomy. The latter patient has gastrin levels that exceed 1,000 but hepatic angiograms have not as yet been made. The remaining 12 patients had total gastrectomies. While these 15 patients are currently doing well, it must be assumed that more than one, especially in the less than 5-year survival group, will get into difficulty from further tumor growth.

Of 23 living patients including those with or without metastases, 22 are working. One patient who had total gastrectomy and excision of a solitary hepatic metastasis four and one-half years ago, has remained a nutritional problem with a body weight of 76 pounds. A dietary evaluation of the majority of these patients showed an average intake of 1700 to 3500 calories per day. Several patients improved their nutrition by stopping smoking and dramatically reducing their coffee intake from 10 or 15 cups to two a day. Approximately 60% of the survivors who had total gastrectomy have reached or exceeded their calculated ideal weight.

Regardless of how the data were evaluated, it was evident that approximately 60% or more of the patients had died or were in difficulty because of a tumor that behaved as a malignancy. Wilson,[13] in a survey of 621 reported cases, concluded that approximately 59% proved malignant, 35% proved benign, and 6% demonstrated islet cell hyperplasia. Of the 40% of our patients living with apparently benign disease, one has lived over 22 years and another, 14 years, 7 have lived from 5 to 10 years, while 6 patients have yet to pass the 5-year mark. It may well be that the incidence of malignancy judged to be approximately 60%, accounts for the postoperative tumor growth behavior of the gastrin-producing islet cell tumor. The persistence of elevated postoperative gastrin levels suggests either metastaes or multicentric islet cell tumor involvement in almost every patient. Perhaps acceptance of the adage of "once a tumor always a tumor" would be a useful philosophy in the long-term care of these patients.

Conclusions

The adage "once a tumor always a tumor" may be relevant to the truth about gastrinoma; an elevated fasting gastrin level found on routine postoperative testing suggests the presence of retained or progressive tumor in almost all patients.

Fasting gastrin levels may not indicate the extent of tumor involvement. Provocative infusions of calcium gluceptate, 15 mg per kg of body weight, should be made routinely at periodic postoperative evaluation. This test appears to be superior to and more consistent than the secretin or magnesium sulfate provocative infusions.

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