Usefulness of Selective Arterial Secretin Injection Test for Localization of Gastrinoma in the Zollinger–Ellison Syndrome

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Secretin was injected into a feeding or nonfeeding artery of a gastrinoma and blood samples were taken from the hepatic vein (HV) or a peripheral artery (PA) to measure the changes of serum immunoreactive gastrin concentration (IRG). The IRG in the HV rose within 40 seconds and in the PA rose within 60 seconds after the injection of secretin into a feeding artery, but not after secretin was injected into a nonfeeder. These results indicated that secretin directly stimulates a gastrinoma to release gastrin *in vivo*. The selective arterial secretin injection test (SASI test) was applied in three patients in whom gastrinomas could not be located by computed tomography, ultrasonography, or arteriography, and functioning gastrinomas were located in all three patients. In one patient, malignant gastrinomas in the head of the pancreas and in the duodenum could be resected radically with the help of this test.

SINCE ISENBERG ET AL.[1] discovered the paradoxical rise of serum gastrin levels after the intravenous injection of secretin in patients with the Zollinger–Ellison syndrome (ZE syndrome), the differential diagnosis of the ZE syndrome has become easier.[2] *In vitro* studies of this reaction have shown that secretin directly stimulates gastrinoma to release gastrin.[3,4] To ascertain whether this is also true *in vivo*, secretin was injected into the feeding arteries of the tumors visualized by arteriography in two patients with the ZE syndrome, and serial changes in the serum immunoreactive gastrin concentration (IRG) in the hepatic vein (HV) or a peripheral artery (PA) were recorded. On the basis of the results, a new technique for localization of gastrinoma, Selective Arterial Secretin Injection Test (SASI test), was invented and applied to three patients in whom computed tomography (CT), ultrasonography (US), or arteriography could not visualize the functioning gastrinoma.

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Methods

Selective Arterial Secretin Injection Test (SASI test)

At the time of abdominal arteriography in patients with the ZE syndrome, 30 units of secretin in a 2-mL solution were injected into the splenic or gastroduodenal or common hepatic or superior mesenteric artery, and 3 mL of blood was drawn from the HV through a catheter inserted *via* a femoral vein before the injection and 20, 40, 60, 90, and 120 seconds after the injection. Blood samples were also taken from a PA every minute for 3 minutes (Fig. 1). The secretin used in this study was Secrepan® (Eisai Co. Ltd, Tokyo, Japan), which is a pure extract of porcine duodenum and jejunum and has no glucagon, vasoactive intestinal peptide, cholecystokinin, or somatostatin activity.[5,6] One unit of Secrepan® is equal to one Crick, Haper and Raper unit.

Radioimmunoassay of Serum Gastrin and Insulin

Blood samples were centrifuged and serum was frozen at −80 C until measurement of immunoreactive gastrin (IRG) and immunoreactive insulin (IRI). IRG was measured with a gastrin radioimmunoassay kit (Otsuka Assay Co. Ltd., Tokyo, Japan), and IRI was measured with an insulin radioimmunoassay kit (Dinabot Co. Ltd., Tokyo, Japan). In Case 3 the intraoperative changes of serum IRG were measured by the shortening of the incubation time with antibody 1611 (generous gift from Dr. J. H. Walsh, Los Angeles, CA) as described before[7]; *i.e.*, the

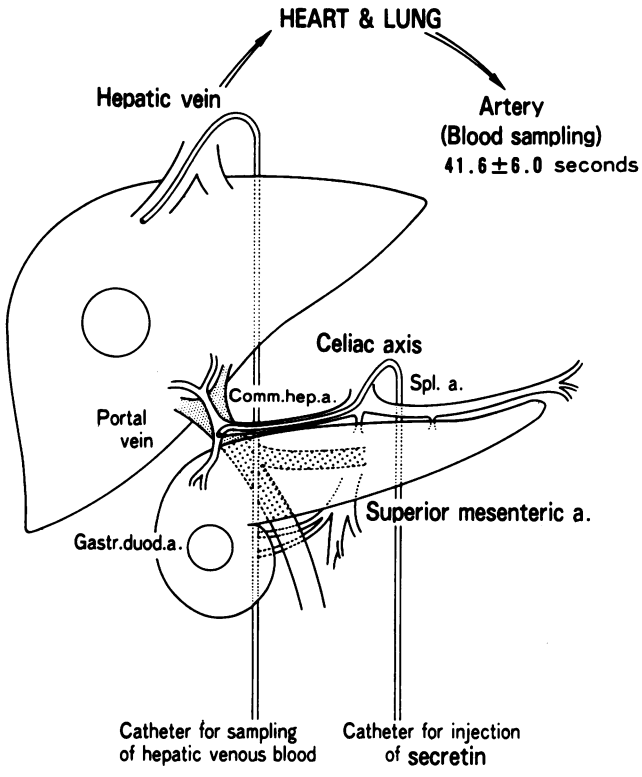

FIG. 1. Diagram of SASI test for localization of functioning gastrinomas. The tip of a catheter for arteriography was selectively inserted into a branch of the celiac axis or the superior mesenteric artery, and secretin was injected into the artery as a bolus. Blood samples were taken from the HV and a PA for a few minutes. If a gastrinoma is present in the area fed by the artery and releases gastrin after direct stimulation by secretin, serum IRG is expected to rise within 40 seconds in the HV and within 70 seconds in a PA. We could ascertain that secretin stimulates gastrinoma to release gastrin *in vivo*, and this test is useful for localization of gastrinoma in the following cases.

reaction mixtures were incubated 1 hour at room temperature. In a preliminary study we obtained a good interassay coefficient between 1 hour of incubation at room temperature and 20 hours of incubation at 4 C.

Pathologic Examination of the Resected Tumor

A piece of the tumor was fixed in both Bouin's solution and 10% formalin solution and embedded in paraffin. Paraffin sections were stained with Masson-Fontana, Grimelius, and Hellerstrom-Hellman silver stains. Immunohistochemical staining was done with either Sternberger's peroxidase antiperoxidase (PAP) method[8] or Nakane's indirect method.[9] Antisera prepared for this study were rabbit antigastrin serum (a gift of Professor N. Yanaihara, Shizuoka College of Pharmacy, Shizuoka, Japan), guinea pig antiporcine insulin serum (Miles Lab., Slough, England), rabbit antiglucagon serum (Japan Immunoresearch Lab., Tokyo, Japan), and rabbit antibovine pancreatic polypeptide serum (a gift of Professor R. E. Chance, Eli Lilly Co., Indianapolis, IN). Peroxidase activity was demonstrated with 3,3-diaminobenzidin by the method of Graham and Karnovsky.[10]

For the electron microscopic examination, specimens of the tumor were fixed in 2% glutaraldehyde in 0.05 M phosphate buffer (pH 7.2) and embedded in Epon 812. Thin sections were cut with a Potter-Blum MT II ultramicrotome (Ivan Sorvall, Norwalk, CT), stained with 2% uranyl acetate and Reynold's lead citrate solution, and observed under a Hitachi HU 12A electron microscope (Hitachi Co., Tokyo, Japan).

Results

Patients with the ZE Syndrome in whom Tumors were Visualized with Arteriography

Case 1. A 35-year-old female had been treated medically for a duodenal ulcer for a few years when she visited Kishiwada Tokushuukai Hospital. Her serum IRG was 550 pg/mL. Gastric juice analysis revealed a basal acid output (BAO) of 31.3 mEq/h, a maximum acid output (MAO) of 32.3 mEq/h, and a BAO/MAO ratio of 0.97. Intravenous injection of 3 U/kg of secretin raised the serum IRG basal 2,900 pg/mL to 41,000 pg/mL 5 minutes later. CT demonstrated a space occupying lesion in the head of the pancreas and multiple metastatic lesions in both lobes of the liver. Chemotherapy with tegafur and streptozotocin was without success and the serum IRG reached 15,000 pg/mL.

On July 27, 1984, abdominal arteriography showed multiple gastrinomas in the liver, one of which had invaded the diaphragm and was partly fed by the right inferior phrenic artery. The SASI test was performed first through the right inferior phrenic artery, which was feeding a gastrinoma (Fig. 2). Thirty units of secretin were injected into the right inferior phrenic artery. Blood samples were taken from a peripheral artery before the injection and 1, 2, 4, and 7 minutes after the injection of secretin. Twenty minutes later, 30 U of secretin were injected into the proper hepatic artery, and peripheral arterial blood was sampled again. Then, embolization of the hepatic gastrinoma that had invaded the diaphragm was performed through the right inferior phrenic artery with spongel powder. Ten minutes later, 30 U of secretin were injected into the right inferior phrenic artery again, and blood samplings were performed. Table 1 shows the results of the study. When the secretin was

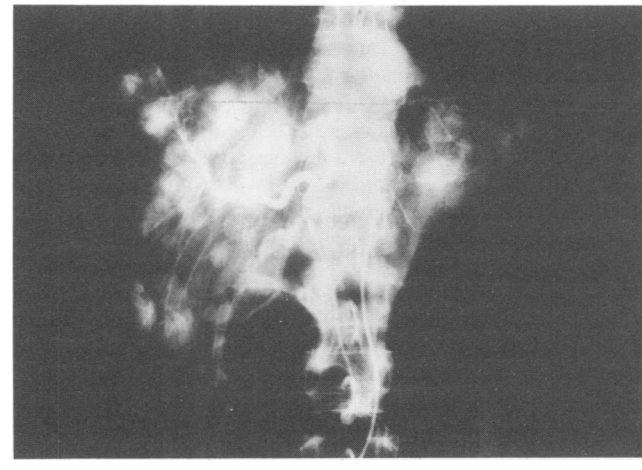

FIG. 2. Case 1: superselective arteriography *via* the proper hepatic artery. Multiple metastases of a pancreatic gastrinoma were visualized. The SASI test was performed *via* the right inferior phrenic artery, which was feeding one of the hepatic metastatic gastrinomas, and the proper hepatic artery.

TABLE 1. *Changes of IRG and IRI in a PA after Injection of Secretin into the Inferior Phrenic Artery and the Common Hepatic Artery*

Time (min)	Secretin (30 U)	IRG (pg/mL $\times 10^{-4}$)	IRI (μU/mL)
0	into inferior	1.49	10.4
1	phrenic artery	2.03	11.8
2		1.99	14.3
4		2.09	12.8
7		1.82	12.7
Arteriography			
0	into common	1.75	11.2
1	hepatic artery	3.03	12.1
2		3.03	13.0
4		2.65	10.2
7		2.28	11.7
Embolization			
0	into inferior	1.78	11.4
1	phrenic artery	2.73	12.2
2		2.72	13.1
5		2.55	10.0

injected into the inferior phrenic artery that was feeding a gastrinoma, arterial IRG rose to a maximum 1 minute after the injection and then began to decrease. The difference in the basal IRG and the maximum IRG was 5,200 pg/mL. The arterial IRG rose to a maximum at 1 minute in the subsequent two injections as well. The difference between the basal IRG and the maximum IRG was 10,000 pg/mL after the second injection and 9,000 pg/mL after the third injection.

Case 2. A 47-year-old male had an emergency subtotal gastrectomy and gastrojejunostomy after Billroth II anastomosis for a bleeding duodenal ulcer on January 25, 1982. On the second postoperative day, tarry stools began and an anastomotic leak complicated the postoperative course. Serum IRG was 800 pg/mL, and a total gastrectomy was performed on February 25, 1982. In the resected specimen we found an ulcer in the remnant stomach and two ulcers in the anastomotic jejunum. An intravenous injection of 3 U/kg of secretin elevated the serum IRG from the basal 580 pg/mL to 830 pg/mL at 2 minutes on July 22, 1982. Celiac arteriography that was performed on July 27, 1982, revealed a hypervascular tumor stain in the body of the pancreas (Fig. 3). At that time 2 U, 5 U, and 15 U of secretin were injected into the splenic artery successively at intervals of 10 minutes, and arterial blood samples were taken before the injection and 40 seconds, 1 minute, 2 minutes, and 5 minutes after the injection. The results are shown in Table 2. Neither arterial IRG nor IRI rose after the injection of 2 U and 5 U of secretin. Changes in serum IRG and IRI after the injection of 15 U of secretin were as follows: IRG (pg/mL) was 305 before the injection, 275 at 40 seconds, 320 at 1 minute, 370 at 2 minutes, and 365 at 5 minutes; and IRI (μg/mL) was 14 before the injection, 14 at 40 seconds, 23 at 1 minute, 23 at 2 minutes, and 22 at 5 minutes after the injection (Table 2). Thus, the injection of 15 U of secretin into the splenic artery raised the arterial IRI but did not raise the arterial IRG at 1 minute after injection. One month later, the SASI test was performed again to confirm the former results. This time 50 U of secretin were injected into the splenic artery. Changes in the arterial IRG and IRI were as follows: IRG (pg/mL) was 800 before the injection, 790 at 1 minute, 1160 at 2 minutes, 1090 at 5 minutes, and 950 at 10 minutes; IRI (μg/mL) was 14 before the injection, 17 at 1 minute, 25 at 2 minutes, 32 at 5 minutes, and 17 at 10 minutes after the injection (Table 2). Even with a large dose of secretin, the arterial IRG did not rise at 1 minute although the arterial IRI rose 1 minute after injection.

On August 4, 1982, laparotomy was performed. There was a tumor 1.0 × 1.5 × 2.0 cm in the body of the pancreas, and a distal pancre-

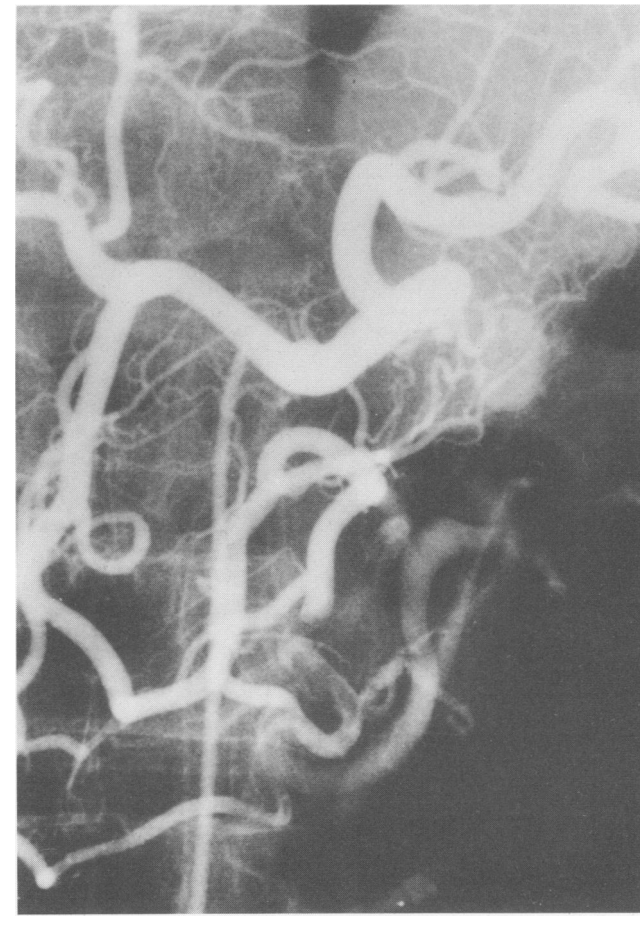

FIG. 3. Case 2: celiac arteriography. A tumor stain is visualized in the body of the pancreas. No other tumor was visualized with abdominal arteriography.

TABLE 2. *Changes of IRG and IRI in a PA after Injection of Secretin into the Splenic Artery of a Patient with Gastrinoma (Case 2)*

Time (min)	Secretin (U)	IRG (pg/mL)	IRI (μU/mL)
0	5	230	14
40 seconds		275	14
1		225	15
2		315	16
5		285	16
10		310	14
20	15	305	15
40 seconds		275	14
1		320	23
2		370	23
5		365	22
10		370	15
20		340	10
One month later			
0	50	797	14
1		785	17
2		1155	25
5		1085	32
10		948	17
20		612	15

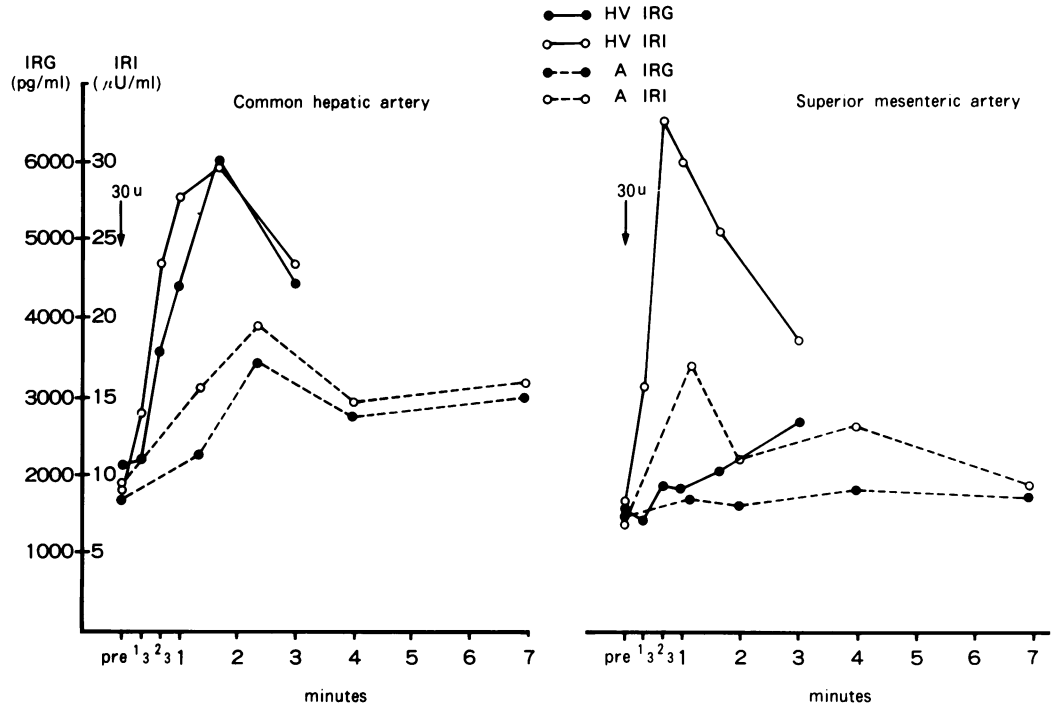

FIG. 4. Case 2: results of SASI test performed 13 months after distal pancreatectomy. Changes of IRG and IRI in the HV and a PA after the injection of 30 U of secretin into the common hepatic artery and the superior mesenteric artery are shown. IRG and IRI in the HV rose within 40 seconds, and within 70 seconds in the PA. The injection of secretin into the superior mesenteric artery caused no rise of IRG in either the HV or the PA for 2 minutes, although IRI rose at 20 seconds in the HV and at 70 seconds in the PA.

atectomy was performed. Half of the tumor was cultured in the culture medium by the method we described 4 years ago[3]; however, no immunoreactive gastrin activity was detected in the culture medium. The serum IRG of the patient did not decrease after the distal pancreatectomy. Serum IRG was 4828 pg/mL on the third postoperative day, and 5000 pg/mL 10 months later. An immunohistochemical examination revealed that about 20% of the tumor cells reacted with antisomatostatin serum, about 15% of the cells reacted with antigastrin serum, and about 10% of the cells reacted with antiglucagon serum. The resected tumor had not secreted gastrin in the culture medium or *in vivo*, and gastrinomas were still present somewhere in the patient's body. On November 26, 1983, the SASI test was performed again. This time the tip of the catheter was placed in the common hepatic artery close to the opening of the gastroduodenal artery, and another catheter was inserted into the right HV *via* the right femoral vein. Then, 30 U of secretin was injected into the common hepatic artery, and blood samples were drawn from both the HV and a PA (Fig. 4). Both serum IRG and IRI in the HV started to rise at 40 seconds and reached a peak 100 seconds after the injection (Table 3). Serum IRG and IRI in a PA started to rise 70 seconds after the injection. After the injection of secretin into the superior mesenteric artery, the serum IRI in the HV rose significantly at 20 seconds, although the serum IRG did not rise for 60 seconds.

TABLE 3. *Changes of IRG and IRI in the HV and a PA after Selective Arterial Injection of Secretin in Case 2 after Distal Pancreatectomy*

		HV		PA	
Time (sec)	Secretin (30 U)	IRG (pg/mL)	IRI (μU/mL)	IRG (pg/mL)	IRI (μU/mL)
0	Common	2087	8.4	1672	9.2
20	hepatic	2223	14.0		
40	artery	3617	23.6		
60		4349	27.9		
90				2272	15.5
100		5977	29.3		
130				3427	18.3
180		4499	23.5		
240				2714	14.6
420				2948	16.0
0	Superior	1601	7.7	1401	6.5
20	mesenteric	1382	16.6		
40	artery	1865	32.2		
60		1783	30.2		
70				1674	16.8
90		2085	25.4		
120				1558	11.3
180		2735	18.1		
240				1773	13.0
420				1652	8.6

Patients with the ZE Syndrome in whom Diagnostic Imaging Techniques were not Useful for Localization of Gastrinoma

Case 3. A 53-year-old man had three operations for complications of a peptic ulcer before he visited our clinic on March 31, 1986; partial gastrectomy with Billroth II reconstruction for a duodenal ulcer on June 20, 1974; partial resection of the jejunum for perforation of the anastomotic jejunum on April 5, 1984; and partial resection of the stomach and the jejunum for bleeding gastric ulcers on November 10, 1984. The serum IRG was 225 pg/mL on December 10, 1984, and between 100 and 230 pg/mL since then. The intravenous secretin injection test with 3 U/kg of secretin was positive; the serum IRG (pg/mL) was 100 before the injection of secretin, 172 at 2 minutes, 184 at 4 minutes, 156 at 6 minutes, 146 at 10 minutes, and 139 at 15 minutes after the injection. Cimetidine had been administered 1 gram/day for a year and 4 months since the last operation, but tarry stools were sometimes noticed and had become more frequent during the last few months.

After admission, CT, US, and arteriography were performed, but they revealed no abnormality in the abdomen. Endoscopic examination of

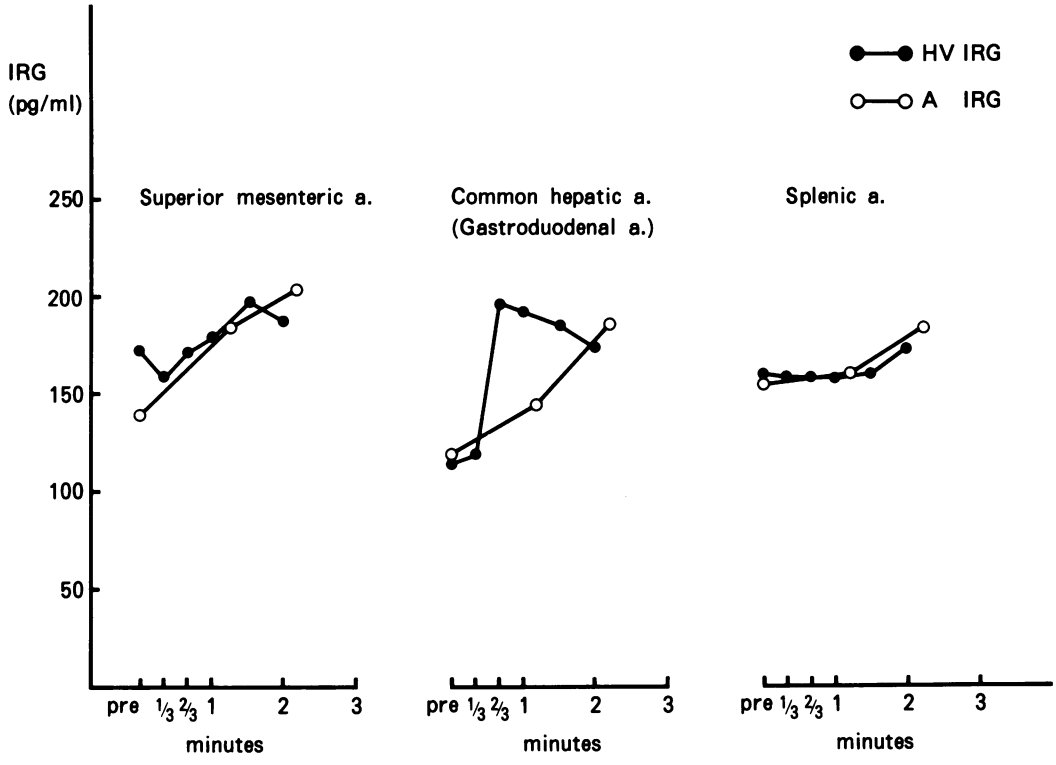

FIG. 5. Case 3: results of SASI test performed 20 days before enucleation of the tumor in the head of the pancreas. IRG in the HV rose within 40 seconds after the injection of secretin into the common hepatic artery close to the opening of the gastroduodenal artery, but not after the injection of secretin into either the superior mesenteric artery or the splenic artery.

the upper gastrointestinal tract revealed a gastric ulcer and two anastomotic jejunal ulcers. The SASI test was performed at the time of arteriography on April 2, 1986 (Fig. 5). The serum IRG rose 40 seconds after the injection of 30 U of secetin into the common hepatic artery very close to the opening of the gastroduodenal artery. The difference between the basal IRG and the maximum IRG was 100 pg/mL. No significant rise of serum IRG was observed in the HV for 1 minute after the injection of the same dose of secretin into either the splenic artery or the superior mesenteric artery.

Laparotomy was performed on April 22, 1986. Kocher's mobilization of the duodenum and the head of the pancreas revealed a pea-sized purple tumor on the posterior superior surface of the head of the pancreas (Fig. 6). The tumor was enucleated. Intraoperative pathologic examination of a frozen section showed a metastatic tumor consistent with a diffuse endocrine system tumor (possibly G cell tumor or G cell carcinoid). Careful palpation and inspection revealed no other abnormalities of the duodenum, pancreas, gallbladder, or hepatoduodenal ligament, so the abdomen was closed. After operation, a part of the tumor was cultured, as described above. The IRG in the culture medium was as high as 20 ng/mL. Immunohistochemical examination of the tumor revealed that about 60% of the tumor cells reacted with antigastrin serum, and about 15% of the cells reacted with antisomatostatin serum, but the postoperative serum IRG level did not decrease and was as high as 100 pg/mL. The intravenous secretin injection test with 3 U/kg of secretin was still positive, with a serum IRG (pg/mL) of 91 before injection, 116 at 2 minutes, 150 at 4 minutes, 162 at 6 minutes, 138 at 10 minutes, and 117 at 15 minutes after injection. The SASI test was performed again on May 12, 1986 (Fig. 7). An injection of 30 U of secretin into the gastroduodenal artery caused a prompt rise of serum IRG in the HV at 20 seconds, but injection of 50 U of secretin into the splenic artery did not. The injection of 30 U of secretin into the superior mesenteric artery caused a gradual rise of serum IRG in the HV for 60 seconds.

A laparotomy was performed again on June 6, 1986. A pancreatoduodenectomy was performed, although no tumor was palpable in the pancreas or the duodenum. The pancreas was resected along a line 1 cm left of the edge of the superior mesenteric vein. The gallbladder was extirpated, and lymph nodes in the hepatoduodenal ligament or around the common hepatic artery were removed. This time the intraoperative measurement of serum IRG was performed by the rapid incubation technique. At the beginning of the operation, the serum IRG was 116 pg/mL. Thirty minutes after the pancreatoduodenectomy, an intraoperative intravenous secretin injection test with 3 U/kg of secretin was performed. Changes in the serum IRG (pg/mL) were as follows: 66.8 before injection, 58 at 2 minutes, 66 at 4 minutes, and 62 at 6 minutes after injection. The test

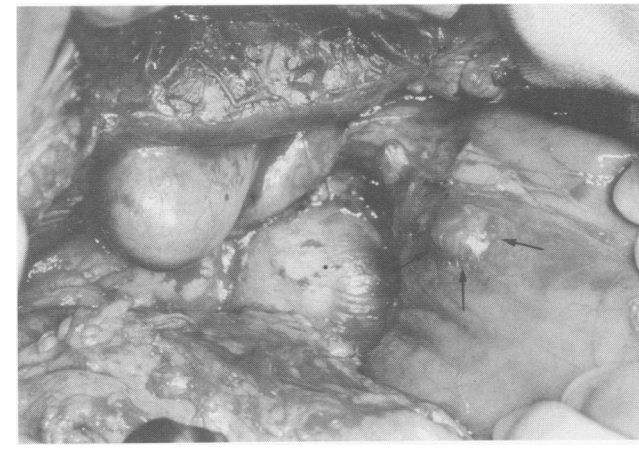

FIG. 6. Intraoperative findings of Case 3. A pea-sized tumor was present on the superior posterior surface of the head of the pancreas (arrows). The tumor was extirpated. No other tumor was palpable in the duodenum or the pancreas.

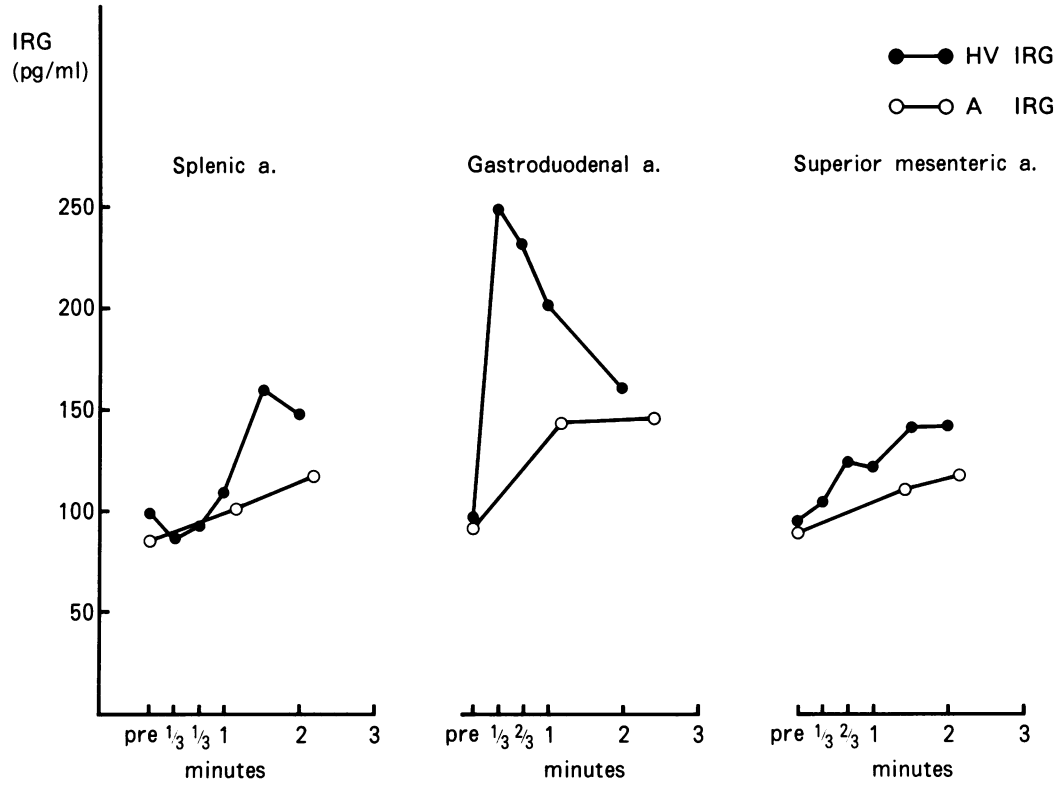

FIG. 7. Case 3: results of SASI test after enucleation of the gastrinoma, which was proved pathologically to be a lymph node metastasis at the head of the pancreas. IRG in the HV rose within 20 seconds after the injection of secretin into the gastroduodenal artery, but not after the injection of secretin into either the splenic or the superior mesenteric artery. These results indicated that gastrinomas were probably still present in the superior part of either the duodenum or the head of the pancreas.

was negative, so we closed the abdomen. Immunohistochemical study of the resected specimen revealed two minute submucosal gastrinomas 1.0 mm in diameter in the duodenum and eight microscopic gastrinomas about 0.8 mm in diameter in the head of the pancreas (Fig. 8). A duodenal submucosal tumor was barely palpable in the resected specimen. No other tumors could be detected either by palpation or by inspection. They could be diagnosed only by a microscopic pathologic study. After operation, the serum IRG was as low as 34 pg/mL, and the intravenous

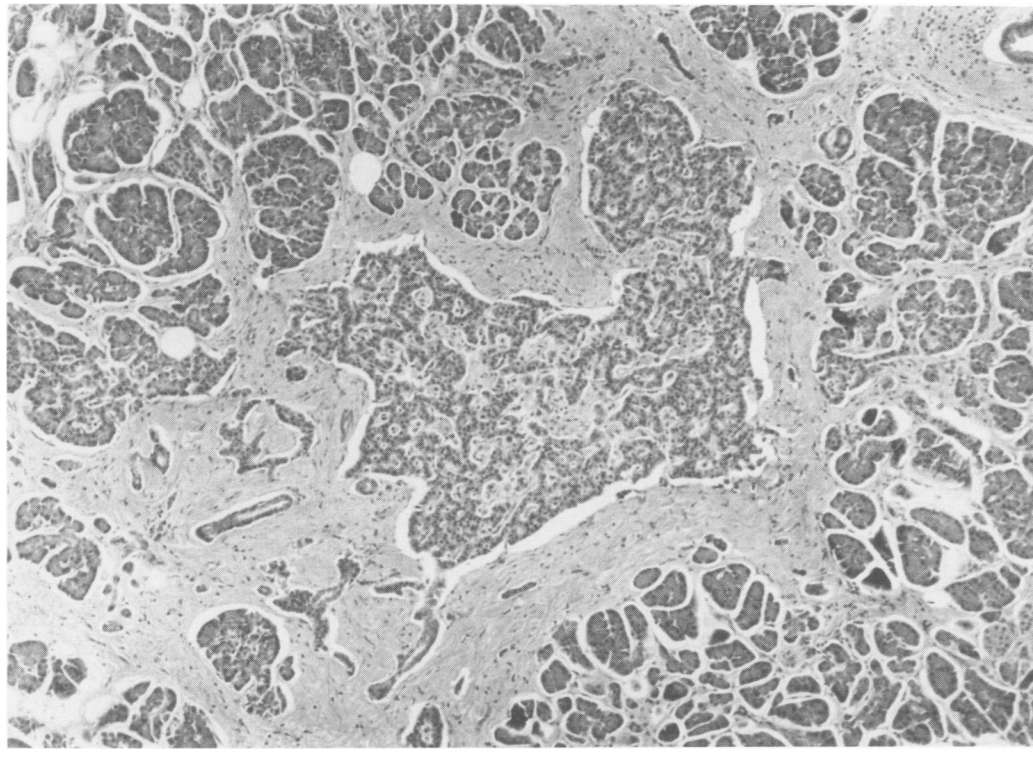

FIG. 8. Case 3: microscopic appearance of the intrapancreatic minute gastrinoma (hematoxylin and eosin stain, ×40). There were eight such tumors in the superior head of the pancreas and two minute gastrinomas in the duodenum. Immunohistochemical study revealed that 60% of the tumor cells reacted with antigastrin serum, 30% with antiglucagon serum, and a few cells with anti-insulin and antisomatostatin serum.

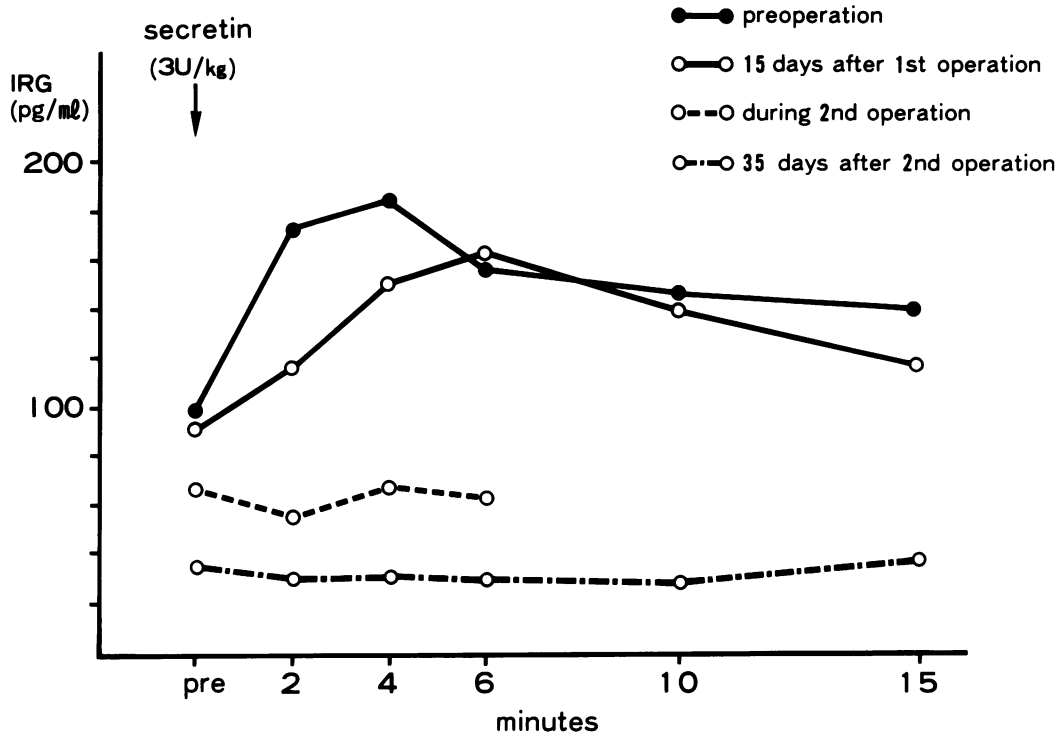

FIG. 9. Case 3: results of intravenous secretin injection test before and after the first operation, during the second operation, and 30 days after the second operation. The second pancreatoduodenectomy appears to have been successful in removing all gastrinomas.

secretin injection test was negative on the 30th postoperative day (Fig. 9).

Case 4. A 67-year-old female vomited occult blood in September, 1982, and was found to have a gastric ulcer. Analysis of the gastric juice revealed a BAO of 10.8 mEq/h, MAO of 16.4 mEq/h, and BAO/MAO of 0.86. The serum IRG was 1200 pg/mL at that time. ZE syndrome was diagnosed and treated with 1 g/day of cimetidine and some acid neutralizing agents. CT, US, and arteriography revealed no abnormality in the abdominal cavity. The serum IRG was 1300 pg/mL in June, 1984. The SASI test was performed on February 25, 1986 (Fig. 10). The serum IRG in the HV rose 20 or 40 seconds after the injection of secretin into the common hepatic or the splenic or the superior mesenteric artery. The serum IRI in the HV also rose within 40 seconds after the injection of secretin into any of these arteries.

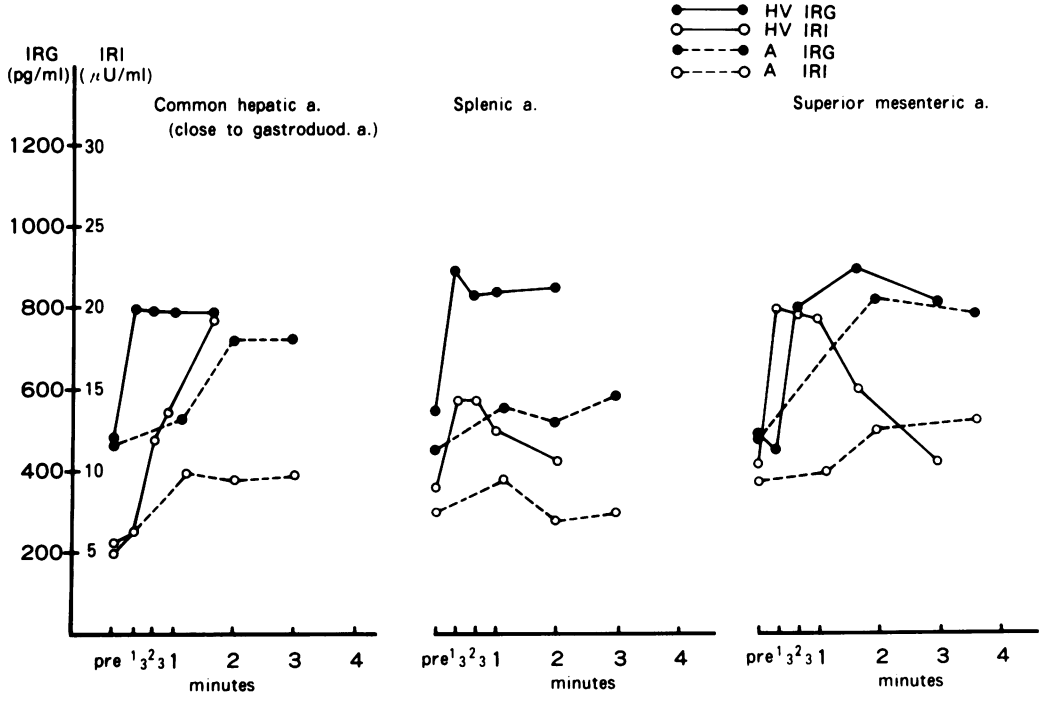

FIG. 10. Case 4: results of SASI test. IRG in the HV rose within 40 seconds of the injection of secretin into any arteries around the pancreas. These results suggest that gastrinoma cells were distributed diffusely throughout the pancreas.

Volunteers and Patients without the ZE Syndrome

Two healthy volunteers, eight patients after partial gastrectomy (four of them reconstructed with Billroth I anastomosis and four with Billoroth II anastomosis), and a patient with chronic atrophic gastritis were examined with the SASI test. The serum IRG in neither the HV nor the PA rose after the injection of 30 U of secretin into the common hepatic, the splenic, or the superior mesenteric artery. Serum IRI in the HV rose within 40 seconds in all after the same procedures.

Discussion

Isenberg et al. first reported the paradoxical effect of secretin on the serum gastrin level in a patient with the ZE syndrome.[1] They suggested that the serum gastrin response to intravenous secretin infusion might be of diagnostic value in patients suspected of having the ZE syndrome.[1] Since then a number of authors have supported their conclusion.[2,11,12] Recently, some investigators have reported a rise of IRG in the culture medium in which gastrinoma cells were cultured when secretin was added,[3,4] and the gastrinoma cells were considered to have receptors that bind with secretin, resulting in the release of gastrin.[3,4]

In the current study we tried to ascertain whether secretin stimulates gastrinoma cells to release gastrin *in vivo* as well. Secretin was injected into a feeding artery of a gastrinoma through a superselectively inserted catheter, and changes in serum IRG in the HV and a PA were measured. It takes 42 ± 6 seconds for the arterial blood in the abdominal viscera to pass through the portal vein, the liver, the HV, the heart and lung, and appear in a PA again.[13] If the secretin injected into a feeding artery of a gastrinoma stimulates a gastrinoma directly to release gastrin into the portal vein, the serum IRG in a PA would be expected to rise within 70 seconds and serum IRG in the HV would be expected to rise within 40 seconds.

In Case 1, secretin was injected into the metastatic gastrinoma in the liver through the right inferior phrenic or the common hepatic artery, and serum IRG in the PA rose in 60 seconds. In Case 3, secretin was injected into the common hepatic artery very close to the opening of the gastroduodenal artery or into the gastroduodenal artery itself, which was feeding gastrinomas in the head of the pancreas and metastatic lymph nodes, and serum IRG in the HV rose at 20 or 40 seconds. In Case 2, after distal pancreatectomy, the serum IRG in the HV rose after the injection of secretin into the common hepatic artery. These results indicate that secretin also directly stimulates a gastrinoma to release gastrin *in vivo*. We cannot tell whether secretin directly stimulated gastrin-secreting cells or whether secretin first stimulated other cells in the gastrinoma such as somatostatin-secreting cells that stimulated gastrin-secreting cells to release gastrin, but gastrin release certainly took place when secretin came into contact with a gastrinoma.

In Case 2, we injected various doses of secretin into the splenic artery that was feeding an angiographically visualized tumor in the body of the pancreas to ascertain the direct action of secretin on the gastrinoma, but with no results. The serum IRG in the PA rose 2 minutes after the injection but did not rise 1 minute after the injection of any dose. Secretin certainly stimulated the body and tail of the pancreas, because serum IRI rose within 1 minute in each case. After the operation, the tumor proved to be a non–gastrin-secreting tumor. The delayed rise of serum IRG in the PA in this case is considered to be due to the stimulation caused by the secretin injected into the splenic artery of a non–gastrin-secreting tumor not to release gastrin, and the stimulation of a gastrinoma located in an area other than the body or tail of the pancreas to release gastrin at the second circulation. These results suggest that the SASI test can be a diagnostic aid in the localization of a functioning gastrinoma.

The splenic artery feeds the body and tail of the pancreas. The gastroduodenal artery feeds the upper half of both the head of the pancreas and the duodenum. The lower half of the head of the pancreas and of the duodenum is fed by the inferior pancreaticoduodenal artery, a branch of the superior mesenteric artery. If we inject a solution of secretin into one of the arteries around the pancreas and take blood samples from the HV and a PA to measure the serial changes in serum IRG, it is possible to determine whether or not the functioning gastrinomas is in the feeding area of each artery.

In Case 2, if we had injected secretin into the common hepatic artery before the distal pancreatectomy, we might have found that the angiographically visualized tumor in the body of the pancreas was a non–gastrin-secreting tumor and that gastrinomas were present in the area fed by the common hepatic artery. But at that time we had tried to identify the direct action of secretin on a gastrinoma *in vivo* and could not speculate that the well-visualized tumor in the body of the pancreas on the arteriogram might be a tumor that did not secrete any hormone.[14] As no activity of the immunoreactive gastrin was detected in the culture medium of the resected pancreatic tumor cells, the tumor was found to be a non–gastrin-secreting tumor. A year after the distal pancreatectomy, we tried the SASI test again. Serum IRG in the HV rose after the injection of secretin into the common hepatic artery very close to the opening of the gastroduodenal artery. Nearly all hepatic metastases of gastrinomas 5 mm in diameter or larger can be visualized by arteriography.[15] Thus, the results of the second SASI test indicated that at least one gastrinoma was present in the feeding area of either the

proper hepatic artery or the gastroduodenal artery, except for the liver and the lower half of both the head of the pancreas and the duodenum.

In Case 3, the location of the gastrinoma could not be identified by US, CT, or arteriography. The results of the first SASI test taught us that at least one functioning gastrinoma was present in the area fed by the proper hepatic artery or the gastroduodenal artery. As mentioned above, the possibility of a hepatic metastasis was very small. Laparotomies were performed twice; a metastatic lymph node was extirpated first, and later, two minute duodenal submucosal gastrinomas and eight microscopic gastrinomas in the head of the pancreas were extirpated in a pancreatoduodenectomy. We did not measure the changes in serum IRG during the first operation and closed the abdomen because no tumor was palpable after the resection of the retropancreatic tumor. After the first operation the serum IRG did not decrease and the intravenous secretin injection test was still positive, although the amount of gastrin secreted for 10 minutes by stimulation with the same amount of secretin seemed to be decreased (Fig. 9).

A repeat SASI test indicated that gastrinomas were still present in the area fed by the gastroduodenal artery. During the second operation we could not identify any tumor by palpation or inspection, and a pancreatoduodenectomy was performed. This time the intraoperative measurements of serum IRG and an intraoperative intravenous secretin injection test were performed to determine whether or not all the gastrinomas had been extirpated in the operating room. This test, performed 30 minutes after the resection of both the head of the pancreas and the duodenum, clearly proved that all the functioning gastrinomas had been extirpated. In the resected specimen, only one minute duodenal submucosal tumor was suspected of being a gastrinoma, but other gastrinomas in the duodenum and the pancreas could be identified only by immunohistochemical techniques. It was very impressive that such small functioning gastrinomas could release gastrin when stimulated by intra-arterially injected secretin. The intravenous injection of secretin did not raise the serum IRG 1 month after the operation; therefore, the patient seems, so far, to have been cured completely. This case suggests that an early diagnosis of small gastrinomas is possible with the SASI test. Therefore, in a patient with multiple gastrinomas in the head of the pancreas or the duodenum, we should not hesitate to perform a pancreatoduodenectomy if the SASI test indicates that the gastrinoma is not in the body or tail of the pancreas.

In Case 4, the serum IRG in the HV rose after the injection of secretin into any of the three arteries. G cells are believed to be distributed diffusely throughout the pancreas. In healthy volunteers and in patients who had partial gastrectomy, the serum IRG in the HV did not rise after the injection of secretin into any of the three arteries. Thus, the SASI test is believed to be specific for patients with the ZE syndrome.

With the increased use of the H_2 receptor antagonists, the need for emergency total gastrectomy has decreased. Recently, many surgeons have recommended extirpation of the gastrinoma as well as total gastrectomy.[16–18] Deveney et al. recommended that resection should be seriously considered in every patient with the ZE syndrome, and it should be possible to cure about 25% of the patients with gastrinomas who do not have multiple endocrine neoplasia (MEN) and over 70% of those without MEN who appear to have a solitary tumor.[16] Zollinger stated that it is critical to recognize that the gastrin-producing islet cell tumor is a solid malignant tumor that grows inexorably each year.[19] For extirpation of the gastrinoma, accurate preoperative diagnosis of the location of the gastrinoma is indispensable. The rate of visualization of gastrinomas with US, CT, or arteriography is as low as 40 or 60%.[15,20,21] Besides, as we experienced in Case 2, there are some cases in whom a visualized tumor is not a functioning gastrinoma, and true functioning gastrinomas are not visualized. Therefore, we believe that for preoperative localization of gastrinomas, physiologic examinations such as percutaneous transhepatic portal catheterization or our SASI test should be performed as well as diagnostic imaging techniques.[22]

The SASI test is useful for surgeons to determine what part of the pancreas, the duodenum, or organs in the upper abdomen should be examined carefully during surgery and resected for permanent cure, but it cannot tell how many gastrinomas exist in the area that responds to secretin. The intraoperative intravenous secretin injection test can show whether all of the gastrinomas have been extirpated completely.

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