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# Curative Resection of Multiple Gastrinomas Aided by Selective Arterial Secretin Injection Test and Intraoperative Secretin Test

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Recently a number of surgeons have recommended radical resection of gastrinomas in Zollinger–Ellison syndrome (ZES). We have developed a useful technique for preoperative localization of gastrinomas—the selective arterial secretin injection test (SASI)—and we recommend an intraoperative secretin test (IOS) for deciding the radicality of resection of gastrinomas. Here the results of SASI and IOS tests in 11 patients with ZES are examined and compared with the results of other techniques. The SASI test localized gastrinomas in all of the patients, while the sensitivity of ultrasonography, computed tomography, arteriography, or portal venous blood samplings was between 1/11 and 5/11. On the basis of the results of the SASI test, radical resection of gastrinoma was performed in four patients (three pancreatoduodenectomies and one extirpation). After pancreatoduodenectomy, immunohistologic study of the specimen revealed multiple microgastrinomas and lymph node metastases in two patients and the coexistence of a microgastrinoma and a gastinoma in one patient. The IOS test was useful in the estimation of the advisability of radicality, and in two patients total gastrectomy was not performed because of the results of the IOS test. These four patients are well and have returned to work, and their serum gastrin levels are below 35 pg/mL. Thus we believe SASI and IOS tests are helpful for planning curative resection of gastrinomas.

**R**ECENTLY RADICAL RESECTION of gastrinomas has been recommended by a number of surgeons.<sup>1–3</sup> We have described the usefulness of the selective arterial secretin injection test (SASI) and of the intraoperative secretin test (IOS) for surgical treatment of this tumor.<sup>4,5</sup> In eleven patients with Zollinger–Ellison syndrome (ZES), the SASI test was performed for preoperative localization, as were ultrasonography (US), computed tomography (CT), abdominal arteriography (SAG), and portal venous blood samplings (PVS). On the

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basis of the results of SASI tests, radical operation was performed in four patients. We report here the results of SASI tests, IOS tests, and surgery.

## Patients and Methods

Eleven patients with documented ZES were treated in our departments (Table 1). All of the patients had been treated for gastric ulcers (cases 4 and 5) or duodenal ulcers (the other nine patients) before admission to our clinic; two of them had previous total gastrectomy (cases 2 and 7) and five had previous partial gastrectomy (cases 5, 6, 9, 10, and 11). Tarry stool was noted at the time of admission in eight patients, but not in those who had previous total gastrectomy (cases 2 and 7) or in case 4. Anastomotic ulcers were demonstrated after admission in cases 3, 5, 6, 9, and 10. Criteria for the diagnosis of ZES were gastric hyperacidity, a serum gastrin concentration (IRG) more than 200 pg/mL (more than 100 pg/mL in patients who underwent antrectomies), and increase of serum gastrin ( $\Delta$ IRG) more than 100 pg/mL after a bolus injection of secretin (3 U/kg) into a cubital vein. The secretin that was used in this study was Secrepan<sup>R</sup> (Eizai Co., Ltd., Tokyo, Japan). Gastrinomas were located by US, CT, SAG, PVS, and SASI tests. The details of the SASI test have been listed elsewhere.<sup>4</sup> Briefly they are as follows. We inserted the tip of the catheter into an artery near the pancreas, such as the gastroduodenal artery, the splenic artery, or the superior mesenteric artery. Then we injected 20 to 30 U of secretin into the artery, took blood samples from the hepatic vein before and 20, 40, 60, 90, and 120 seconds after the injection of secretin, and measured the changes of hepatic venous (HV)IRG. When the secretin

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TABLE 1. Patients with Zollinger-Ellison Syndrome

Case No.	Age (years)	Sex	Gastric Juice		Secretin Test		Localization Test					Treatment	Prognosis	
			BAO (mmol/hr)	BAO/MAO	Basal IRG (pg/mL)	ΔIRG	US	CT	SAG	PVS	SASI			
1	35	F	31.3	0.97	2900	1,200	hep met	hep met, panc head	np	hep met, panc head	np	hep met, panc head	STZ, 5FU	2 years, died
2	47	M	Total gastrectomy		580	250	nl	panc body	np	upper half of panc head or duod	np	upper half of panc head or duod	Distal pancreatectomy	6 years, alive
3	53	M	Partial gastrectomy 2.03 (bile)	0.43	100	184	nl	nl	np	nl	np	upper half of panc head or duod	(1) Extir of a lymph node (2) Pancreato-duodenectomy	2 years, alive (IRG 30)
4	68	F	10.84	0.86	1200	230	nl	nl	np	nl	np	whole panc	cimetidine	6 years, alive
5	43	M	Partial gastrectomy	—	733	312	nl	panc head	np	panc head	np	upper half of panc head or duod	(1) SMS201-995 (2) Pancreato-duodenectomy	10 months, alive (IRG 23)
6	57	M	9.00	0.81	1200	350	panc head	nl	nl	panc tail	nl	upper half of panc head or duod	cimetidine	1 year, alive
7	44	M	11.08	0.80	1018	375	nl	nl	nl	nl	nl	upper half of panc head or duod	(1) Extir of a lymph node (2) Pancreato-duodenectomy	4 months, alive (IRG 30)
8	13	M	23.7	0.78	905	5666	panc head	panc head	panc head or duod	nl	panc head or duod	upper half of panc head or duod	cimetidine	2 years, alive
9	40	F	66.4	0.99	1750	3810	panc head	panc head	nl	nl	nl	upper half of panc head or duod	cimetidine	1 year, alive
10	62	F	51.4	0.71	12,500	30,500	panc body	panc body	nl	panc body	nl	panc body & 1t gast a area	Extir of a tumor	1 year, alive
11	50	F	30.1	0.85	400	200	nl	nl	nl	nl	nl	upper half of panc head or duod	parathyroidectomy cimetidine	5 years, alive (IRG 120)

BAO: basal acid out put; MAO: maximum acid out put; SAG: selective arteriography; PVS: portal venous blood samplings; M: male; F: female; panc: pancreas; duod: duodenum; SASI: selective arterial secretin injection test; np: not performed; nl: not localized; 1t gast a area: area fed by the left gastric artery; hep: hepatic; met: metastasis; ΔIRG: maximum increase of IRG after injection of 2 μ/kg of secretin; STZ: streptozotocin; Extir: extirpation.

is injected into a feeding artery of the gastrinoma, the HV-IRG rises more than 80 pg/mL within 40 seconds to at least 120% of the basal HV-IRG (Fig. 1).

The gastroduodenal artery feeds the upper half of the head of the pancreas and the upper duodenum. The splenic artery feeds the body and tail of the pancreas. The lower half of the head of the pancreas and the lower duodenum are fed by the inferior pancreaticoduodenal artery, which is a branch of the superior mesenteric artery.<sup>6</sup> Thus we can first demonstrate feeders of functioning gastrinomas, and then we can locate the functioning gastrinoma(s).

The intraoperative secretin test is performed by the bolus intravenous injection of 3 U/kg of secretin.<sup>5</sup> Blood samples were taken from a cubital vein before and 2, 4, and 6 minutes after the injection of secretin. Rapid radioimmunoassay of serum IRG was performed by shortening the incubation time with antibody 1611 (a gift from Dr. J. H. Walsh, Los Angeles, CA) as described before; *i.e.*, the reaction mixtures were incubated for 1 hour at room temperature.<sup>5</sup>

As soon as the specimen was removed, the duodenum and pancreas were carefully palpated in a search for microgastrinomas in the duodenal wall, pancreas or the lymph nodes. Any suspected tumors or lymph nodes were 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 method or Nakane's indirect method.<sup>7,8</sup> Antisera prepared for this study were rabbit antigastrin serum (a gift from Professor N. Yanaihara, Shizuoka College of Pharmacy, Shizuoka, Japan), rabbit antiglucagon serum (Japan Immunoresearch Lab., Tokyo, Japan) and rabbit antiovine pancreatic peptide serum (a gift from Professor R. E. Chance, Eli Lilly Co., Indianapolis, IN).

## Results

US, CT, SAG, and SASI tests were performed in all patients, and PVS was performed in six patients (Table 1). US, CT, and SAG were useful in the detection of liver metastases, but they were not useful in locating main gastrinomas; that is, US, CT, and SAG visualized tumors in and around the pancreas in 4, 4, and 5 patients, respectively. The diameters of the visualized tumors were between 1.5 and 5.0 cm. PVS was useful in only one patient. The SASI test localized functioning gastrinoma(s) in all patients. Case 1 had a large gastrinoma in the head of the pancreas and multiple hepatic metastases, which were identified by all diagnostic techniques. In case 2, SAG visualized a tumor in the body of the pancreas. This patient underwent a distal pancreatectomy. The resected tu-

mor was not a gastrinoma, but a nonfunctioning tumor; that is, his serum IRG did not change at all after the operation and the resected tumor cells did not secrete gastrin into the culture medium, although 10% of the tumor cells were stained with antigastrin serum. One year later, the SASI test located functioning gastrinomas in the upper part of the pancreas and the upper duodenum in this patient. His serum IRG is now 4500 pg/mL.

The results of the SASI test in the other patients (cases 3 to 11) are shown in Table 2. The increase of HV-IRG 40 seconds after the injection of secretin into each artery above the basal IRG ( $\Delta\text{IRG}_{40}$ ) was calculated. The ratio of the percentage of  $\text{IRG}_{40}$  to the basal HV-IRG ( $\%\Delta\text{IRG}_{40}$ ) was also calculated. We determined that an artery was a feeder of a functioning gastrinoma when the  $\Delta\text{IRG}_{40}$  was more than 80 pg/mL and the  $\%\Delta\text{IRG}_{40}$  was more than 20%. In six patients who were examined at surgery or autopsy, the results of the SASI test were correct.

In three patients (cases 3, 5, and 7), pancreaticoduodenectomy was performed on the basis of the results of the SASI test, which identified gastrinomas located in the upper half of the head of the pancreas or duodenum, but not in the tail or body of the pancreas. We resected the head of the pancreas, the duodenum, and the gallbladder, cleaning out the lymph nodes around the pancreas even when we could not detect any tumors or any positive lymph nodes. In each resected specimen, multiple gastrinomas were detected by immunohistologic examination as shown in Figures 2 to 4. Two patients had lymph node metastasis. They are well and have returned to work after operation. Their serum IRG levels have been less than 30 pg/mL during their postoperative courses of 4 months to 2 years. These patients do not have multiple endocrine adenomatosis type I. In case 3, there were 2 microgastrinomas that measured 5 mm in diameter in the duodenal wall, 8 microgastrinomas in the parenchyma of the head of the pancreas, and 1 metastatic lymph node<sup>4</sup> (Fig. 1). Details of cases 5 and 7 will be described as case reports.

In one patient (case 10), the SASI test showed gastrinomas in the area fed by the left gastric artery and the splenic artery but not in the head of the pancreas or in the duodenum. Laparotomy revealed a tumor in the lesser omentum fed by branches of the left gastric artery and of the splenic artery. The tumor was extirpated and her serum IRG is less than 40 pg/mL. Two patients (cases 6 and 8) are waiting for operation.

## Case Reports

### Case 7

This 44-year-old man had been treated with 800 mg/day of cimetidine for 3 years when he developed perforation of his duodenal ulcer and underwent an emergency partial gastrectomy on February 22, 1987. The massive postoperative output of gastric juice (more than 2 L per day) and the high serum IRG level of 606.9 pg/mL, as well as a positive

TABLE 2. Results of Selective Arterial Secretion Injection Test

Case No.	Age	Sex	Artery	IRG (pg/mL)		$\Delta$ IRG <sub>40</sub> (pg/mL)	% $\Delta$ IRG <sub>40</sub>	Feeding Arteries	Surgery
				Basal	40 sec				
3	53	M	GDA	97	227	130	134.0	GDA	PD
			SMA	96	124	28	29.2		
			SPA	97	93	-4	-4.1		
4	68	F	GDA	242	368	126	52.1	GDA, SMA SPA	—
			SMA	249	403	154	61.8		
			SPA	273	386	113	41.4		
5	43	M	GDA	467	624	157	33.6	GDA	PD
			SMA	888	814	-74	-8.3		
			DPA	574	544	33	5.7		
			SPA	606	639	33	5.5		
6	57	M	GDA	2396	3638	1242	51.8	GDA & SMA	—
			SMA	1125	1542	417	37.1		
			SPA	1951	1932	-19	-1.0		
7	44	M	GDA	151	244	93	61.6	GDA	PD
			SMA	96	94	-2	-2.1		
			SPA	97	97	0	0		
8	13	M	GDA	1446	6996	5550	383.8	GDA	—
			SMA	3600	3462	-138	-4.9		
			SPA	2826	2364	-462	-12.8		
9	40	F	GDA	2335	3430	1095	46.9	GDA	—
			SMA	3200	3390	190	5.9		
			SPA	2145	2335	190	8.9		
10	62	F	GDA	20,500	18,700	-1800	-8.9	LGA & SPA	Extir
			LGA	13,400	22,700	9300	69.4		
			SPA	16,200	31,900	15,700	97.0		
11	50	F	GDA	130	234	104	80.0	GDA & SMA	—
			SMA	133	287	154	115.8		
			SPA	143	155	12	8.4		

M: male; F: female; GDA: gastroduodenal artery; DPA: dorsal pancreatic artery; SMA: superior mesenteric artery; SPA: splenic artery; LGA: left gastric artery;  $\Delta$ IRG<sub>40</sub> = IRG<sub>40</sub> - Basal IRG; PD: pancreatodu-

denectomy; Extir: Extirpation; % $\Delta$ IRG<sub>40</sub> =  $\frac{\Delta$ IRG<sub>40} \times 100}{\text{Basal IRG}}.</sub>

secretin test, confirmed the diagnosis of ZES. None of the diagnostic imaging techniques used (US, CT, and SAG) could demonstrate a tumor, and PVS also could not localize a gastrinoma. On April 7, 1987, surgeons opened his abdomen to search for a gastrinoma and found a metastatic lymph node on the surface of the head of the pancreas. Frozen sections were diagnosed as carcinoidlike tumor that was confirmed after operation by immunohistochemical study to be a metastatic lymph node from a gastrinoma. The main gastrinoma was not found and a total gastrectomy was performed. He was then transferred to Kyoto University Hospital for SASI testing.

The results of the SASI test are shown in Figure 5. The increase of HV-IRG( $\Delta$ IRG<sub>40</sub>) from the basal level was 100 pg/mL 40 seconds after the injection of 25 U of secretin into the gastroduodenal artery, although  $\Delta$ IRG<sub>40</sub> was 2 pg/mL and 0 pg/mL after the injection of the same dose of secretin into the splenic artery and the superior mesenteric artery, respectively. This significant difference led us to conclude that functioning gastrinomas were present in the upper part of the head of the pancreas or duodenum. On July 5, 1988, we performed a pancreatoduodenectomy with cleaning of the lymph nodes, although we could not identify any gastrinomas in the head of the pancreas or in the duodenum during the operation. Intraoperative secretin test performed immediately after the pancreatoduodenectomy was negative, that is, IRG(pg/mL) was 82.3, 80.1, 75.0, and 75.8, before and 2, 4, and 6 minutes after the injection

of 3 U/kg of secretin into a cubital vein (Fig. 6). Thus we confirmed the completeness of the resection and closed his abdomen. Eight hours after the resection serum IRG became 27 pg/mL. His postoperative course was uneventful and he was discharged 4 weeks later. He is well and back at work. A secretin test on November 1, 1988 was negative; that is, IRG(pg/mL) was 25, 26, 23, and 22, before and 2, 4, and 6 minutes, respectively, after the injection of 3 U/kg of Secrepan<sup>R</sup> into a cubital vein. Pathologic examination of the resected specimen revealed a microgastrinoma that measured 4 mm in diameter in the duodenal submucosa and three metastatic lymph nodes (Fig. 7). A metastatic lymph node had been extirpated before, so he had had four metastatic lymph nodes around the head of the pancreas (Fig. 2).

### Case 5

This 43-year-old man had been treated medically for a gastric ulcer for 6 years when he underwent a partial gastrectomy on April 23, 1984. Six months after operation epigastralgia recurred and medical treatment was required again. On November 25 he visited Yukawa Gastrointestinal Disease Hospital in Osaka and was found to have hypergastrinemia of more than 150 pg/mL. US and CT could not visualize a tumor, so he was transferred to Kyoto University Hospital for SASI testing on January 14, 1988. The results of the SASI test are shown in Figure 8 and Table

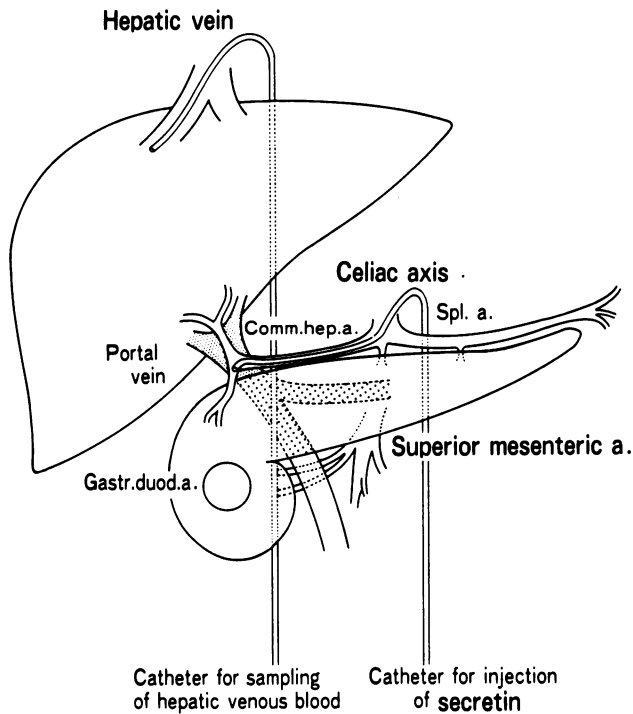


FIG. 1. Diagram of SASI test. Secretin was injected into the gastroduodenal artery, the splenic artery or the superior mesenteric artery through the tip of a catheter for arteriography. Then hepatic blood was sampled every 20 seconds three times and 90 seconds after the injection of secretin.

1. HV-IRG rose more than 150 pg/mL 40 seconds after the injection of 30 U of secretin into the gastroduodenal artery, but did not change for 60 seconds after the injection of the same dose of secretin into either the

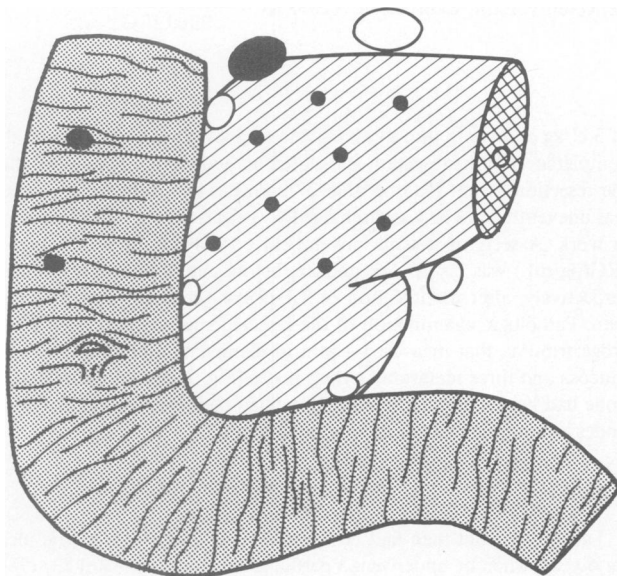


FIG. 2. Location of multiple gastrinomas in case 3. Immunohistochemical study revealed 2 duodenal microgastrinomas, 8 intrapancreatic microgastrinomas, and 1 metastatic lymph node on the upper edge of the head of the pancreas. None of them could be identified during the operation. Two duodenal microgastrinomas were palpable in the specimen but could not be identified macroscopically as gastrinomas.

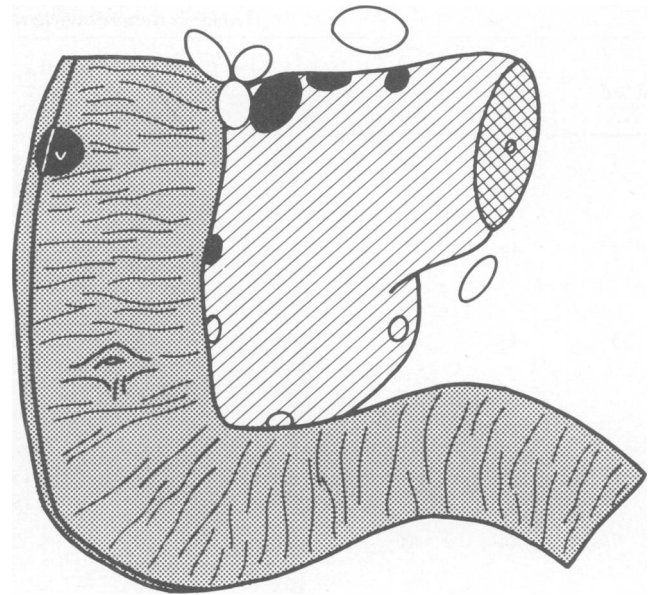


FIG. 3. Location of gastrinomas in case 7. One duodenal microgastrinoma was located 1 cm anal from the stump of the duodenum. Four metastatic lymph nodes were detected in the upper half of the head of the pancreas.

dorsal pancreatic artery or the splenic artery. A rise of HV-IRG two minutes after injection of secretin into the splenic artery is due to the stimulation of gastrinomas located in an area other than the body or tail of the pancreas with release of gastrin in response to the second circulation of secretin. The  $\Delta\text{IRG}_{40}$  after the injection of secretin into the gastroduodenal artery was 175 pg/mL, although it was -40 pg/mL and 5 pg/mL after the injection of secretin into the dorsal pancreatic artery and the splenic artery, respectively.

This significant difference led us to diagnose gastrinomas located in the feeding area of the gastroduodenal artery, *i.e.*, the upper part of the head of the pancreas or the upper duodenum and not in the body or tail

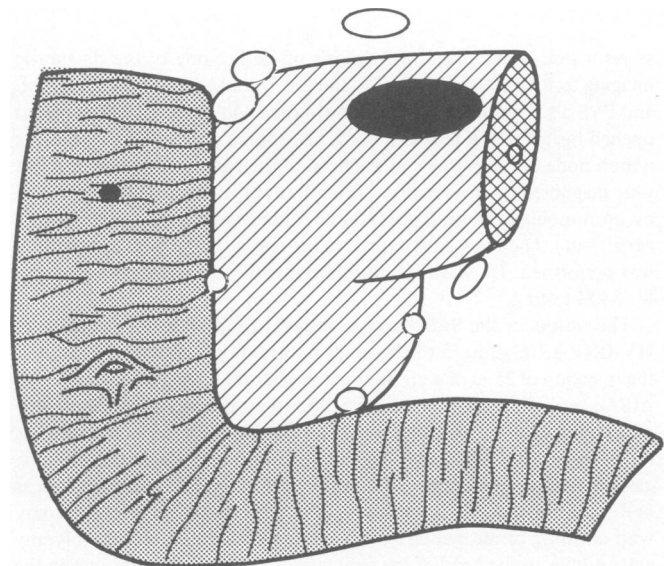


FIG. 4. Location of gastrinomas in case 5. One intrapancreatic gastrinoma was palpable during the operation, but one duodenal microgastrinoma was revealed by postoperative immunohistochemical study.

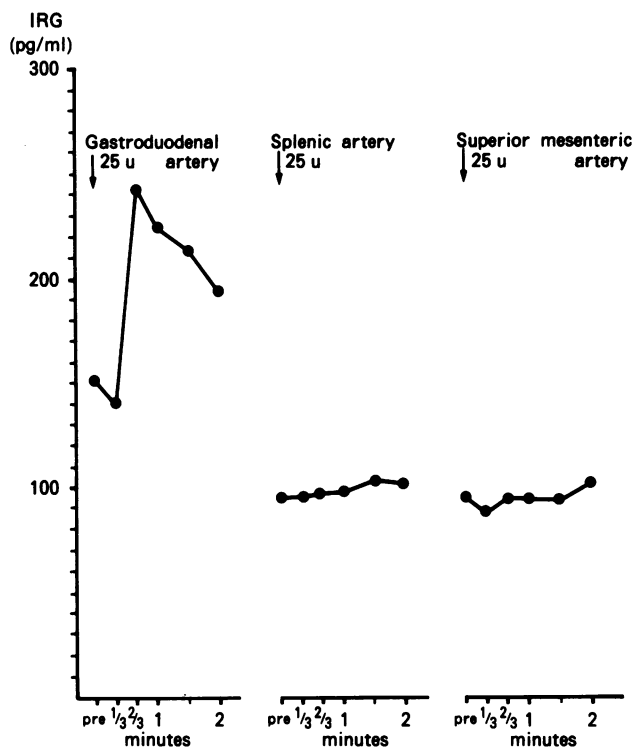


FIG. 5. Results of SASI test in case 7. HV-IRG was increased 40 seconds after the injection of 25 U of secretin into the gastroduodenal artery, but it did not change for 60 seconds after the injection of secretin into the splenic artery or the superior mesenteric artery.

of the pancreas. Superselective arteriography through the gastroduodenal artery demonstrated a hypervascular tumor in the head of the pancreas.

On January 21, 1988, surgery was performed. A tumor that had been demonstrated by SAG was palpable in the head of the pancreas and thus we performed a pancreatoduodenectomy. Intraoperative secretin test performed with 3 U/kg of secretin was negative; that is, serum IRG (pg/mL) was 228.0, 194.8, 201.0, and 204.1 before and 2, 4, and 6 minutes after the injection of secretin, respectively. Thus we could confirm that all functioning gastrinomas had been resected. The pathologic study of the specimen revealed a minute gastrinoma in the duodenal submucosa in addition to the gastrinoma palpated during the operation. No metastatic lymph nodes were found (Fig. 4). After operation he complained of left hypochondralgia and abdominal fullness. An upper gastrointestinal barium study revealed narrowing of the proximal jejunum. We opened his abdomen on February 18, 1988, and found the jejunum adherent to the abdominal wall, which was well separated. He was discharged 3 weeks later. He is well and has returned to work. His serum IRG is less than 35 pg/mL.

### Discussion

Preoperative localization of gastrinoma in patients with ZES is often difficult.<sup>2,3,9</sup> It is not unusual for gastrinomas to be multiple and to coexist with nonfunctioning endocrine tumors.<sup>10</sup> The sensitivity of US, CT, and SAG has been reported to be between 40% and 70%.<sup>2,3,11,12</sup> In our study these techniques were useful in locating hepatic metastases, but the number of main tumors visualized was low; SAG gave the best results (5 of 11). In the three

resected specimens of the head of the pancreas and the duodenum after pancreatoduodenectomy, immunohistologic study revealed 18 gastrinomas (including metastatic lymph nodes), of which only two tumors had been demonstrated by preoperative diagnostic imaging techniques, and these could not show whether a visualized tumor was a functioning gastrinoma. Therefore we must conclude that these techniques are not adequate for the preoperative localization of gastrinomas and the decision of whether radical resection is indicated. The usefulness of PVS has been discussed many times, but is still controversial.<sup>2,9-11</sup> Good results of superselective catheterization into a branch of the portal vein near the pancreas have been reported.<sup>12</sup> But the results of our study were poor. We think that PVS does not provide clear data, and it is technically difficult.

The SASI test is easy if the tip of the catheter can be inserted selectively into the gastroduodenal artery, the splenic artery, or the superior mesenteric artery. Each study ends within two minutes after the injection of se-

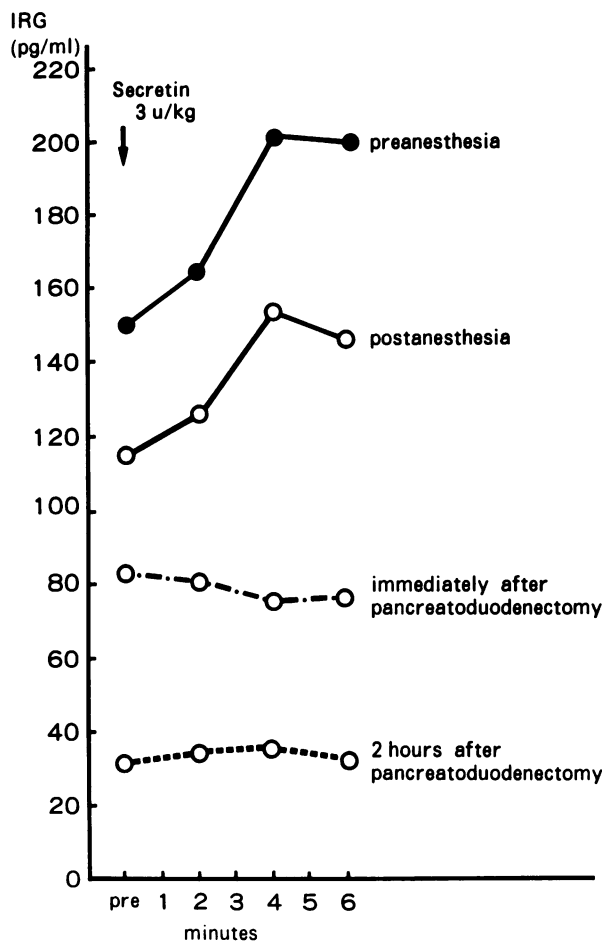


FIG. 6. Case 7. The intravenous secretin test was positive before and after general anesthesia but became negative after pancreatoduodenectomy. Thus we could confirm the completeness of the resection during the operation.

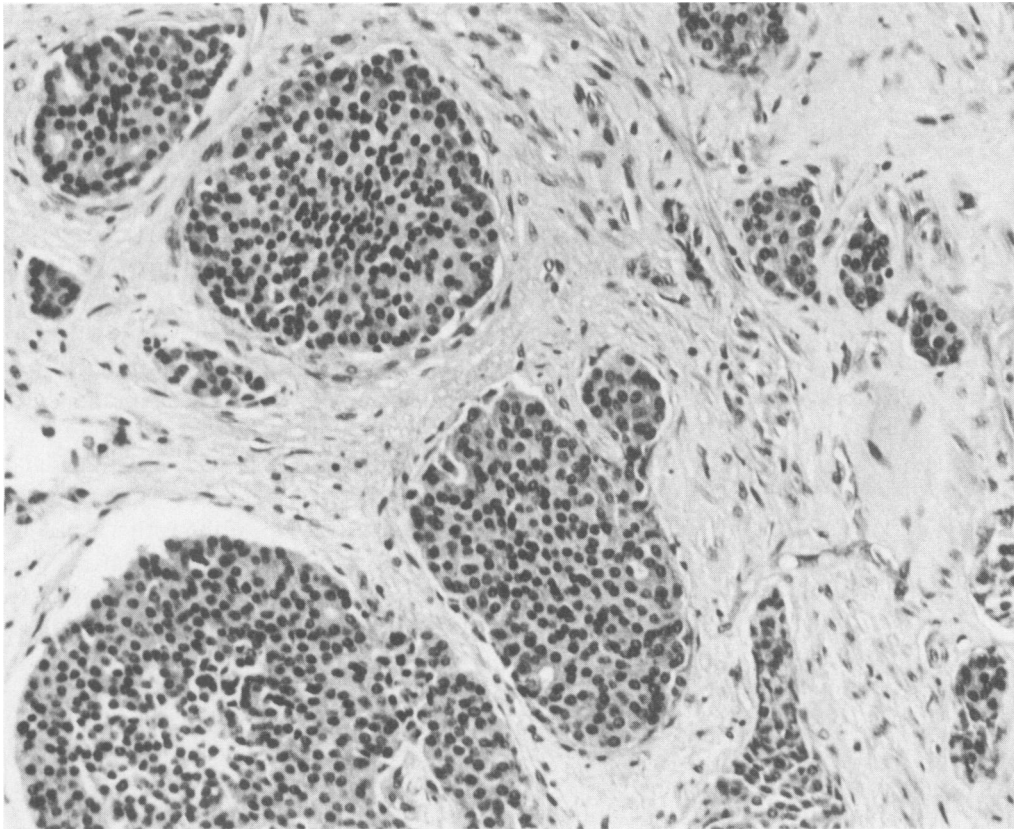


FIG. 7. Microscopic appearance of the duodenal submucosal microgastrinoma in case 7. Tumor cells with cellular atypism form solid nests that vary in size and shape and show invasive growing. (Hematoxylin and eosin,  $\times 428$ )

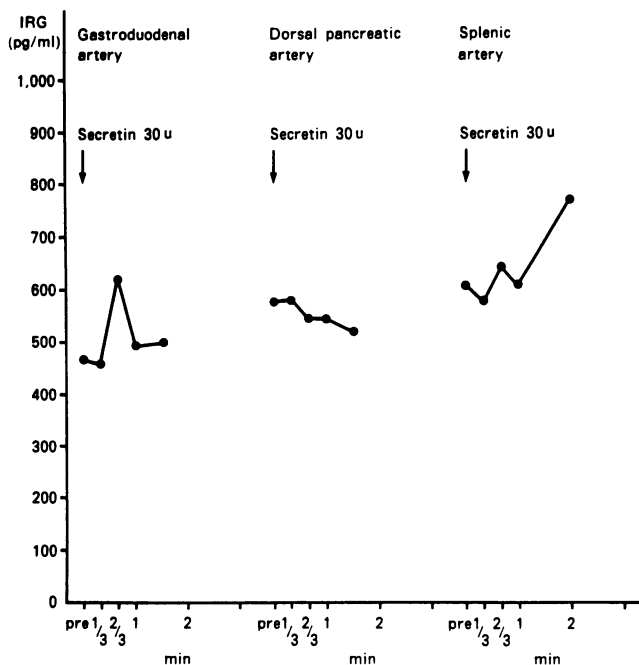


FIG. 8. Results of SASI test in case 5. HV-IRG rose 40 seconds after the injection of 30 U of secretin into the gastroduodenal artery but it did not change for 60 seconds after the injection of secretin into the dorsal pancreatic or the splenic artery. The rise of HV-IRG 90 seconds after the injection of secretin into the splenic artery is believed to be due to the stimulation of a gastrinoma in the head of the pancreas or the duodenum to release gastrin at the second circulation.

cretin into an artery near the pancreas.<sup>4</sup> It is easy to determine which arteries feed the gastrinoma if one makes a graph of the changes of HV-IRG as in Figures 5 and 7 and compares the rise of HV-IRG after the injection of secretin into a different artery. If an artery is a feeder, HV-IRG rises significantly within 40 seconds, but if an artery is not a feeder HV-IRG does not change for 60 seconds. Table 2 shows our calculations of  $\Delta\text{IRG}_{40}$  and  $\% \Delta\text{IRG}_{40}$  and our criteria for a feeder of gastrinomas; that is, if  $\Delta\text{IRG}_{40}$  is more than 80 pg/mL and  $\% \Delta\text{IRG}_{40}$  is more than 20%, the artery is a feeder. These criteria are useful when microgastrinomas are present in the duodenal wall or when a large gastrinoma is present in the lesser omentum.

In this series the SASI test localized gastrinomas in all of the patients. In most cases in which tumor stains were demonstrated by diagnostic imaging techniques, the SASI test also showed the existence of gastrinomas in the same area. But in two patients (cases 2 and 6) the visualized tumor was diagnosed not to be a functioning gastrinoma by the SASI test. In case 2, SAG showed a tumor in the tail of the pancreas and a distal pancreatectomy was performed, although the SASI test did not indicate that there was a functioning gastrinoma in the body or tail of the pancreas. The resected tumor was not a functioning gastrinoma, but a nonfunctioning endocrine tumor. The



SASI test performed 1 year after the operation localized gastrinomas in the upper part of the head of the pancreas or the upper duodenum. In case 6, SAG demonstrated a tumor, but the SASI test localized gastrinomas in the upper part of the head of the pancreas or duodenum. The tumor visualized in the hilar portion of the spleen seems to be an accessory spleen. We are preparing to perform a pancreatoduodenectomy in this case.

In four patients who had radical resections of gastrinomas, localization by the SASI test was correct and useful. In case 10 there was a single large gastrinoma in the lesser omentum and extirpation seems to have been curative. In the other three patients who underwent pancreatoduodenectomies (cases 3, 5, and 7) there were multiple microgastrinomas in the duodenum or the head of the pancreas and in two of them there were lymph node metastases. These results suggest the necessity of pancreatoduodenectomy when the SASI test shows that a gastrinoma is located in the head of the pancreas or in the duodenum.

Recently a few authors have reported that in patients with severe peptic ulcer symptoms, sometimes leading to death, duodenal microgastrinomas were found only at autopsy or surgery.<sup>13,14</sup> They speculated that in many ZES patients it is not diagnosed because no tumor is found during surgery. Two of our patients (cases 3 and 5) with microgastrinomas that were not found at the first operation developed anastomotic jejunal ulcers after operation, despite cimetidine treatment. Thus occult gastrinomas in ZES are not always asymptomatic or benign.<sup>13-15</sup> Zollinger reported that five of eight patients in whom no gross tumor was found at operation survived more than 10 years.<sup>16</sup> We believe that the SASI and IOS tests will help to raise the survival rate of such patients.

A few authors have recommended aggressive treatment for duodenal gastrinomas with or without lymph node involvement and have reported excellent clinical results after surgery.<sup>17-19</sup> Lander treated a patient who has been asymptomatic for 2.5 years after the extirpation of a minute duodenal submucosal gastrinoma and three metastatic lymph nodes.<sup>20</sup> We deliberated carefully before deciding to perform a pancreatoduodenectomy on the first patient (case 3); we opened the duodenum first, examined its interior carefully, and took a biopsy of an elevated area near the duodenal stump, which showed no pathologic abnormality. No gastrinoma was found during surgery, and we performed Whipple operation, believing the results of the SASI test. Immunohistologic study of the resected specimen revealed 2 minute submucosal gastrinomas, 1 metastatic lymph node, and 8 microgastrinomas in the head of the pancreas. He has been asymptomatic for the 2 years since surgery. This experience has led us to conclude that it is very difficult to search for small duodenal or pancreatic gastrinomas or metastatic lymph nodes

during surgery. If the IOS test is not negative after extirpation of a few gastrinomas in the head of the pancreas or the duodenum but the SASI test points to the presence of gastrinomas in the feeding area of the gastroduodenal artery, Whipple operation should be performed for curative resection of potentially malignant gastrinomas.<sup>1,9</sup>

Whipple operation for the resection of gastrinomas has been performed in relatively few institutions, and the results show considerable variation.<sup>4,9,12</sup> We believe that pancreatoduodenectomy in patients with gastrinomas should be performed just as in those with cancer of the head of the pancreas because of the high gastrinoma malignancy rate.<sup>1-3</sup> The postoperative mortality rate after pancreatoduodenectomy for pancreatic cancer is quite different in various reports. In our department it has been 0% for the past 3 years. Thus we have not found any reason not to perform pancreatoduodenectomy when the SASI test indicates the presence of gastrinomas in the head of the pancreas or in the duodenum. Three patients who underwent pancreatoduodenectomy recovered without complications and their serum IRG has been less than 30 pg/mL during their postoperative courses of four months and 2 years.

In patients with ZES whose stomachs have not been totally resected, we must decide whether the residual stomach should be resected after the removal of the gastrinomas. If we can confirm the radicality of the resection at the time of the operation, we can save the stomach. We believe that the IOS test is useful in the estimation of the radicality of the resection because the results of the IOS tests with rapid radioimmunoassay of serum gastrin in three patients were not different from those of the postoperative secretin test. On the basis of the results of the IOS test we did not resect the residual stomach in case 5, whose serum IRG remains less than 35 pg/mL after operation and whose secretin test (3 U/kg) is negative.

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