Articles

Insulinoma—Experience from 1950 to 1995

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Insulinomas are rare tumors that originate from the islet cells of the pancreas. The purpose of this study was to analyze our experience in patients with insulinoma and present our approach to these patients. Medical records of 67 patients treated at the University of California, San Francisco (UCSF) Medical Center, 56 surgically and 11 medically, from 1954 to 1995 were retrospectively reviewed. Presenting symptoms, physical findings, laboratory data, pre and intraoperative localization studies, operative management, operative success, and post-operative complications were analyzed. Among the entire cohort, there were 11 patients with Multiple Endocrine Neoplasia type I (MEN 1) and 7 patients with multiple tumors. 46 out of 48 patients (96%) having first operations for benign tumors and 5 out of 8 patients (63%) having reoperations for benign tumors were successful, as were 6 out of 12 patients (50%) having operations for islet cell carcinoma. Overall, preoperative localization studies were positive in only 46% of patients and therefore failed to improve our surgical outcome. Careful palpation with intraoperative ultrasonography gave the best localization results. Enucleation of solitary tumors is curative in sporadic cases and gives the lowest complication rate. In patients with MEN1, subtotal pancreatectomy with enucleation of tumors from the pancreatic head and uncinate process is recommended over simple enucleation because of frequent multiple tumors.

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Although rare, insulinoma is the most common tumor of the endocrine pancreas, occurring in about one person per million population per year. Langerhans, while a medical student, described pancreatic islets and their possible function 70 years before the first patient with an insulinoma was reported.[1,2] The association between hyperinsulinism and a functional islet cell tumor was established by Wilder et al[3] in 1927; he performed an operation on a patient with hypoglycemia and found an islet cell carcinoma with hepatic metastases. Whipple thought that symptoms of hypoglycemia provoked by fasting, a circulating glucose level below 50 mg/100 cc at the time symptoms presented, and relief of symptoms with glucose administration were the basis for making the diagnosis of insulinoma, thus establishing "Whipple's Triad."[4] The first surgical cure of an islet cell adenoma was achieved by Graham in 1929.[5]

Islet cell tumors occur predominantly in the pancreas but also in the duodenum and peripancreatic nodes. 99% of insulinomas are found within the pancreas. The incidence of islet cell tumors is estimated to be less than 1-1.5 cases per 100,000 of the general population. Approximately 50% of islet cell tumors are insulinomas, 30% gastrinomas, 10%-15% vasoactive intestinal peptide secreting tumors (VIPomas), and 5-10% other tumor types, including glucagonomas, somatostatinomas, and pancreatic polypeptide-secreting tumors (PPomas).[6,7]

Our report retrospectively analyzes the clinical and diagnostic features, surgical course, pathologic findings, and long-term outcome of 67 patients with insulinoma.

Patients and methods

During a 41 year period between 1954 and 1995, 67 patients were referred to UCSF Medical Centers with a biochemical diagnosis of organic hyperinsulinism. There were 22 male and 45 female patients. Their ages ranged from two weeks to 85 years, with a mean age of 46 years and a peak incidence from 40 to 50. (Figure 1). Fifty-one of these patients were treated since 1975, a time when ultrasound and CT scanning became available.[8] Sixteen patients were treated between 1954 and 1975. Such disparity in the numbers of patients seen in these two 20-year periods could be due to the increased

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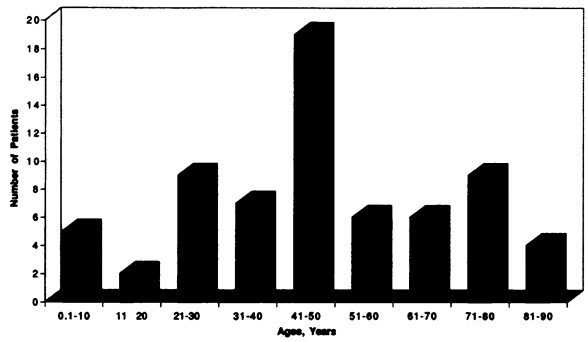

Figure 1.—Age distribution in patients.

awareness of this condition, more accurate diagnosis and more patient referral.

A total of 68 operations were performed in the 56 patients treated operatively. Out of those, 54 were primary and 14 were reoperations (nine first and five second reoperations). Seven of these patients had their initial pancreatic explorations elsewhere and were referred for persistent or recurrent insulinoma. Eleven patients (16%) had MEN 1, and seven of these MEN 1 patients or 63% had multiple insulinomas. Ten patients (15%) had malignant insulinomas, including one-third of patients with MEN 1. Among the 16 patients in the 1954–1975 group, four patients had MEN 1 and three patients had cancer. Among the 51 patients in the 1975–1995 group, seven patients had MEN 1 and seven patients had cancer. Five patients had hyperplasia, three being children aged two weeks, one month and three months, and two being adults aged 36 years and 70 years. Eleven patients were treated with medicine only.

Results

Symptoms

Symptoms of hypoglycemia including hunger, headache, palpitations, and confusion occurred at various times, but in 39 of the 67 patients occurred before meals or during fasting. In nine patients, symptoms were precipitated by exercise. Six patients experienced symptoms post prandially and five patients had continuous symptoms unrelated to eating. To avoid falling into comas, four patients set alarms in order to awaken and eat during the night. Six patients had histories of being unable to awaken in the morning due to severe hypoglycemia. Many patients exhibited hysterical and bizarre behavior with weakness and tremors, and nine had been treated for seizures before a proper diagnosis was made. Similar symptoms have been reported by others. [9–11] The incidences of the various symptoms are listed in Figure 2.

Overall, 75% of patients presented with altered mental states and/or confusion. The duration of symptoms ranged from five minutes to several hours. A few patients, including three infants, had clinical manifestations such as lethargy and irritability, and two infants had convulsions. Six of the patients with insulinoma were being treated by a psychiatrist.

Since many patients frequently eat to avoid symptoms, it is surprising that only 14% of the patients in our study gained weight. For 45 patients, the clinical manifestations of hypoglycemia became more severe and increased in frequency the longer the tumors were present, whereas in 14 patients symptoms were not progressive.

Among the 60 patients, where the information was available, the duration of symptoms prior to diagnosis

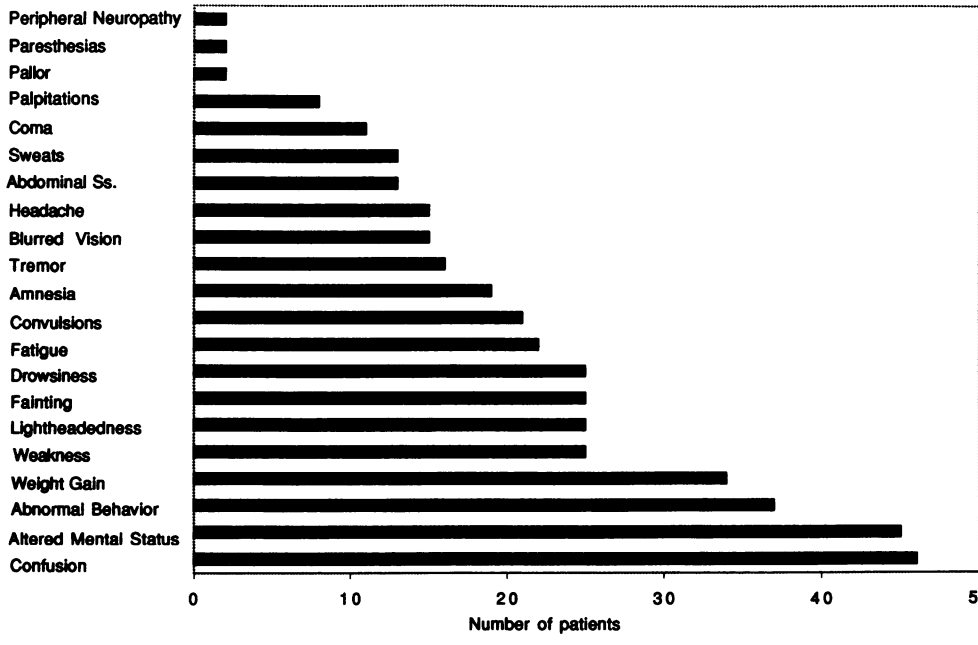

Figure 2.—Symptoms during hypoglycemic spells.

TABLE 1.—*Test Results of the Various Localization Techniques for Insulinoma.*

Technique	Test Results			
	TP	TN	FP	FN
CT	13	1	1	20
Arteriography	14		1	15
MRI	3		1	4
MRI w/Gadolinium	3		1	2
Pre-operative Ultrasound	4			2
Intra-operative Ultrasound	9	1		1
THPVS	7			3
Palpation	42	1		14

THPVS=Transhepatic Portal Venous Sampling; TP=True Positive; TN=True Negative; FP=False Positive; FN=False Negative

ranged from one hour in a newborn to 34 years, with a mean duration of 3.8 years. The diagnosis of insulinoma was delayed for various reasons, including the infrequency of attacks, and the fact that the symptoms could be aborted by eating. Two of our patients were retarded, possibly due to delay in diagnosis or treatment of hypoglycemia.[4,12]

Diagnosis

The knowledge that the fasting insulin-to-glucose ratio was higher than 0.3 was helpful in making the diagnosis in 48 of our patients. The C-peptide levels in all of our patients ranged from 0.9 to 8.1 (normal fasting is 0.8 to 4.0 ugs/L). Fasting with determination of insulin-to-glucose ratios was used in 37 patients and various provocative tests were used infrequently. Glucagon and tolbutamide tests were both used in 23% of the patients, mostly in the early years of the study. The tolbutamide test is no longer done. In most patients the fasting glucose-to-insulin ratio with an elevated C-peptide and a negative urinary sulfonylurea level were sufficient for making the diagnosis.

The blood sugar levels recorded in our patients were under 10 mg/100 ml in four patients, between 10 and 20 mg/100ml in 17 patients, between 21 and 30 in 25 patients, between 31 and 40 in 12 patients, between 41 and 50 in six patients, and above 50 in two patients.

Among our patients with MEN 1, other endocrine syndromes or pathology included: hyperparathyroidism(10), pituitary adenomas (6), two of which were prolactinomas, gastrinomas (5), thyromegaly (2), papillary carcinoma of thyroid (1), hyperaldosteronism (1), and hypotestosteronism (1).

Localizing studies

Preoperative localization studies were done in 56 patients. The results of the preoperative localization studies including arteriography, transhepatic portal venous sampling (THPVS), computed tomography (CT), Magnetic Resonance Imaging (MRI) with gadolinium are shown in Table 1. Intraoperative ultrasonography was positive in 90% of the cases, and intraoperative palpation was positive in 75%. Among 10 tumors identified by intraoperative ultrasonography, there were no false-positive studies. Four insulinomas that were non-palpable or non-visible were identified by intraoperative ultrasonography. These adenomas were all soft in consistency and were not palpable even after being identified by ultrasound. CT scanning was primarily used in our patients to identify large tumors with possible liver or nodal metastases. Our data document that intraoperative techniques including palpation and ultrasound are considerably more reliable for identifying insulinoma than any preoperative study.

In patients from whom this information was available, the median diameter of the 52 solitary tumors was 1.6 cm. Twelve patients had tumors less than 1 cm in maximum diameter. Two patients had tumors larger than 6 cm. The size distribution of the insulinomas is shown in Figure 3.

Seven of the 67 patients, all with MEN 1, had multiple tumors (mean number 7) ranging from microscopic to 3 cm in diameter (mean size 2.1 cm). Three of these patients had more than 10 tumors , one patient had nine and one patient had two. Among our entire group of patients, the insulinomas were evenly distributed throughout the pancreas (38% head, 37% body, and 25% tail). None of the insulinomas identified in our patients was located outside the pancreas, although one patient remained hypoglycemic after a Whipple operation for islet cell cancer. Among our 67 patients, 10 (15%) had malignant insulinoma, which is comparable to a 10% malignancy rate reported in other literature. [8,10,11] Four of the 10 patients with islet cell carcinomas had MEN 1 and two of these patients also had gastrinomas. Eight patients had metastases, four in the lymph nodes, two in the lower abdomen, one in the brain and one in the lung. Nesidioblastosis was identified in three children and two adults.

Treatment

Preoperative treatment

After the diagnosis was established, patients were maintained on frequent feedings to reduce the risk of hypoglycemic episodes. Diazoxide was used in 41 patients. In 34 patients, there was a favorable response; however, 14 patients had complications [palpitations (13), hirsutism (5), edema (5), nausea (2), gastrointestinal discomfort (2), elevated uric acid (2)], and seven patients failed to respond. Five patients had complications so severe that they needed to discontinue diazoxide. Thus, diazoxide was successful in only 29 patients out of 41. Other pre-operative medical treatment included somatostatin in five patients, dilantin in four patients and chemotherapy in one patient.

Surgical treatment and outcome

Sixty-eight surgical procedures were performed in 54 patients, including enucleation of the insulinoma in 40 patients, distal pancreatectomy in 11, subtotal pancreatectomy in 12, Whipple procedure in four and one nega-

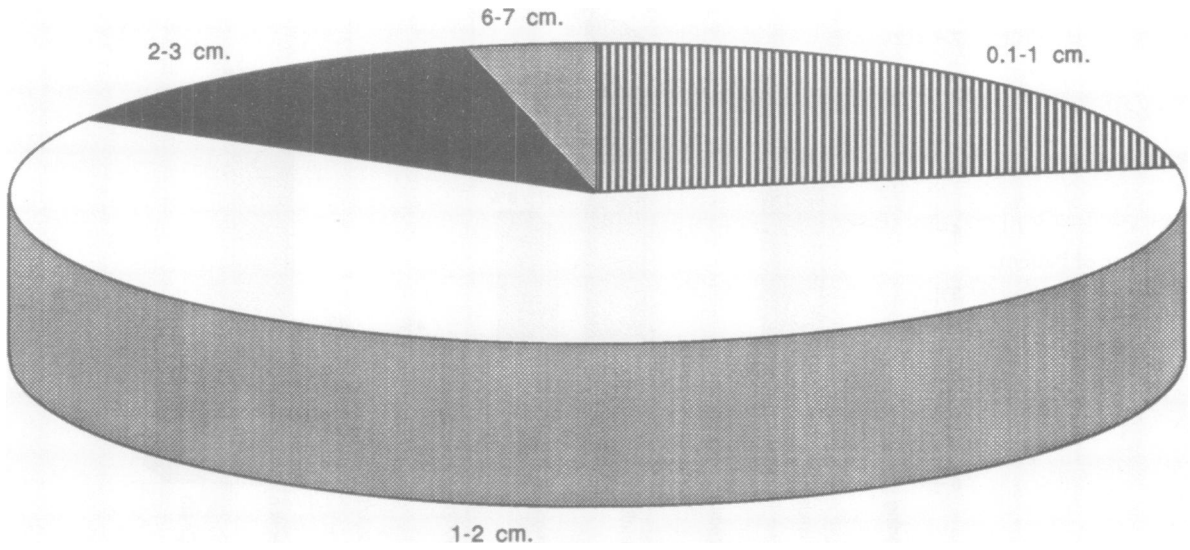

Figure 3.—Size distribution of insulinomas.

tive exploration with biopsy only. In four patients (two initial and two reoperations), no insulinoma or abnormal pancreatic tissue was identified or removed. Splenectomy was performed in 24% of all these patients and in 55% having distal pancreatectomy.

Eleven of our 68 operations (16%) were unsuccessful, six in patients who had reoperations. (Table 2). Six of these patients had MEN 1, three of whom had malignant tumors, five of whom had sporadic disease, and one of whom had a malignant tumor. Multiple tumors or nesidioblastosis accounted for four failures (two with MEN 1 and two with sporadic disease). Successful operations ensued in 89% of our patients having an initial pancreatic exploration at our medical centers, including patients with cancer, and in 96% of patients having initial operations and benign solitary tumors. Two patients died 17 days and 25 days after operation due to complications. One patient, 47 years old, had MEN 1 and a malignant insulinoma as well as hyperplasia/nesidioblastosis, and the other, 85 years old, had nesidioblastosis. Nine patients underwent reoperation for persistent (8) or recurrent (1) disease. In the patient with recurrence, symptoms appeared 18 years following her initial procedures. This fascinating yet unfortunate patient was originally thought to have a "benign" insulinoma, but hypoglycemia recurred after 18 years. At reoperation a Whipple procedure was unsuccessful, and she subsequently died of brain and lung metastases. Eight other patients underwent a first reoperation because of the persistent hyperinsulinism or recurrence within eight months. Unfortunately, three were not cured.

TABLE 2.—*Patients Who Underwent a Failed Surgical Exploration for Insulinoma.*

Patients	MEN	Reason for Status	Pathology Exploration	Age	Sex	Operation	# tumors*	Reasons for Failure	Histology
#1	MEN 1	Persistent	Malignant	28	F	Subtotal Pancreatectomy	>10	2 Missed tumors	Multiple Adenomas
#2	MEN 1	Persistent	Benign	36	M	Subtotal Pancreatectomy	N/A	2 Hyperplasia	Hyperplasia
#3	MEN 1	Persistent	Malignant	43	M	Exploration only	N/A	2 No tumor found	Insulinoma
#4	MEN 1	Primary	Benign	36	M	Distal Pancreatectomy	N/A	1 Hyperplasia	Hyperplasia
#5	MEN 1	Primary	Benign	31	F	Subtotal Pancreatectomy	>10	1 Missed tumors	Insulinoma
#6	MEN 1	Primary	Malignant	28	F	Enucleation	>10	1 Missed tumors	Multiple Adenomas
#7	MEN 0	Persistent	Benign	0.8	F	Subtotal Pancreatectomy	N/A	1 Nesidioblastosis	Nesidioblastosis
#8	MEN 0	Persistent	Benign	41	F	Distal Pancreatectomy	N/A	2 No tumor found	Insulinoma
#9	MEN 0	Recurrent	Malignant	49	F	Whipple	N/A	3 Ectopic tumor	N/A
#10	MEN 0	Primary	Benign	4	F	Subtotal Pancreatectomy	N/A	1 No tumor found	Negative
#11	MEN 0	Primary	Benign	0.8	F	Subtotal Pancreatectomy	N/A	1 Nesidioblastosis	Nesidioblastosis

1=Initial Operation; 2=First Reoperation; 3=Second Reoperation

*Number of the exploration for insulinoma.

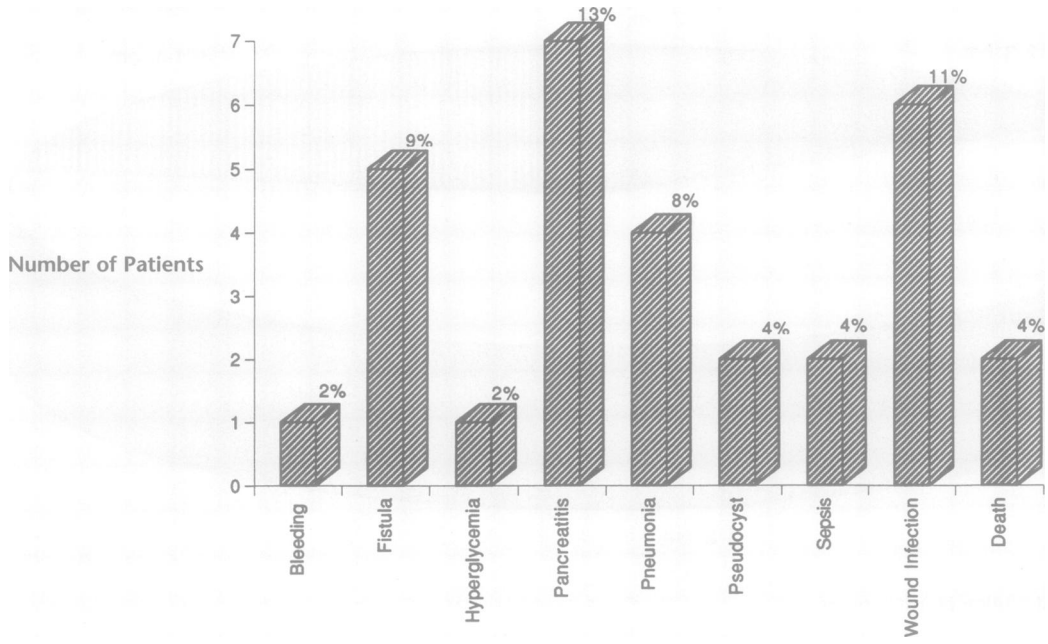

Figure 4.—Postoperative complications after 23 (43%) of 54 operations.

One infant with nesidioblastosis and hyperinsulinism had persistent hypoglycemia, even after a subtotal pancreatectomy. During the second operation, half of the 5% of the pancreas that remained was resected. After a Whipple procedure his hyperinsulinism and hypoglycemia resolved, but he requires insulin.

One patient with MEN 1 and insulinoma and gastrinoma had persistent disease after one malignant insulinoma was enucleated. Unfortunately, even though additional metastases were found and removed during a second operation and distal pancreatectomy, her hyperinsulinism persisted. She subsequently was cured after a Whipple procedure and liver resection when additional tumors were found in the head of her pancreas and liver. This patient also requires insulin.

A third patient underwent a second pancreatic operation after a distal pancreatectomy with negative histology. The patient remained hypoglycemic after a near total pancreatectomy, as no tumor was found. She subsequently had a Whipple procedure and a 1.3 cm tumor was removed. She is diabetic and requires insulin.

Five other patients underwent reoperation for persistent hyperinsulinism. Four were successfully treated and are euglycemic: Two had distal pancreatectomy and two had tumors enucleated from the uncinate process. One of these five patients required a second reoperation and had a malignant islet cell tumor removed.

Among 14 patients who required reoperations at UCSF (nine after an initial reoperation and five after two reoperations), only nine patients were successfully treated. The reason for the eleven unsuccessful operations in patients having primary (2) or reoperations (9) include: missed tumors (seven patients) and hyperplasia/nesidioblastosis (four patients). Four of these patients had malignant tumors. Among the seven failed operations due to missed tumors, two were performed on a patient with both malignancy and multiple tumors, and one was performed on a patient with metastatic islet cell tumor with no primary pancreatic islet cell tumor identified. (Table 2)

Sixty-five of 67 patients survived one or more operations. Of these 65 patients, 62 are no longer hyperinsulinemic but four patients are diabetic after subtotal or total pancreatectomy. Among the three surviving patients who remain hypoglycemic, one had extensive metastases and two elected not to undergo a reoperation.

The overall outcomes in terms of the operative success were similar between the 1954–1975 and the 1975–1995 treatment groups. For the 1954–1975 group, 14 out of the 18 operations (78%) performed were successful, as compared to 43 out of the 50 operations (86%) for the 1975–1995 group. Out of the four failed operations for the 1954–1975 treatment group, two were initial and two were second operations. The range of the procedures performed was also similar between the two groups. In the 1954–1975 group, enucleation was performed in eight (44%) patients, distal pancreatectomy in four (22%) patients, subtotal in three (17%) patients, total in one (6%) patient, and Whipple procedure in two (11%) patients. In the 1975–1995 group, enucleation was performed in 32 (64%) patients, distal pancreatectomy in seven (14%) patients, subtotal pancreatectomy in nine (18%) patients, and Whipple procedure in two (4%) patients.

Medical treatment and outcome

Eleven of the 67 patients with insulinoma were treated with medicine only. Nine of these patients chose not to undergo operation due to their satisfactory maintenance

with diazoxide therapy; only two (12 and 22 years old) of the 11 experienced significant complications of the diazoxide therapy; two other patients did not undergo an operation due to serious pre-existing medical conditions. One of these two patients had liver cancer with metastases and died three weeks after the diagnosis of his insulinoma. The other patient had metastases to lung and brain and chose not to undergo an operation.

Complications

Among the 54 patients having initial operations, complications (fistula, hemorrhage, sepsis, pleural effusion, etc., excluding diabetes) occurred in 43%, as illustrated in Figure 4. The post operative complication rate rose to 55% (five out of nine patients) in patients after a first reoperation and to 60% in those requiring second reoperations (three out of five patients). Diabetes mellitus developed as a result of near or total pancreatectomy in one patient who underwent one reoperation and in three out of the four patients (75%) who underwent second reoperations.

Complications differed depending upon the surgical procedure employed and were more common during the initial period of this study. As expected, more extensive pancreatic resection was associated with more complications. Thirty-five percent who were treated with enucleation had complications versus 69% and 75% with complications after subtotal and distal pancreatectomies, respectively. Enucleation of tumors from the head and uncinate process were associated with more complications. The higher incidence of complications such as wound infection, pneumonia and fistula that developed after subtotal or distal pancreatectomy than after enucleation documents that enucleation is a safer procedure.

The four patients who required reoperation for complications were all treated after 1975. In three of them, those complications had arisen after the first reoperation: two of these three were enucleations from the uncinate process, and one was subtotal pancreatectomy with enucleation from the head. Although the numbers are small, this data suggests that enucleations from the uncinate process and the pancreatic head region seem to pose particular dangers in terms of complications. Out of the whole patient cohort, only four patients underwent enucleations from the uncinate process, and two of them had to undergo additional operations because of complications: one patient had small bowel obstruction with abdominal adhesions and another one had thrombus formation, infection and pseudocyst. In one of those four patients, there was a complication of five pseudocysts into the stomach as a result of the primary enucleation from the tail. These were successfully treated at a subsequent operation.

In the 1954–1975 treatment group only three patients (19%) had complications due to surgery, compared to 27 patients (54%) in the 1974–1995 group.

There were two deaths (one operative). Both occurred after 1975. One, an 85-year-old woman, died 25 days after her initial subtotal pancreatectomy for nesidioblastosis after being transferred to a chronic care facility. At autopsy she was found to have a pancreatic abscess. A 47-year-old woman expired 17 days after her initial exploration and gastro-jejunostomy due to metastatic insulinoma.

Discussion

Our experience at UCSF medical centers documents that 89% of patients having initial pancreatic exploration for insulinomas are successfully treated, including 96% (46 out of the 48) with benign solitary tumors. Similar results have been reported by others.[13,14] Among the patients having initial pancreatic exploration for insulinoma, 60% (three out of five) with multiple tumors and 86% (six out of seven) with malignant tumors are successfully treated. In patients who had positive localization procedures, the success rate was 85% (18 patients) versus a success rate of 90% when tests were negative (18 patients) or not done (11 patients). Preoperative localization studies such as CT scans do provide useful information because they identify large tumors or hepatic metastases. Appropriate operative planning can therefore be done. Intraoperative ultrasonography identified non-visible and non-palpable tumors in four patients, but missed one tumor in the distal tail in the hilum of the spleen. Therefore, intraoperative ultrasonography appears to influence the success of the surgical treatment of patients with insulinoma, as reported by others.[15,16] Ultrasonography probably also decreases the need for "blind" distal pancreatectomy.

Our success rate at initial reoperation was only 55% (five out of nine) and at subsequent reoperation 80% (four out of five). The main reasons for failures were a) islet cell cancer or metastatic disease (four patients), b) nesidioblastosis/hyperplasia (four patients), c) multiple neoplasms (two patients), and d) missed solitary adenomas (three patients). Some of these patients had more than one reason for failure.

Insulinomas associated with MEN 1 syndrome in many respects differ from insulinomas in patients with sporadic hyperinsulinism.[17,18] In patients with MEN 1, multiple islet cell tumors are scattered throughout the pancreas. The median number of tumors among our seven patients with multiple tumors and MEN 1 was seven. The tumors tended to vary in size, ranging in size from microscopic to 3 cm. Consequently, detection of all the tumors was difficult either by localization studies or intraoperative palpation. Fifty-five percent (six out of eleven) of the failed operations were performed on patients with MEN 1, which comprise only 16% of our patient cohort. Three of these patients also had malignant islet cell tumors. Three of the failures occurred after the initial operation and three after subsequent or reoperation. We and others have previously reported that subtotal pancreatic resection with enucleation of tumors from the head of the pancreas is necessary to avoid unsuccessful operations or recurrence.[17–20] Among the entire group of 56 patients treated surgically, hyperinsulinism has recurred or persisted in six of the twelve patients who had subtotal pancreatectomy, in one patient with distal pancreatectomy and in one patient who had a benign tumor enucleated. We and others believe that intraoperative

ultrasonography in combination with careful palpation provides the best results, thus deeming pre-operative localization studies unnecessary until better studies are developed. [13,14,18]

Intraoperative ultrasonography added to our operative success rate in four patients with nonpalpable tumors. In accordance with our findings, there are numerous publications that have recorded cases of nonpalpable tumors, which could be detected only with the help of the intraoperative ultrasonography.[21-23] In patients with MEN 1, subtotal pancreatectomy rather than enucleation is the treatment of choice because of the high probability of multiple islet cell tumors.[17,19,20] The operative failure in adults with nesidioblastosis or hyperplasia can be reduced by histological analysis of a pancreatic biopsy during the operation when no discrete tumor can be identified. If the histological analysis is confirmed, a subtotal pancreatectomy should be considered. Enucleation gave the lowest complication rate of 35% as compared to 60% and 80% complication rates for initial partial and subtotal pancreatectomies, respectively. Our mortality rate of 3% (one who died of progressive metastatic disease), and our complication rate of 43% was comparable with the 20%to 43% complication rates reported in other patient series.[18,24] Even though the fewest complications occurred after enucleation, pancreatic resections are indicated for patients with malignant insulinoma, MEN 1 and/or multiple tumors, and for large tumors in the tail of the pancreas. The complication rate and diabetes mellitus are higher for patients requiring reoperation; therefore, every effort should be made to localize and remove the islet cell tumor or tumors during the initial surgical procedure.[25]

When no tumor can be identified during the operative procedure, we favor either obtaining pancreatic vein sampling for insulin analysis or a distal pancreatectomy to diagnose patients with nesidioblastosis and hyperplasia.

REFERENCES

1. Moss NH, Rhoads JE. Hyperinsulinism and islet cell tumors of the pancreas. In: Howland JM, Jordan GL, editors. Surgical diseases of the pancreas. Philadelphia: Lippincott; 1960, p 321

2. Howard JM, Moss NH, Rhoads JE. Hyperinsulinism and islet cell tumors of the pancreas. Surg Gynecol Obstet 1950; 90:417–55

3.Wilder RM, Allan FN, Power MH, Robertson HE. Carcinoma of the islands of the pancreas, hyperinsulinism hypoglycemia. JAMA 1927; 89:348

4. Whipple AO, Frautz VK. Adenomas of islet cells with hyperinsulinism: a review. Ann Surg 1935; 101:1299–1335

5. Howland G, Campbell WR, Maltby EJ, Robinson WL. Dysinsulinism:convulsions and coma due to islet cell tumor of the pancreas, with operation and cure. JAMA 1929; 93:674

6. Perry RR, Vinik AI. Clinical Review 72:Diagnosis and management of functioning islet cell tumors. J of Clin Endoc Metab 1995; 80(8):2273–2278

7. Delcore R, Friesen JR. Gastrointestinal neuroendocrine tumors. J Am Coll Surg 1994; 178:187–211.

8. Edis AS, Mcllrath DC, van Heerden JA, Fulton RE, Sheedy PF, Service FJ, Dale AS. Insulinoma—current diagnosis and surgical management. Curr Prob Surg 1976; 13(10): 1–45

9. Conn JW, Pek S. On spontaneous hypoglycemia. Current Concepts. Kalamazoo (Mich): . The Upjohn Company, 1970

10. Shatney CH, Grage TB. Diagnostic and surgical aspects of insulinoma: a review of twenty -seven cases. Ann J Surg 1974; 127:174

11.Filipi CJ, Higgins GA. Diagnosis and management of insulinoma. Ann J Surg 1973; 125:231

12. Laroche GP, Ferris DO, Priestley JT, Scholtz DA, Dockerty MB. Hyperinsulinism. Arch Surg 1968; 96: 763

13. Grant CS, van Heerden MB, Charboneau WJ, James ME, Reading CC. Insulinoma. The value of intraoperative ultrasonography. Arch Surg 1988;123:843–848

14. Dagget PR, Goodburn EA, Kurts AB, Le Quesne L P, Morris DV, Nabarro JD, Raphael MJ. Is preoperative localization of insulinomas necessary? Lancet 1981; I(8218):483–486

15. Norton JA, Shawker TH, Doppman JL, Miller DL, Fraker DL, Cromack DT. Localization and surgical treatment of occult insulinomas. Ann Surg 1990; 212(5):615–620

16. Owens LV, Huth JF, Cance WG. Insulinoma: pitfalls in preoperative localization. Eur J Surg Onc 1995; 21(3): 326–328

17. Demeure MJ, Klonoff DC, Karam JH, Duh QY, Clark OH. Insulinomas associated with multiple endocrine neoplasia type I: the need for a different surgical approach. Surg 1991; 110(6): 998–1005

18. Van Heerden JA, Grant CS, Czako PF, Service FS, Charboneau JW. Occult functioning insulinomas: Which localizing studies are indicated? Surg 1992; 112:1010–1014.

19. O'Riordain DS, O'Brien MS, van Heerden JA, Service FS, Greant CS. Surgical management of insulinomas associated with multiple endocrine neoplasia type I. World J of Surg 1994; 18(4):488–194

20. Rasbach DA, van Heerden JV, Telander RL, Grant CS, Carney AS. Surgical management of hyperinsulinism in the Multiple Endocrine Neoplasia Type I syndrome. Arch Surg 1990; 120(3): 584–589

21. Angelini L, Bezzi M, Tucci G, Lirici MM, Candiani F, Rubaltelli L. The ultrasonic detection of insulinomas during surgical exploration of pancrease. World J Surg 1987; 11: 642–649

22. Bottger T, Schafer W, Beyer J, Junginger T. Is preoperative localization diagnostic in organic hyperinsulinism necessary or not?— A National Review.Dig Surg 1991; 8:220

23. Gorman B, Charboneau JW, James EM, Reading CC, Galiber AK, Grant CS. Benign pancreatic insulinoma: preoperative and postoperative sonographic localization. AJR 1986; 147:929.

24. Lo CY, Lam KY, Kung AW, Lam KS, Tung PH, Fan ST. Pancreatic insulinomas. Arch Surg 1997; 132(8):926–930

25. Thompson GB, Service JF, van Heerden JA, Carney AS, Charboneau W, O'Brien PC, Grant CS. Reoperative insulinomas, 1927 to 1992. An institutional experience. Surg 1993; 114(6):1196–1206