The Surgical Aspects of Insulinomas

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The clinical diagnosis of insulinoma rests on the demonstration of Whipple's triad (symptoms of hypoglycemia, low circulating glucose and prompt relief of symptoms after glucose administration). Biochemically, the association of an increased value of immunoreactive insulin with a low glucose value is diagnostic of insulin-mediated hypoglycemia. Angiographic localization of these tumors is accomplished in more than 90% of cases. The pathologic changes are usually due to a single adenoma, for which surgical enucleation is the procedure of choice. Malignancy and persistent hypoglycemia occur in slightly less than 10% of cases and can be fairly successfully managed by diazoxide and streptozotocin.

THE INNOCUOUS-APPEARING PANCREAS, hidden deep in the lesser sac, continues to excite, challenge and frustrate many disciplines in the field of medicine. Of special interest has been the discovery and elucidation of the syndromes related to the overproduction of different hormones by the seemingly totipotential cells of the islets of Langerhans—cells that were first described 100 years ago. The list of these syndromes and the hormones is long and continues to grow (Table 1).

Of these APUDomas (Amine content, Precursor Uptake of amine, Decarboxylase), we have been particularly involved with the β cell tumors ever since W. J. Mayo undertook exploration in 1927 of a 40-year-old South Dakota surgeon who had a malignant insulinoma. To the present day, the report of this patient by Wilder et al.[14] remains a descriptive classic.

Our Series

The surgical experience at our institution since 1927 has involved 226 patients with functioning insulinomas; some of these patients have been previously reported.[2,4] Since 1965, 72 patients have been surgically treated, and data on these form the basis for this paper. The successful management of patients with insulinoma entails a close liaison among endocrinologists, surgeons, radiologists and pathologists.

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Clinical Features

Of the 72 patients, 49 were females and 23 were males (2:1). At the time of definitive operation, the ages ranged from 14 to 75 years, with a mean of 46.3 years.

All patients had varying degrees and combinations of the classic hypoglycemic symptoms (sweating, tachycardia, visual disturbances, bizarre behavior, amnesia, coma and convulsions), some for a few weeks and others for years. Symptoms were aggravated or precipitated by food deprivation, and many patients had unrecognized subtle changes in food intake. Both the nonspecificity and the intermittency of the symptom complex led to a long diagnostic delay. One of our patients, for example, developed symptoms only one day a year, that is, at Yom Kippur.

In our experience,[9] insulinoma occurs twice as often in women as in men and is uncommon below the age of 20 years; about half the patients are more than 50 years old. Although the median duration of symptoms before diagnosis was 19 months in our study,[9] the duration appears to be decreasing in recent years; nearly half the patients have had their symptoms for less than one year before a firm diagnosis is made. Hypoglycemic symptoms occur most often late in the afternoon, early in the morning before breakfast or several hours after a meal. Although hyperepinephrinemic symptoms are not unusual, the most prominent symptom is impairment of cerebrocortical function, with 80% of patients having confusion or abnormal behavior and 50% being amnesic during the episode or in frank coma. Although most patients recognize that food intake relieves their symptoms and most increase their food intake, only about 16% actually gain weight. Occasionally a neurologic or psychiatric diagnosis is made in such cases; in our experience, this was noted in 20% of the cases before the correct diagnosis was made.

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TABLE 1. *Hormones and Associated Syndromes Related to Overproduction by Islets of Langerhans*

Hormone	Syndrome
Glucagon	Glucagonoma
Insulin	Hypoglycemia
Gastrin	Zollinger-Ellison
Secretin	Verner-Morrison
Serotonin	Carcinoid
Corticotrophin	Cushing's
Melanocyte-stimulating	Hyperpigmentation
Somatostatin	Somatostatinoma

Laboratory Findings

The diagnosis of an insulinoma depends on two factors: a plasma glucose level ≤45 mg/dl at the time of classic hypoglycemic symptoms and the presence of hyperinsulinemia, that is, insulin concentration ≥6 μU/ml. This has been documented in all patients.[9] With repeated demonstration, no further diagnostic procedures are required. Factitious hyperinsulinemia can be excluded by the absence of insulin antibodies. If symptoms are not frequent enough for ready documentation, provocative testing is necessary. The most reliable provocative test is the prolonged withdrawal of food. In our series, one-third of the patients had typical symptoms within 12 hours of fasting, 80% within 24 hours, 90% within 48 hours and 100% within 72 hours. The most widely used diagnostic short screening test for the diagnosis of insulinoma is the intravenous tolbutamide test, which we have found to be positive for insulinoma if, during the last hour of the test, the plasma glucose level is less than 55 mg/dl and the serum insulin concentration is greater than 20 μU/ml. Recently a suppression test, based on the suppressibility of C-peptide during insulin-induced hypoglycemia, has been developed.[10] When contrasted with normal subjects in whom C-peptide is suppressed to less than 1.2 ng/ml when the plasma glucose level is ≤40 mg/dl, patients with insulinoma fail to show this degree of suppression; 17 of 18 patients in our group who have been tested failed to show normal suppression of C-peptide.[11]

Radiologic Features

In our experience, selective angiography continues to be the modality of choice for localization of tumor. The use of stereoscopic filming with magnification and subtraction techniques ensures a high success rate. The subtraction films have been the most helpful (Fig. 1). In this series, of 58 patients who underwent preoperative selective angiography, 53 (91.4%) had positive findings. Of the last 24 patients studied, 23 (95.8%) had positive findings—the only missed tumor was a 1.5 cm lesion in the body of the pancreas. The false-positive and false-negative rates have been consistently less

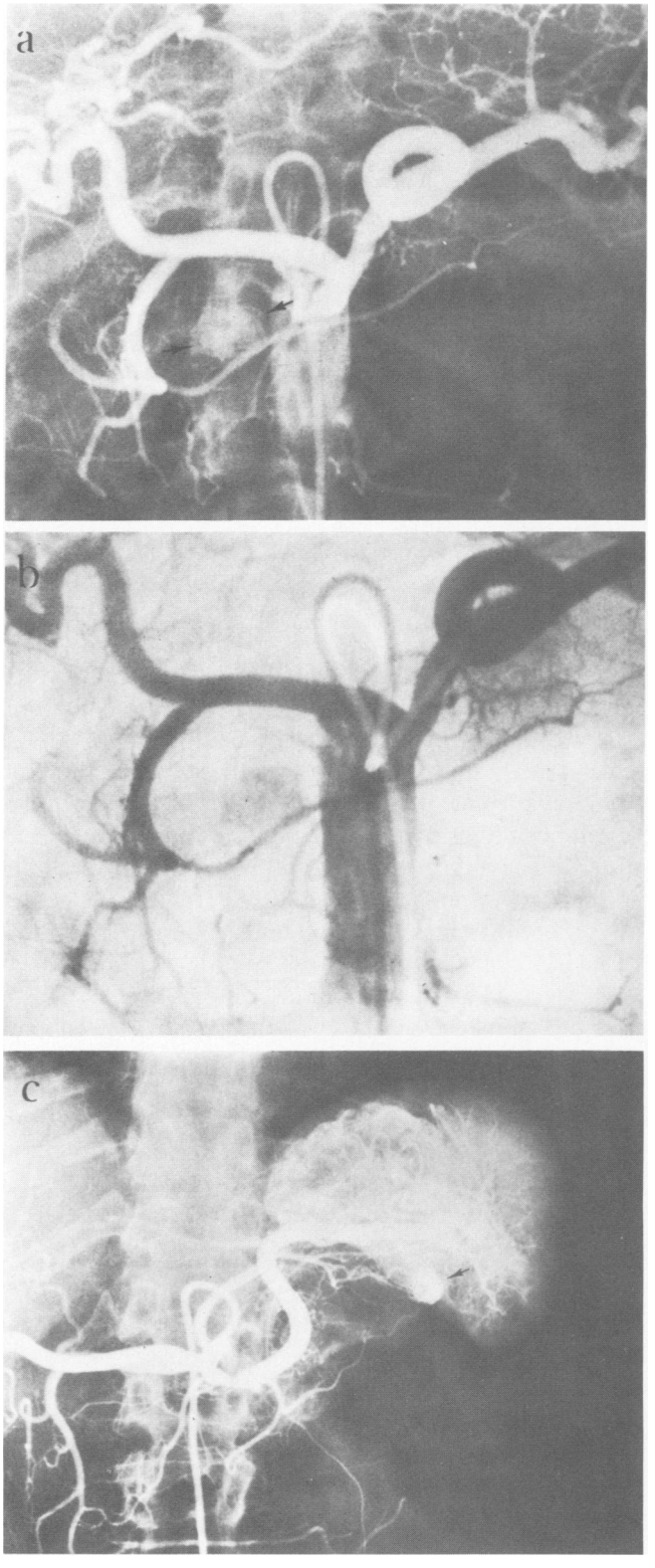

FIG. 1. Celiac angiogram A) A 2-cm insulinoma (between arrows) partially obscured by vertebral body. B) Subtraction film of A. Tumor is easily seen. C) A 1.2-cm insulinoma in tail of pancreas (arrow). (A and B from Edis, A. J., McIlrath, D. C., van Heerden, J. A. et al.: Insulinoma—Current Diagnosis and Surgical Management. Curr. Probl. Surg., 13 No. 10:1, 1976. By permission of Year Book Medical Publishers.)

than 5%, and there have been no complications of concern.

In our limited experience with computed tomography for insulinomas,[12] we located a definite tumor in only one of seven patients studied. Computed tomography will probably not be as useful as angiography in these patients.

Pathologic Features

Most insulinomas are relatively small, benign adenomas (Fig. 2). Sixty-six of the patients had such adenomas, and six (8.3%) had malignant lesions. Forty-seven (71%) of the adenomas were less than 1.5 cm in diameter. As with most endocrine neoplasms, malignancy is based more on the presence of tumors at sites distant from the primary lesion and on evidence of perineural or vascular invasion than on histologic criteria.

The tumors were evenly distributed throughout the pancreas: 23 in the head, 27 in the body and 31 in the tail. Eight patients (11%) had multiple tumors. Three of the eight patients had insulinomas as one manifestation of the MEN-I syndrome. An additional patient with MEN-I had a single lesion. Thus far, we have not encountered any ectopic insulinoma.

Grossly, the tumors were typically reddish brown, somewhat bosselated and of a slightly firmer consistency than the pancreas. Despite the common occurrence of an amyloid stoma, which would tend to decrease the vascularity, most of the tumors could be visualized angiographically, in contrast to gastrinomas.

Surgical Management

Prior to surgery, the diagnosis usually is confirmed in all cases, although the exact location is unsure in less than 10%. The success of the procedure is complemented by intraoperative monitoring.

Except for the few patients who cannot tolerate 8 hours of fasting, the administration of glucose is discontinued at midnight before surgery. This allows the blood glucose level to be between 50 and 70 mg/dl—a level that facilitates intraoperative monitoring. Glucose-containing solutions are not used during the operative procedure.

A transverse epigastric incision usually is made, as has been detailed previously.[2] A careful search is made for extrapancreatic spread before detailed attention is given to the pancreas. The pancreas must be palpated methodically so as not to miss subtle differences in its consistency. Most adenomas are not visible, being covered by a thin layer of normal pancreas. Almost all adenomas can be enucleated once this layer has been excised. The defect should be closed meticulously with interrupted permanent sutures, and the area should be drained by appropriate suction drains.

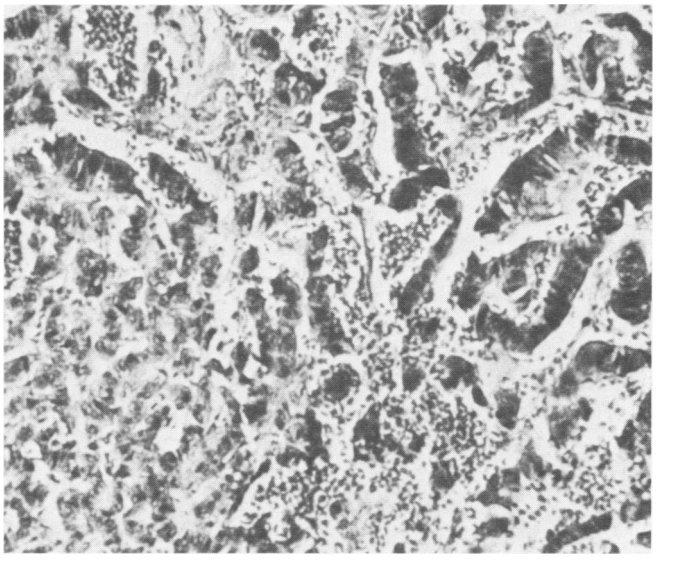

FIG. 2. Typical histologic appearance of insulinoma. (Hematoxylin and eosin, ×150)

The surgical procedures performed for insulinoma varied: 43 patients had enucleation, 22 partial pancreatectomy, three enucleation and partial pancreatectomy, two Whipple's procedure, one biopsy only and one total pancreatectomy. Of the 72 procedures, 62 were primary and ten were secondary. Blind distal pancreatectomy (left of the superior mesenteric vessels) is seldom employed presently, being reserved for the rare situation in which both the preoperative and the intraoperative localization are unsuccessful. The extent of pancreatectomy in multiple and malignant tumors is dictated by the extent of the disease.

Intraoperative Monitoring of Blood Glucose

We have utilized intraoperative monitoring of blood glucose as initially described by McMillan and Scheibe[6] in 1951 and have found it to be of value. Three to 5 ml of venous blood are drawn at designated intervals before and after tumor removal (Fig. 3). A hyperglycemic rebound of 30 mg/dl confirms the removal of all hyperfunctioning islet tissue. If there is no increase in blood glucose level during the first 30 minutes after tumor removal, one should be concerned that additional tumors remain undetected. However, on the basis of our recent experience,[3] we are somewhat reluctant to recommend blind distal pancreatectomy if the blood glucose level does not rebound (these data will be presented in a future publication). At the present time, measurement of immunoreactive insulin levels during operation are of little practical value in patient management[8] because the results are not available until several days after the operation.

Forty-nine of our 72 patients had monitoring. Only one patient had a false-positive result, while a small

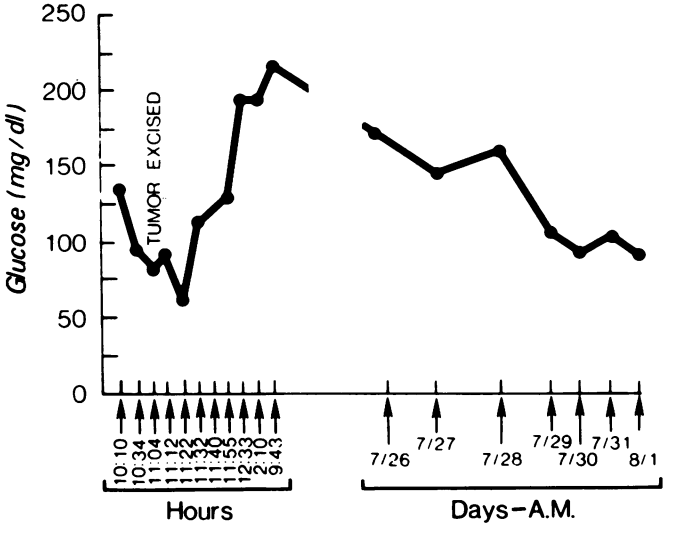

FIG. 3. Glucose monitoring in patient with insulinoma.

number of patients had false-negative (delayed rebound) results. Because of this success (94%), we continue to use this simple, yet effective, monitoring technique.

Results

No operative deaths occurred in our series, and none has occurred for insulinoma at our institution during the past 25 years.

There were 11 (15.2%) immediate postoperative complications: three patients had unexplained fever, two pancreatic pseudocyst, two intraperitoneal abscess and one each peritonitis, pancreatitis, intestinal obstruction and biliary fistulas plus gastrointestinal hemorrhage. Analysis of the long-term results revealed that 66 (91.7%) patients were cured, and six had persistent hypoglycemia (Table 2). In only one of the six patients with malignant insulinoma was the condition uncontrolled, and this patient died 6 weeks postoperatively. The other five patients achieved control by diazoxide, either with or without streptozotocin (Table 3).

Although these patients may experience significant neuropsychiatric disturbances,[5] such problems must be rare. With follow-up of these patients, which now averages 36.5 months, we are aware of only one patient who has been institutionalized and that because of continued child abuse.

TABLE 2. *Six Patients With Persistent Postoperative Hypoglycemia After Surgical Treatment of Insulinoma*

Insulinoma	Status	Follow-up (mos)
Malignant	Dead	34
Malignant	Dead	1
Malignant	Dead	48
Malignant	Alive, chemotherapy	60
Adenoma (0.4 mm)	Alive, diazoxide	33
Adenoma (1.5 cm)	Alive, diazoxide	145

TABLE 3. *Postoperative Status of Six Patients With Malignant Insulinoma*

Sex and Age (yrs)	Treatment	Metastasis	Status	Follow-up (mo)
M, 58	Biopsy only	Liver	Dead	1
M, 27	Partial pancreatectomy	None	Alive	66
M, 55	Partial pancreatectomy	Nodes	Alive with "spells"	60
M, 61	Partial pancreatectomy	Liver	Dead	48
F, 74	Whipple procedure	None	Alive	31
F, 55	Biopsy only	Nodes	Dead	39

Discussion

The diagnosis of insulinoma begins with a high index of suspicion and an awareness of the characteristic clinical situation. We cannot improve on the description by Wilder et al.:[14]

> beginning as sudden attacks of faintness and weakness, with paresthetic numbness of the tongue and lips. As time passed these attacks occurred more frequently and were more severe, producing greater weakness, profuse perspiration and trembling. They came when meals were delayed or if unusual exertion was undertaken, and the patient himself discovered that he could prevent them by eating between meals and by taking sweet drinks.

Whipple's triad (symptoms of hypoglycemia, low concentration of circulating glucose and prompt relief of symptoms with the administration of glucose) is the main basis for diagnosis. All 72 of our patients had this triad. Ancillary testing consisting of a prolonged fast (most reliable) and the provocative intravenous tolbutamide test were done in about 90% of our patients. In order to attribute the hypoglycemia to hyperinsulinism, associated increased levels of serum insulin (IRI) have to be demonstrated. The association of an increased value of IRI with a low glucose value is diagnostic of insulin-mediated hypoglycemia. All 72 of our patients met this criterion.

We have not had extensive experience with other provocative tests, such as the glucagon, leucine or epinephrine tests, but we believe that they do not add much to the diagnosis.

Angiography for localization is an excellent procedure, with a success rate of more than 90%. The

roles of computed tomography and venous catheterization with selective venous sampling of insulin are yet to be determined.[13] At the present time, venous catheterization does not seem to be a promising or practical procedure.

The operative technique is well standardized and is complemented by the intraoperative monitoring of glucose, which has a success rate of about 94%. The declining incidence of "blind" pancreatectomies and of persistent postoperative hypoglycemia is a direct result of better preoperative and intraoperative diagnostic and monitoring techniques, coupled with increasing surgical experience.

Somewhat less than 10% of the patients have malignancy, and malignant lesions are the most frequent causes of persistent hypoglycemia. In contrast to the ordinary type of pancreatic cancer, malignant insulinomas have a higher resectability rate (four of six patients) and a better prognosis (four of six patients survived 3 years and two of six survived 5 years). The adjunctive therapeutic agent of choice in patients with metastases is streptozotocin. This agent is isolated from cultures of *Streptomyces achromogenes* and selectively destroys the pancreatic β cells by inhibiting the synthesis of deoxyribonucleic acid. About 50% of patients have objective tumor regression.[1]

Persistent hypoglycemia, whether from a benign or malignant insulinoma, usually can be controlled by the use of diazoxide. This drug has no antitumor effect. It accumulates within the β cell, where it inhibits the release of insulin, thus reducing the level of plasma insulin to an asymptomatic concentration. Two of our patients are presently on long-term diazoxide therapy and are doing well. The side effects of this drug are hirsutism, edema and, rarely, hypotension and granulocytopenia. If malignancy exists, streptozotocin and diazoxide may be used in combination.

The possibility of multiple endocrine neoplasia should always be considered when an insulinoma has been diagnosed, because the insulinoma may be one manifestation of the MEN-I syndrome (pituitary tumors, hyperparathyroidism and pancretic adenoma). Four patients (5.5%) in our series had the MEN-I syndrome.

In the Moynihan Lecture on hyperinsulinism by our colleague, Dr. J. T. Priestley, in 1962,[7] he stated, "It has always seemed to me that one of the most significant attributes which a teacher of surgery can possess is the ability to inspire and stimulate the young." In this field of hyperinsulinism, he has seemingly taught us well.

References

1. Broder, L. E. and Carter, S. K.: Pancreatic Islet Cell Carcinoma: II. Results of Therapy With Streptozotocin in 52 Patients. Ann. Intern. Med., 79:108, 1973.
2. Edis, A. J., McIlrath, D. C., van Heerden, J. A. et al.: Insulinoma—Current Diagnosis and Surgical Management. Curr. Probl. Surg., 10:1, 1976.
3. Edis, A. J., van Heerden, J. A. and Tutt, G. O.: Intra-operative Blood Glucose Monitoring in Surgery for Insulinomas (unpublished data).
4. Laroche, G. P., Ferris, D. O., Priestley, J. T. et al.: Hyperinsulinism: Surgical Results and Management of Occult Functioning Islet Cell Tumor; Review of 154 Cases. Arch. Surg., 96:763, 1968.
5. Markowitz, A. M., Slanetz, C. A. Jr. and Frantz, V. K.: Functioning Islet Cell Tumors of the Pancreas: 25-Year Follow-Up. Ann. Surg., 154:877, 1961.
6. McMillan, F. L. and Scheibe, J. R.: Islet Cell Tumor of the Pancreas. Am. J. Surg., 82:759, 1951.
7. Priestly, J. T.: Hyperinsulinism. Ann. R. Coll. Surg. Engl., 31:211, 1962.
8. Schnelle, N., Molnar, G. D., Ferris, D. O. et al.: Circulating Glucose and Insulin in Surgery for Insulomas. JAMA, 217:1072, 1971.
9. Service, F. J., Dale, A. J. D., Elveback, L. R. et al.: Insulinoma: Clinical and Diagnostic Features of 60 Consecutive Cases. Mayo Clin. Proc., 51:417, 1976.
10. Service, F. J., Horwitz, D. L., Rubenstein, A. H. et al.: C-Peptide Suppression Test for Insulinoma. J. Lab. Clin. Med., 90:180, 1977.
11. Service, F. J. and Palumbo, P. J.: Factitial Hypoglycemia: Three Cases Diagnosed on the Basis of Insulin Antibodies. Arch. Intern. Med., 134:336, 1974.
12. Sheedy, P. F. and Berquist, T.: Personal communication.
13. Turner, R. C., Lee, E. C. G., Morris, P. J. et al.: Localisation of Insulinomas. Lancet, 1:515, 1978.
14. Wilder, R. M., Allan, F. N., Power, M. H. et al.: Carcinoma of the Islands of the Pancreas: Hyperinsulinism and Hypoglycemia. JAMA, 89:348, July 1927.

Discussion

DR. SAMUEL A. WELLS, JR. (Durham, North Carolina): It is always impressive how The Mayo Clinic can accrue such a large number of patients with a seemingly rare disease.

I would like to ask Dr. van Heerden four questions. The authors mentioned in the text that, clinically, they considered a fasting glucose level below 40 mg/dl indicative of an insulinoma. Merimee at the University of Florida and other investigators as well, have reported that in some normal subjects, particularly women, who have fasted for 72 hours, the blood glucose level may drop to levels of 40 g/dl. This has led most of us to equate the fasting plasma glucose level with the concomitant insulin level. I wonder if Dr. van Heerden could tell us, in the Mayo Clinic experience, what ratio of insulin to fasting blood glucose is of diagnostic significance.

From the standpoint of diagnosis, I would also like to ask if he has used any other provocative agents than tolbutamide? Specifically, has calcium been used? This cation is certainly an excellent provocative agent for several of the other neural crest tumors such as medullary thyroid carcinoma and gastrinomas and might well be useful in the diagnosis of insulinomas. Recently, Kaplan, at the University of Chicago, has demonstrated that patients with insulinomas have a very rapid increase in insulin after the intravenous administration of calcium ion.

Last, I wonder if you would say something about malignant insulinomas. This is a somewhat difficult pathologic state to diagnose preoperatively; however, several investigators have demonstrated that patients with these lesions frequently secrete a large amount of high molecular weight insulin. Not only is this helpful in the preoperative diagnosis, but it is also useful in following patients in