Current Surgical Management of Functioning Islet Cell Tumors of the Pancreas

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ENDOGENOUS HYPERINSULINISM and its surgical correction has been the subject of numerous recent reports.[4,6,7,16,20,23,34] It is not our intention to add another description to those which already outline, carefully and well, the surgical correction of hyperfunctioning islet cell tumors of the pancreas. It is the purpose of this report to develop a few special considerations which have arisen in our care of 35 patients, aged 13–74 years, with endogenous hyperinsulinism in the 13-year period, 1960–1972. Thirty-two of these patients have been treated since 1965 enabling us to obtain experience and form convictions on the role of modern innovations in diagnosis, preoperative evaluation and pathology underlying pancreatic hyperinsulinism. This experience has influenced our attitudes concerning contemporary efficient surgical management of endogenous hyperinsulinism.

Diagnosis

Soon after Wilder's initial description of functioning islet cell carcinoma[33] and Graham's initial cure of endogenous hyperinsulinism following removal of a solitary hyperfunctioning islet cell adenoma,[18] the diagnosis of hyperinsulinism became suspected in any situation of hypoglycemia in which the clinical impression of fasting hypoglycemia was confirmed by measurement of a blood glucose level less than 50 mg./100 ml. A third feature considered to be of clinical importance was the relief, following the ingestion of glucose, of the frequently bizarre central nervous systems. These three features were set forth most vigorously by Whipple[31] and constituted, 'Whipple's Triad' which has remained inescapably welded to surgically oriented diagnostic thinking to this day.

Whipple's Triad is not specific for patients with hyperinsulinism due to pancreatic islet cell disease as it may occur in patients with other types of hypoglycemia. Furthermore, five of our last 32 patients (16%) with hyperinsulinism had overnight fasting blood glucose levels above 60 mg./100 ml. during the first 5 days of study.[12] The advent of the radioimmunoassay for plasma insulin[35] has refined the specificity and precision of the diagnosis of endogenous hyperinsulinism from hyperfunctioning islet cell lesions. Current diagnostic criteria take advantage of concentrations of plasma insulin and coincident blood levels of glucose after an overnight fast, or after prolongation of the overnight fast for as long as 14 hours or more. One patient required a fast of 31 hours before an abnormal glucose insulin ratio could be demonstrated. Changes in levels of plasma insulin and blood glucose after administration of tolbutamide, leucine and glucagon have been described before[9,10,13,15] and are the subject of a more recent report from this institution[12] which defines our current diagnostic criteria in this disease. Because it is available elsewhere, we shall not review the diagnostic data on our patients in this report. We do wish to emphasize that the crux of the diagnosis of endogenous hyperinsulinism lies in demonstrating coexisting fasting hypoglycemia and absolute or inappropriately elevated plasma insulin, a circumstance which connotes that in-

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

Supported in part by USPHS Grant RR 42 General Clinical Research Center Program, Division of Research Resources and 5 P 11 GM 15559, National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland.

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sulin release is occurring autonomously with respect to the physiologic stimulus provided by the concomitant level of blood glucose. Whereas in the majority of our patients (81%) an absolute elevation of the plasma level of immunoreactive insulin with coincident hypoglycemia has been an important diagnostic point, in all patients inappropriately elevated levels of plasma insulin in relation to the prevailing blood glucose level could be demonstrated by the fifth day of study. In many patients exaggerated increases in plasma insulin in response to the various provocative stimuli mentioned above has provided important diagnostic aid. In a few patients, abnormal elevation and/or prolongation of stimulated insulin increase after provocative stimuli has been of critical aid to the diagnosis as in one of our patients who, over a 4-year period, had diagnostic studies repeated on five occasions before the diagnosis of hyperinsulinism could be made with sufficient conviction to justify exploration. This lesion proved to be a multi-centric islet cell carcinoma in a patient from a family with multiple endocrine adenomatosis.

The differential diagnosis of fasting hypoglycemia has, for some time, been recognized to include a variety of diagnostic possibilities other than primary pancreatic islet 'beta cell' lesions. Among these other diagnostic possibilities are nonpancreatic tumors associated with hypoglycemia, patients with diffuse and extensive liver disease as well as those with anterior pituitary hypofunction and adrenal cortical hypofunction. In addition to these, a variety of specific hepatic enzymatic defects, alcohol hypoglycemia and a heterogeneous group of entities termed 'idiopathic hypoglycemia of infancy and childhood' all occur with no consistently recognizable anatomical defect in the pancreas but, nevertheless, with marked, relentless hypoglycemia. Factitious hypoglycemias are also well known. In infancy and childhood some patients with 'idiopathic hypoglycemias' also have inappropriately elevated levels of plasma insulin and pose the greatest problem in differential diagnosis. These and other entities to be considered in differential diagnosis have been described in greater deatil in previous reports from this institution.[5,12]

These few remarks concerning the diagnosis of endogenous hyperinsulinism and the differential diagnosis of hypoglycemia which may be brought on by fasting, should be sufficient to indicate that Whipple's Triad, although of undeniable historical interest, is useful in our current thinking concerning hyperfunctioning lesions of pancreatic islets, only in the sense that it brings patients with fasting hypoglycemia, from any cause, under the detailed scrutiny of current specific diagnostic technics.

Solitary Islet Cell Adenomas

By far the most common lesion, occurring in 25 of our 35 patients, was solitary islet cell adenoma. These lesions were symmetrically distributed through the entire pancreas, Figure 1. Twenty-four of these lesions were removed and verified histologically. One lesion, never found, is presumed to be a solitary adenoma in a 15% pancreatic remnant. In one patient a carotid body tumor was discovered and removed at a subsequent operation.

Angiography, selective and superselective, has been pursued aggressively by us since 1964[2,25] and has demonstrated solitary lesions in nine of 21 patients, 43%, with histologically verified solitary adenomas in whom this localizing procedure was used.

Four patients with solitary adenomas had lesions which were not palpable, Figure 1. Angiography had been used in three of these patients and demonstrated the two lesions which were subsequently removed by us. These two patients with non-palpable adenomas had pancreatic explorations performed in other hospitals previously and these were unsuccessful in locating the adenomas. They had not undergone selective arteriography until their referral to our hospital. One presumed non-palpable adenoma was not visualized angiographically and was not found in the course of an 85% blind distal pancreatectomy we performed. Since the concentration of proinsulin in her peripheral plasma was elevated,[29] the diagnosis of an islet tumor seems assured. This patient did not wish further operation and has been easily controlled for six years with Diazoxide and Trichlormethiazide.[11] She is fully active and not inconvenienced by the disease or its treatment and there

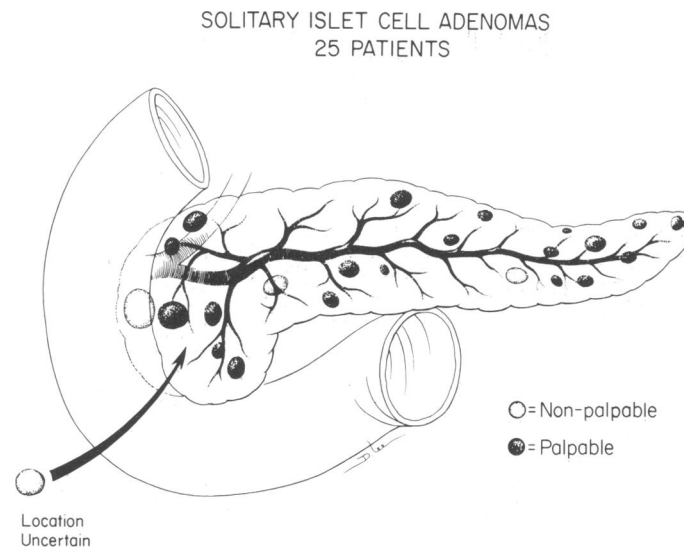

FIG. 1. The location of 24 histologically verified solitary adenomas is shown. The smallest lesion measured 1 × 1 × 3 mm and the largest was 2.50 cm in diameter.

has been no reason to advise further operation. The fourth non-palpable solitary adenoma was found in the body of an 80% distal (tail, body and neck) pancreatic resection early in our experience before angiography was available to us. Palpation of the reassembled specimen directly after its removal did not reveal this 1 cm. diameter lesion even after its location had been identified visually on sectioning the specimen.

Of the two broad gross morphologic types of solitary adenomas, white firm tumors and softer purple or reddish-brown lesions, the non-palpable lesions have appeared in the latter group. Neither morphologic type has been distinctly the more angiographically identifiable. In the 25 patients with solitary adenomas simple excision of the adenoma was performed in 12 and pancreatectomy, 50–90%, was performed at our primary operation in 13 patients.

Other than operative complications which will be reviewed subsequently, these patients have done well following removal of their solitary adenomas and, with one exception, have exhibited no serious metabolic problems such as diabetes or recurrent hyperinsulinism. This exception, a patient with a 90% pancreatectomy, has been diabetic for the two years we followed him after the operation.

Microscopic Adenomatosis with or without Macroscopic Tumors

Four of our 35 patients with hyperinsulinism proved to have pancreatic adenomatosis, Figure 2. In none of these four patients has there been any reason to suspect the presence of multiple endocrine adenomatosis. In one patient with severe fasting hypoglycemia the disease was microscopic, being first appreciated by the pathologist on examination of the permanent histopathologic sections of an 80% distal pancreatic resection, Figure 3. The surgeon had found no abnormality of the pancreas when he removed it. This patient was the first in this series and it is now 13 years since the operation. She is doing perfectly well and requires no special diet and remains euglycemic after fasting for 72 hours.

Two other patients with well defined autonomous hyperinsulinism had, at initial exploratory operation at our hospital, adenomas that sufficiently explained the findings. One adenoma was non-palpable in a patient whose pancreas had been explored elsewhere. These two patients' adenomas had been identified by angiography preoperatively. The adenomas were removed. Within 2 weeks it was clear tht hyperinsulinism had recurred. Several months later, when no lesion was palpable at re-exploration, 80% distal pancreatectomy was performed. Both patients had multiple lesions, three to six in number, visible in the resected pancreas. Subsequently myriads of microscopic adenomata were seen on examination of permanent sections. These microadenomata were distributed through all sections of the resected pancreas along with other islets which were perfectly normal in microscopic appearance and size. One of these two patients was profoundly hypoglycemic before the first operation with intermittent coma and had an excessively high plasma insulin. Symptoms and blood glucose levels are now adequately controlled with Diazoxide treatment, ten months after the second operation. The levels of plasma insulin are now in the normal range. Before the first and second operations it had been impossible to control her profound hypoglycemia with Diazoxide.

The second of the two patients with adenomatosis who had two operations is mildly hyperinsulinemic since the second operation, an 80% distal pancreatectomy. Initially, she was able to control the hypoglycemic symptoms well with judicious spacing of a normal diet throughout the day. Subsequently, Diazoxide has become necessary for her prolonged postoperative management.

The fourth patient with pancreatic adenomatosis had a 50% distal pancreatic resection for two small (0.35 and 0.25 cm. diameter) palpable adenomas. These had been seen angiographically in the tail of the pancreas where they were easily felt. On histopathologic examination of the pancreas, there was also microscopic evidence of islet cell adenomatosis in addition to these two macroscopic lesions. She has been euglycemic with a normal plasma insulin since operation, 1 year ago, and has not required any special medication or diet.

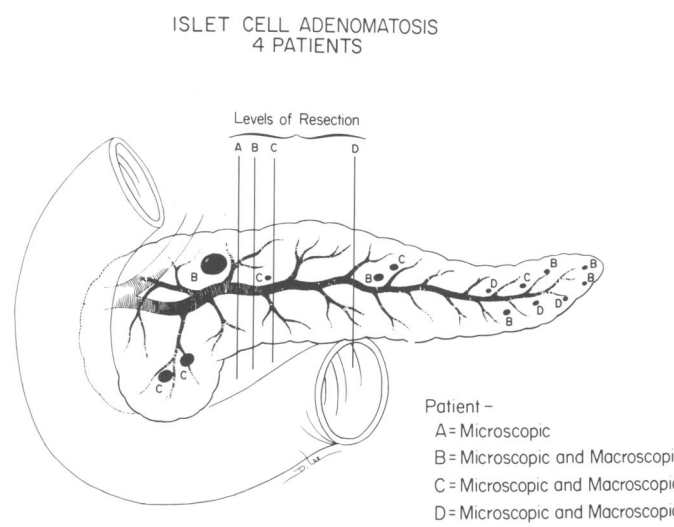

FIG. 2. The location of visible (macroscopic) lesions in three patients with adenomatosis is shown. Levels of distal pancreatic resection in the four patients with adenomatosis are indicated.

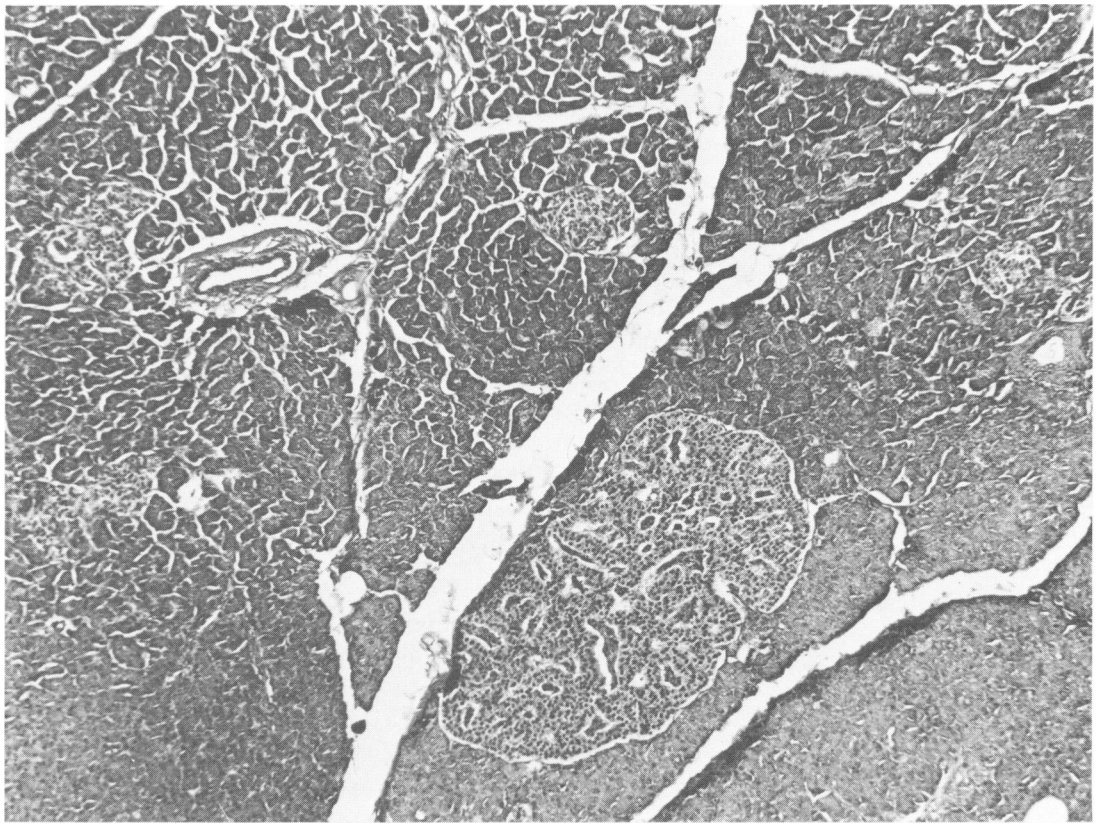

FIG. 3. Magnification, times 325, of a typical lesion of microscopic islet cell adenomatosis. One micro-adenoma is seen as are several normal islets.

However, 36 hours after the beginning of a fast she still develops symptomatic hypoglycemia with failure of normal suppression of plasma insulin.

In none of the four patients with pancreatic adenomatosis has there been any reason for dissatisfaction with their course so far following 80% pancreatic resection in three patients and 50% resection in the fourth. In the three patients of this group in whom angiography was used, lesions were identified but, of course, proved not to be the sole lesions responsible for the hyperinsulinism. At present, we know of no certain means of clinically differentiating solitary adenomas from pancreatic micro-adenomatosis with or without macroscopic adenomas except by identifying several lesions angiographically or macroscopically at operation and/or microscopically in a portion of resected pancreas. Certainly the size of the adenoma is not a dependable help since the largest lesion in the patients with pancreatic adenomatosis measured 2.30 cm. in diameter, exceeding the size of most of the solitary adenomas in this series of patients.

Multiple Endocrine Adenomatosis

Three of the patients in this series with hyperinsulinemia were members of the same family. One was the affected father of two affected siblings, one female and one male. Each of these patients has primary hyperparathyroidism as well. In two, the brother and sister, the primary hyperparathyroidism has been surgically corrected and the parathyroid lesion in both has been primary chief cell hyperplasia of the parathyroids. By contrast the lesions responsible for the hyperinsulinism in all three of these patients varied, Figure 4; in one patient it was a solitary islet cell adenoma, in another it was two islet cell adenomas and in the third, there was multicentric islet cell carcinoma with involvement of two regional lymph nodes. This third patient had an excision of a lesion located in the pancreatic head and a 50% pancreatectomy which widely embraced the carcinoma, two satellite nodules, and the two metastatic nodes in one specimen. In two of these patients with multiple endocrine adenomatosis pancreatic resections were performed and it is of interest that in neither of them was islet cell adenomatosis or hyperplasia found on detailed microscopy of the resected pancreas.

All three patients with multiple endocrine adenomatosis have done well clinically since surgical correction of the hyperinsulinism with normal plasma levels of insulin and euglycemia following resection of the pancreatic lesions. The patient with two adenomas and the patient with the solitary adenoma are now 8 years postoperative and the third patient, with multi-centric islet cell carcinoma, is 1 year postoperative.

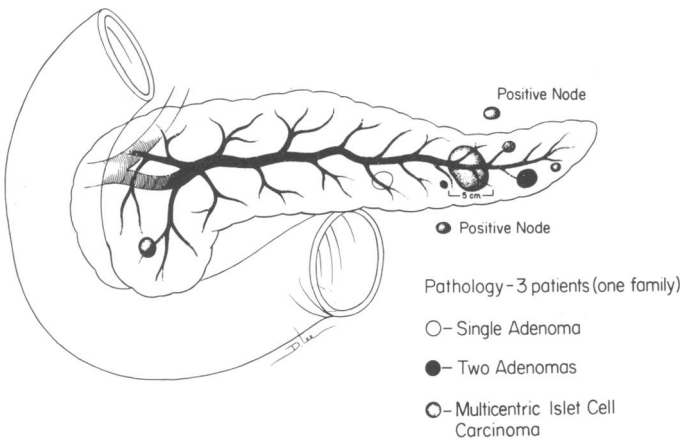

FIG. 4. Depicted are the islet cell lesions found in three patients from a family with multiple endocrine adenomatosis.

Metastatic Islet Cell Carcinoma

During the 13-year experience reflected in this report, three patients have been referred to us with islet cell carcinoma metastatic to liver and regional lymph nodes. Two of these patients had been operated on elsewhere, while the third had a liver biopsy and the diagnosis already established. It was not necessary for us to reexplore these patients. Plasma levels of insulin were exceedingly high in two of the three patients.

One patient died a few days after coming under our care, one lived for 5½ months and the third is living, 1½ years after referral. Symptomatic relief was obtained in two of these patients with Streptozotocin and with cortico-steroids in one after Streptozotocin had become ineffective.

Intraoperative Blood Glucose Measurement as an Indicator of Total Removal of Hyperfunctioning Islet Cell Tissue

We have studied blood glucose levels, measured by the glucose oxidase method, during operation in 16 of our 24 patients with histologically verified solitary adenomas. In these patients no glucose was given after 6:00 AM on the day of operation. The postoperative course of these 16 patients, particularly the persistently normal levels of blood glucose and of plasma insulin and the clinical course have not suggested any further hyperinsulinism. The results summarized in Figure 5 indicate that, after the removal of these solitary adenomas the mean blood glucose content rose at a rate of 29 mg./100 ml. per hour. However, in our patient with a presumed adenoma retained, blood glucose levels rose to 165 mg./100 ml., 40 minutes after 85% pancreatectomy and this rise was progressive with blood glucose reaching 235 mg./100 ml., 2½ hours after the last portion of the 85% pancreatectomy specimen was removed. No lesion was found in the resected pancreas. Twelve hours following operation, blood glucose had fallen to 80 mg./100 ml. On the eighth postoperative day the level of blood glucose was 40 mg./100 ml. Continued study of this patient has demonstrated persistent hypoglycemia and coexisting hyperinsulinemia. She did not wish further operation and, as mentioned before, has been managed for 6 years with Diazoxide therapy. In a patient in whom a single adenoma was removed recently there was a rise in blood glucose from 80 mg./100 ml. to 125 mg./100 ml. within the first 3 hours after removal of the tumor. To date this patient has remained euglycemic.

Three of the four patients with pancreatic adenomatosis have had intraoperative blood glucose determinations. Two of these patients were explored twice. During the first operation on one adenomatosis patient, intravenous glucose was given repeatedly during operation. At one point, 60 minutes after an adenoma was excised, blood glucose fell to its lowest intraoperative level, 79 mg./100 ml. During five other operations in which we now recognize that hyperfunctioning tissue was left *in situ*, blood glucose determinations were made and no glucose was given after 6:00 AM of the day of operation till at least 3 hours after the operative specimen had been removed. As seen in Figure 6, blood glucose concentrations were measured during these five operations on four patients. After removal of pancreatic tissue mean blood glucose levels rose at a rate of 24 mg./100 ml. per hour. This rate is virtually similar to that seen in the 16 patients who had excision

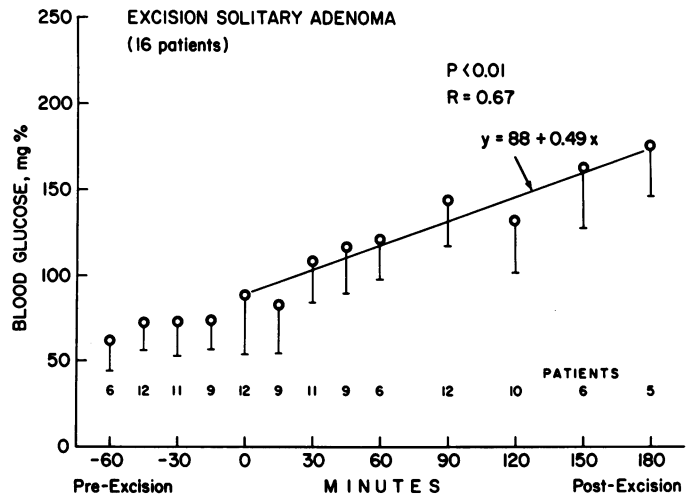

FIG. 5. Mean blood glucose levels minus 1 standard error are shown immediately before and after excision of solitary islet cell adenomas in 16 patients. An ideal curve has been fitted by the method of least squares to all data points from zero through 180 minutes postexcision. The correlation of blood glucose increment, 29 mg./100 ml. per hour, with time is significant as shown. The regression co-efficient and regression constant (intercept) are both significant, $p < 0.001$.

of a solitary adenoma. At no time up to 180 minutes postexcision were there statistically significant differences found in mean blood glucose content when the 16 solitary adenoma patients were compared to the five operations on four patients with retained hyperfunctioning tissue.

Complications of Surgery

Thirty-two of our 35 patients were operated upon by us for control of hyperinsulinism. In two of these patients two operations were performed for this purpose giving a total of 34 operations performed for the control of endogenous hyperinsulinism.

Following these 34 operations, there was one death directly attributable to operation. This was in the eldest patient of our series, a physician, 74 years of age, who had himself initially suspected the correct diagnosis of hyperinsulinism. His lesion was not visualized angiographically and proved to be difficult to find. After an 80% distal pancreatectomy, a solitary adenoma was found embedded deep in the pancreatic head. This area had been carefully palpated earlier in the same operation and considered to be negative for an adenoma. His postoperative course was prolonged and characterized by large quantities of serous drainage accompanied on two occasions by frank hemorrhage from the drainage sites. During both bleeding episodes, he was re-explored meticulously to identify a source of the hemorrhage. Even with active agitation of the original bed of pancreatic dissection, no bleeding points could be found. His condition worsened and he died on the 106th postoperative day.

Seven complications requiring surgical correction occurred and are listed in Table 1. Only two require brief comment. In one patient a pancreatic fistula persisted for 1 year following adenoma excision. Sinus tract injections demonstrated a blind pocket until 1 year postoperatively when there was seen to be communication of the sinus tract with the main duct of the distal pancreas. At re-exploration it was noted that the distal end of the proximal main pancreatic duct, *i.e.* in the head of the pancreas, was completely sealed. The fistula lead only into the main duct of the distal pancreas. The distal pancreas was removed. The patient recovered uneventfully.

One pancreatic duct injury was noticed at the time of removal of a solitary adenoma from the neck of the pancreas. This adenoma was of further interest because it exhibited many ductal elements in addition to islet cell tissue. Duct injury was promptly suspected at the time of injury, confirmed by probing the pancreatic duct in both directions and managed successfully by bringing a Roux-Y loop to the site of injury. This patient recovered uneventfully and has required no further operation.

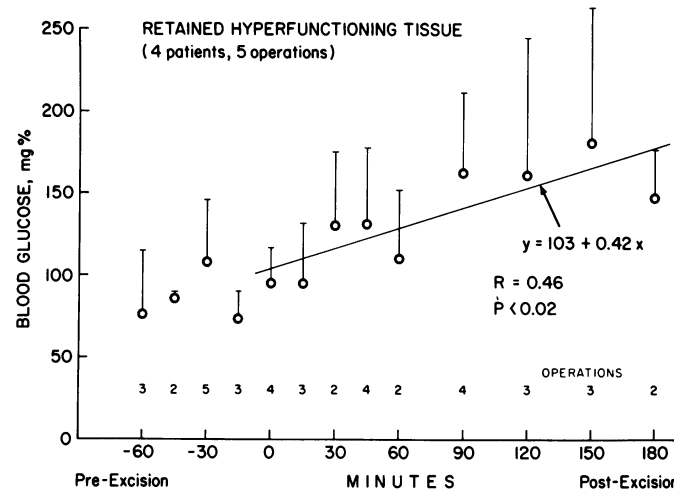

FIG. 6. Mean blood glucose levels plus 1 standard error are shown pre and post pancreatic tissue resection in five operations on four patients known to have retained hyperfunctioning islet cell tissue. The correlation between glucose increment, 24 mg./100 ml. per hour, and time is significant as is the regression coefficient, $p < 0.02$ and the regression constant (intercept) $p < 0.001$. The slope of this curve does not vary significantly from the slope in the curve of Figure 5 with regression carried up to the indicated time. There are no significant group differences at any of the time points between these groups and those in Figure 5.

The five remaining complications represent, we feel, the usual morbidity of pancreatic surgery. Of four postoperative abcesses, three in tracts of drains and one in the right subhepatic space, three occurred following pancreatic resection and one followed simple excision of a solitary adenoma.

Discussion

The clinical triad of symptomatic attacks from fasting hypoglycemia, demonstrably low blood sugar, less than 50 mg./100 ml., and relief by the ingestion of glucose advocated by Whipple,[31] was intended to imply a precise diagnosis of hyperfunctioning islet tissue. Nevertheless, Whipple and Frantz[32] were aware of the

TABLE 1.

1 Surgical Death	
74-year-old male, solitary adenoma, delayed postoperative hemorrhage ×2.	
7 Complications Requiring Surgical Correction:	Treatment:
1 Operative injury main pancreatic duct	— Roux-Y loop.
1 Persistent pancreatic fistula, 1 year	— Hemi-pancreatectomy.
1 Gastric atony and outlet obstruction	— Gastroiejunostomy.
1 Right Sub-hepatic abcess	— Surgical drainage.
3 Drainage tract abcesses	— Surgical drainage.

importance of other etiologies of 'Whipple's Triad'. "As everyone is aware there are many causes of (fasting) hypoglycemia which are not due to lesions of the pancreas, the most important being disturbances of the adrenal, pituitary, thyroid . . . These conditions should be ruled out clinically before exploratory operation is justifiable." That the combination of findings constituting Whipple's Triad occurs with hyperfunctioning islet tissue is not questioned. The consideration that needs emphasis currently is that one cannot attach diagnostic specificity to the demonstration of Whipple's Triad. It is interesting to note in passing that in 35 patients who had undergone operation reviewed by Whipple and Frantz,[32] from the literature available at that time, no hyperfunctioning islet cell lesions were found in 14.

The determination of levels of immunoreactive insulin in the fasting state and after administration of stimuli provoking insulin release has unquestionably established more precise and exact diagnostic criteria for the diagnosis of hyperfunctioning islet cell lesions than that afforded in the past by documenting fasting hypoglycemia *per se*. The heterogeneity of lesions presenting as fasting hypoglycemia is a sharp contrast to the group of islet cell lesions presenting as autonomous hyperinsulinism of endogenous origin. Various publications have dealt with these diagnostic points in detail.[5,9,10,12,13,15,35]

Our success in identifying pancreatic lesions in hyperinsulinism with selective and superselective angiography is approximately 40%.[25] Higher success rates have been reported by others but even with the most modern nuances in angiographic technic and with detailed retrospective analysis of the films after the location of the lesion has been established at operation, our angiography identification rate remains at about 40%.[25]

We believe, nevertheless, that angiography is an important adjunct to the operative management of hyperinsulinism in the hope of localizing islet cell adenoma(s). As noted previously, in two of the three patients with non-palpable solitary adenomas in whom it was used, angiography identified and lead us to successfully remove two solitary adenomas which had been overlooked by other surgeons to whom angiography was not available. A fourth non-palpable adenoma, part of the pathology in a patient with pancreatic adenomatosis, was also found and removed by us after angiography had demonstrated its location. It, too, could not be found in initial pancreatic exploration in another hospital.

The two cases of pancreatic adenomatosis described by Frantz in 1944[17] bear remarkable similarity to the four cases of pancreatic adenomatosis appearing in our series. One patient in the series was operated upon three times, an adenoma being removed on each occasion. Both of Frantz's initial two patients responded favorably when the tail, body and neck of the pancreas had been resected (75 to 80% distal pancreatectomy) and enjoyed normal lives subsequently. The histopathology of the pancreas in both patients was microscopic adenomata but there were many normal islets as well.

For obscure reasons appreciation of pancreatic adenomatosis has almost disappeared from clinical awareness in many series reported since Frantz's description of this lesion. dePeyster[7] and Schwartz and Zwiren[28] are among the few who have referred to the lesion at all. Because of the frequency of pancreatic adenomatosis in our series we believe that pancreatic adenomatosis deserves emphasis once again as a diagnostic possibility in patients with endogenous hyperinsulinism. It is our conviction that any patient with recurrent hyperinsulinism in whom a second adenoma cannot be found and who has no gross stigmata of metastatic islet cell carcinoma should be considered to have pancreatic adenomatosis until proven otherwise. As noted before, microscopy of abnormal islet morphology from a generous pancreatic resection is the only means presently available of establishing the presence of pancreatic micro-adenomatosis.

Awareness of the definite possibility of pancreatic adenomatosis, four of our 35 patients, makes clear the practical point that when confronted with recurrent hyperinsulinism after removal of an islet cell adenoma one is well advised to resect a convenient portion of pancreas, 75 to 80% of the distal gland. This approach will establish whether or not pancreatic adenomatosis is present as well as to treat it effectively at the same operation. Even our two patients with persistent hyperinsulinism from pancreatic adenomatosis have been brought into a condition in which Diazoxide treatment now controls their disease adequately. Possibly a definitive diagnosis of pancreatic adenomatosis can be made reliably on the basis of frozen section but we have not attempted to do so until recently. There is only one patient we have cured from hyperinsulinism by removing two adenomas. He is a member of the family with multiple endocrine adenomatosis. Patients have been described by others whose hyperinsulinism has been cured by the excision of multiple islet cell adenomas.[20,23,26] On those patients the data given do not rule out definitely the possibility of multiple endocrine adenomatosis. We note that pancreatic adenomatosis and hyperplasia have been described in patients with multiple endocrine adenomatosis.[3,30]

None of our patients exhibited pancreatic islet cell hyperplasia but this lesion has been described in children younger than the patients of our series.[16,24]

Because we have not hesitated to perform partial, up to 80% distal pancreteactomy as a primary operation for hyperinsulinism, we feel detailed study of the morbidity associated with doing so is pertinent. Review of our complications does not suggest that partial pancreatectomy has a significantly greater morbidity than does simple excision of a solitary adenoma.

For at least 22 years, the potential usefulness of blood glucose determination during operation for hyperfunctioning islet cell tumors has been appreciated.[21] If blood glucose levels remain low after removal of an islet cell lesion, this is presumed to represent retained hyperfunctioning islet tissue. If there is a definite elevation of blood glucose during operation, unrelated to intravenous glucose administration, the presumption has been that the sole source of excessive insulin release has been removed.

Several authors have recently expressed enthusiasm for the use of blood glucose levels during operation for this purpose.[14,19,27] Unquestionably total operative time is prolonged if one waits to demonstrate this phenomenon convincingly but this need not keep one from using it.

The question of how much importance to attach to intraoperative blood glucose measurements is one which we have studied with interest. Persistently low blood glucose levels two hours after excision of the lesion would certainly be justifiable cause for concern that some hyperfunctioning islet tissue remains and has proved to be a clue to the presence of more than one adenoma in some patients.[27] In the five instances of retained hyperfunctioning pancreatic islet tissue in our series there was, however, elevation of blood glucose during the operation similar to that seen after excision of 16 solitary adenomas. Because of this finding, we currently attach little significance to blood glucose elevation during operation for hyperfunctioning islet cell tissue. Hyperglycemia during other types of operation not involving the pancreas has been documented by others.[1,8] A variety of acute hormonal responses to anesthesia and operation, most notably release of epinephrine, growth hormone, glucagon and hydrocortisone would be expected to raise blood glucose intraoperatively. Others have urged caution in the interpretation of intraoperative blood glucose levels in patients operated upon because of hyperinsulinemia.[7]

If a lesion is not found after thorough exploration at the original operation for hyperinsulinism, 80% distal resection has seemed to us a wise course to follow because of the definite possibility of microscopic adenomatosis or of a non-palpable single adenoma. Primary pancreaticoduodenectomy strikes us as a more complicated and more hazardous way to achieve the same ends accomplished by 80% distal resection. Others have questioned, for different reasons than those given by us, the advisability of primary 'blind' distal pancreatectomy for hyperinsulinism.[16,22] We do believe that before 80% distal pancreatectomy is done meticulous and extensive exploration of the head of the pancreas, including the uncinate process, should be carried out using multiple capsulotomies. We emphasize that we have overlooked one adenoma that would have been included in a conventional pancreaticoduodenectomy. We have also removed one non-palpable adenoma in a blind distal pancreatectomy specimen. It is important that a careful search be made for ectopic pancreatic tissue before primary pancreatic resection is done. These points have already been well made by others and we agree completely that they are important to the efficient surgical management of endogenous hyperinsulinism.

Summary and Conclusions

1. Demonstration of autonomous hyperinsulinism is the crux of modern diagnostic precision in hyperfunctioning islet cell lesions of the pancreas. Abnormally high levels of plasma insulin in the fasting state and/or inappropriate elevations of plasma insulin in relation to prevailing blood glucose levels can be demonstrated in all patients studied carefully. Frequently, stimulation of excessive insulin release and/or prolongation of stimulated insulin release with coincident hypoglycemia have been important in strengthening the diagnosis. Repeated study has been helpful in borderline cases.

2. Microscopic pancreatic adenomatosis, with or without macroscopic tumors, deserves greater emphasis and wider recognition as a cause of endogenous hyperinsulinism in the adult than it is accorded in most current reports.

3. Selective pancreatic angiography has been a significant help in locating some non-palpable solitary islet cell adenomas of the pancreas.

4. Intraoperative blood glucose elevation has not been an invariably reliable sign of removal of all hyperfunctioning islet cell tissue. Persistently low levels of blood glucose intraoperatively did not occur following excision of pancreas or an adenoma in five recognized instances of retained hyperfunctioning islet tissue. Conversely, after removal of a single adenoma there was not a significant rise in blood glucose during the intraoperative period which would have predicted the removal of all pathologic tissue.

Acknowledgment

We gratefully acknowledge the help of Satish K. Vij, M.D. in gathering the blood glucose data presented in this article.

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Discussion

Dr. H. William Scott, Jr. (Nashville): I had been planning to make a few comments about Dr. Harrison's paper and if I could I would like to see the first slide, please.

A year ago, we reported data from 15 patients with endogenous hyperinsulinism studied at the Vanderbilt Medical Center and treated in our affiliated hospitals over the preceding 20-year period. I would like to go over some of the diagnostic considerations in these interesting patients which we derived from our retrospective review.

First of all, I think the clinical manifestations of hypoglycemia