Functioning Beta Cell Tumors (Insulinomas) of the Pancreas

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IN 1927 Wilder [15] and associates first demonstrated the relationship between symptoms of hypoglycemia and beta cell islet tumors of the pancreas (insulinomas). In 1929 Roscoe Graham [5] did the first curative removal of a functioning beta cell islet tumor. Since this time these relatively rare tumors have been diagnosed and successfully removed with increasing frequency. Whipple [13,14] in his lifetime accumulated a series of 30 such cases and from this experience developed the diagnostic criteria known today as Whipple's Triad which continues to be a sound basis for clinical diagnosis of insulinomas. Whipple's Triad consists of (1) hypoglycemic attacks precipitated by fasting or exertion, (2) fasting blood sugar concentrations below 50 mg./100 ml. and (3) symptoms relieved by oral or intravenous administration of glucose. In a review of the literature published between 1929 and 1958, Moss and Rhoads [11] found 766 cases of which only 93 were malignant. This report presents the experience which we have had in the last 20 years with beta cell tumors of the pancreas in the hospitals affiliated with Vanderbilt University, and to suggests current standards of diagnosis and treatment.

Clinical Summaries

During the last twenty years, fifteen patients with the clinical manifestations of hypoglycemia have fulfilled the criteria of Whipple's triad, have been diagnosed preoperatively as having hyperinsulinism due to islet cell tumor of the pancreas and have been submitted to surgical exploration of the pancreas.

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Case Reports

Case 1. M. R., a 33-year-old woman, first entered Vanderbilt Hospital on October 16, 1952 complaining of "blackout spells." She had episodes of loss of consciousness which increased in frequency for 3 years. These episodes were preceded by profuse sweating, paresthesias and restlessness. She had learned to abort these attacks by eating sweets. There had been a 30-pound weight gain. On admission the fasting blood sugar was 32 mg./100 ml. Glucose tolerance test showed a flat curve, and symptomatic hypoglycemia occurred with prolonged fasting. The symptoms were relieved by glucose. Diagnosis was hyperinsulinism due to islet tumor. On 10/18/52 she underwent exploratory laparotomy. The abdominal viscera and pancreas were carefully examined and no adenoma could be found. Therefore, a distal pancreatectomy-splenectomy was performed. The cut edge of the remaining pancreas was oversewn and drained. Serial sections and histologic examination of the specimen showed normal pancreas and no adenoma. Postoperatively there was evidence of persistent hypoglycemia. Blood sugar drawn in the early recovery period while 5% dextrose was infused was 82 mg./100 ml. Blood sugar on the fourth postoperative day when the glucose infusion was discontinued was 36 mg./100 ml. She was given cortisone, 75 mg. per day, a high protein diet and discharged to the care of her physician. She refused to return for re-evaluation for the next 10 years. In the period from 1952 to 1963 she had multiple mild episodes of hypoglycemia. She also had two miscarriages prior to 6 months of gestation. After prolonged efforts, she finally agreed to be readmitted for re-evaluation in May, 1963. Physical examination was unchanged and no signs of Cushing's syndrome were present. While on steroid therapy, a glucose tolerance test, tolbutamide tolerance test, prolonged fasting with concomitant glucose and insulin assays

were all equivocal for hyperinsulinism. After several weeks of weaning from cortisone therapy, full blown hypoglycemic symptoms recurred and repetition of prolonged fasting with glucose and insulin measurements were indicative of hyperinsulinism. It was elected to re-explore the pancreas. The head of the pancreas was exposed and a 15 mm. adenoma was palpated anteriorly near the cut edge of the head beneath its capsule. Incision into the normal pancreatic tissue for approximately 3 mm. exposed the surface of the adenoma which was enucleated and the area drained. Histologically, the lesion was a beta cell adenoma measuring 15 mm. in diameter. Blood sugar in the early recovery period was 286 mg./100 ml. On the second postoperative day the blood sugar was 321 mg./100 ml. By the fifth postoperative day the blood sugar had returned to normal and remained normal thereafter. She made a good recovery and was discharged on the tenth postoperative day in good condition.

She has been followed to the present time and has done well. There has been no recurrence of hypoglycemia. She subsequently underwent radical mastectomy for breast cancer and has developed mild adult onset diabetes which is well controlled by diet alone.

Case 2. H. B., a 54-year-old man, was referred to the Vanderbilt Hospital Emergency Service from Tennessee Central State Psychiatric Hospital on November 7, 1958. He had been comatose for 6 hours prior to admission. He had multiple syncopal attacks, episodes of ataxia and weakness with psychotic behavior and personality changes for 3 years. During one of the syncopal attacks he had broken his left arm. In the emergency service he was given glucose intravenously and responded. Later in the day the blood sugar level was 30 mg./100 ml. with relatively normal consciousness. A prolonged fast was instituted and blood sugar concentrations were monitored; at 5 hours the blood sugar was 37 mg./100 ml. A glucose tolerance test showed a flat curve. The conditions of Whipple's triad were fulfilled. Diagnosis was hyperinsulinism due to islet tumor of pancreas. On 11/14/58 he underwent exploratory laparotomy. A small tumor of the pancreatic tail, at its inferior margin 6 cm. from the splenic hilum, was removed by wedge resection and the area was drained. An additional small area of aberrant pancreas in the mid-jejunum was also excised. Histologically this was normal pancreas. The tumor was a beta cell adenoma 8 mm. in diameter. A blood sugar, drawn on the operating table immediately prior to excision of the adenoma with a constant infusion of 5% dextrose, was 125 mg./100 ml. In the recovery room approximately 1 hour after excision of the adenoma with a similar infusion the blood sugar was 300 mg./100 ml. The postoperative course was uncomplicated. Blood sugars reverted to normal by the fifth postoperative day. The drain was removed on the eighth postoperative day. A glucose tolerance test prior to discharge was normal. He was discharged on the eleventh postoperative day.

However, he was readmitted 2 months later on January 16, 1959 with abdominal distention, epigastric and left upper quadrant pain and anorexia. Clinical diagnosis was peptic ulcer. On January 17, he developed severe epigastric pain, went into shock and the hematocrit fell precipitously. Five units of blood were given with good response. There was no blood in the nasogastric aspirate and paracentesis was negative. Ten days later laparotomy was performed. Subacute hemorrhagic pancreatitis involving the pancreatic tail with early pseudocyst formation was found. The pancreatic area was drained and his condition improved temporarily. However, within 3 weeks he developed a recurrent episode of pancreatitis with severe epigastric pain, nausea and anorexia. A few hours later he developed a massive upper gastrointestinal hemorrhage. He was immediately taken to the operating room where as large pancreatic pseudocyst was found which had spontaneously ruptured into the stomach. Several sites of arterial bleeding within the pseudocyst were sutured transgastrically and the bleeding was controlled. On April 30, 1959, he underwent reoperation in which a resection of the body and tail of the pancreas, including remnants of the pseudocyst and the spleen, was performed. His postoperative course was stormy. One week later he required operative closure of a wound dehiscence. His condition steadily deteriorated and a terminal episode of gram negative sepsis was followed by irreversible cardiac arrest on May 9, 1959. At autopsy he had left pleuro-peritoneal fistula and abscess, extensive purulent peritonitis and renal cell carcinoma of the right kidney.

Case 3. L. M., a 68-year-old woman, was referred to Vanderbilt Hospital in June, 1960 from a nearby sanitarium for evaluation of episodic mental confusion and coma. Fasting blood sugar determination at the sanitarium had been 42 mg./100 ml. There was an 8-year history of episodes of unconsciousness preceded by ataxia, slurred voice, slowed mentation and paresthesias. There was no serious illness in the past history. The family history was negative for diabetes. The patient was a thin, chronically ill elderly woman. She had a very large, slightly mobile non-tender mass in the right lower quadrant and right flank. Upper gastrointestinal series with a small bowel follow-through confirmed the presence of this mass. An intravenous pyelogram showed nonfunction of the right kidney. Glucose tolerance test revealed blood sugar to be 37 mg./100 ml. at five hours. After a 6-hour fast blood sugar fell to 36 mg./100 ml. Preoperatively,

it was felt that this patient most likely had a large sarcoma which secreted an insulin-like substance. On 6/24/60 she underwent exploratory laparotomy and a very large, 30 by 26 cm. hydronephrotic kidney was found on the right with a large calculus impacted in its pelvis. Right nephrectomy was performed and the abdomen explored. On palpation of the pancreas a nodule was felt in the substance of the body. An operative diagnosis of islet tumor was made and a distal pancreatectomy-splenectomy was performed. The pancreatic duct was sutured and the cut edge of the remaining pancreas was oversewn. The area of resection was drained. Histologically, the nodule proved to be a benign beta cell adenoma 13 mm. in diameter. Postoperatively the patient responded well. The blood sugar drawn shortly after operation in the recovery room was 264 mg./100 ml. The blood sugar rose to its highest level of 334 mg./100 ml. on the third postoperative day and returned to normal by the fifth postoperative day with no further tendency to hypoglycemia. Drains were removed on the eighth postoperative day and the patient was discharged on the eleventh day after operation. She has been totally asymptomatic over an 11-year period of follow-up.

Case 4. D. P. was an 18-year-old young man who was first seen at Baptist Hospital in February 1961. He had episodes of ataxia, profuse sweating, paresthesias, and loss of consciousness for 7 years. He also had had several convulsions. He had learned to eat sweets in an effort to prevent these attacks. He was transferred from the Tennessee State Prison after a fasting blood sugar level of 35 mg./100 ml. Admission blood sugar was 59 mg./100 ml. He was evaluated with a glucose tolerance test, a prolonged fast, and an epinephrine stimulation test, all of which were positive for hypoglycemia. An upper gastrointestinal series was normal. On 2/8/61 an exploratory laparotomy was performed and a 4 cm. mass was found in the head of the pancreas. The tumor was embedded deeply in normal pancreatic tissue and enucleation could not be safely performed. A Whipple pancreato-duodenectomy was performed with removal of the tumor and the pancreatic head, leaving the body and tail of the pancreas. Cholecystojejunostomy, pancreaticojejunostomy and gastrojejunostomy were performed in reconstruction of the alimentary tract. Pathologic examination showed this to be a beta cell islet adenoma. An uneventful recovery followed the Whipple procedure. Parenteral fluids with small amounts of insulin were given postoperatively. He began eating regular diet on the tenth postoperative day and had no further hypoglycemic symptoms. He was discharged on the fifteenth postoperative day. He has had no recurrence of hypoglycemia and has done well during the 10 years of follow-up to the present time.

Case 5. A. O., a 72-year-old woman, was admitted to Vanderbilt Hospital 4/1/62 with a 5-year history of episodes of weakness, slurred speech, lethargy, dizziness, syncope, decreased mentation, and emotional lability. She had recently been forced to leave her job as a music teacher. At the time of admission her medications included Dilantin, Thorazine and dessicated thyroid. Past history was negative for any serious illnesses. The admitting fasting blood sugar level was 36 mg./100 ml. A prolonged fast led to a blood sugar level of 29 mg./100 ml. at 6 hours. A glucose tolerance test was equivocal but a tolbutamide tolerance test was strongly positive with early onset of profound hypoglycemia. An upper GI series was normal. On 4/17/62 an exploratory laparotomy was performed through an upper abdominal "bucket handle" incision. A tumor was found in the very tip of the pancreatic tail near the hilum of the spleen. The tumor was excised with a bit of normal pancreatic tissue. The cut edge of the tail of the pancreas was oversewn and the area drained with a Penrose drain. Histologic examination showed the tumor to be a 9 mm. beta cell islet adenoma. The day after operation with 5% dextrose being infused at 50 cc. an hour the blood sugar level was 134 mg./100 ml. It remained in this range for the next several days and subsequently remained at normal levels when infusions of glucose were discontinued. Drains were removed on the tenth postoperative day. The patient made a good recovery and was discharged on the eleventh postoperative day. Follow-up during the last 8 years to the present time has shown her to be completely asymptomatic with no evidence of recurrence of hypoglycemia.

Case 6. P. P., a 10-year-old girl, was brought to the Pediatric Clinic at Vanderbilt Hospital with a 5-year history of seizures and recent inability to awaken in the morning. The child had been treated with numerous anticonvulsants without control of seizures. Family history was important because 1 year prior to this a brother (Case 4) had undergone removal of a functioning beta cell adenoma. There was no family history of diabetes. At admission, fasting blood sugar level was 30 mg./100 ml. A glucose tolerance test, tolbutamide tolerance test and leucine stimulation test and concomitant insulin levels strongly supported a diagnosis of hyperinsulinism caused by a functioning islet cell tumor. On 9/22/62 she underwent exploratory laparotomy. A firm, reddish-yellow tumor lay in the uncinate process of the head of the pancreas just to the right of the superior mesenteric vein. It was attached to the pancreas by a narrow pedicle of pancreatic tissue. Tumor was removed by simply clamping, dividing and suturing the pedicle. The

site of excision was drained with Penrose drains. Histologically the tumor was a beta cell adenoma which measured 19 mm. in diameter. Blood samples for glucose drawn just prior to the operation and in the recovery room approximately 1 hour after resection were 115 mg./100 ml. and 175 mg./100 ml., respectively, while 5% dextrose was infused at a constant rate. The postoperative recovery was uncomplicated. She was discharged on the tenth postoperative day. Due to the family history the other members of the family were evaluated for hypoglycemia and other endocrinopathies. Seven siblings and the mother were found to be normal. The father (H. P., Case 7), however, had a positive evaluation. The patient has been followed for 9 years and at the present time remains healthy, free of any known endocrinopathy and has had no recurrence of hypoglycemia. She is married and has two children who are healthy and show no evident endocrinopathies.

Case 7. H. P., a 40-year-old railroad worker, was admitted to Vanderbilt Hospital 10/10/62 with approximately a 13-month history of episodes in which he was difficult to arouse, especially in the morning, fingertip paresthesias, trembling and lightheadedness. He had had one convulsive seizure. He had learned to abort attacks by eating sweets and had gained 30 pounds. His family history was significant in that two of his children (D. P. and P. P., Cases 4 and 6) had had insulinomas of the pancreas removed. He had extensive skin lesions typical of psoriasis. He had been forced to give up his work 5 weeks prior to admission. On clinical and x-ray evaluation he had a 3 cm. discrete coin lesion in the left lower lobe of his lung. On 10/23/62 a left lower lobectomy removed a "bronchial adenoma" which proved to be adenocarcinoma on histologic study. His recovery was uneventful. Glucose tolerance test, tolbutamide tolerance test, prolonged fasting leucine test were indicative of hyperinsulinism most likely due to islet tumor. Blood sugar reached a low of 8 mg./100 ml. during the tolbutamide test. Upper gastrointestinal x-rays were negative. During the same admission on 11/12/62 he underwent laparotomy and exploration of the pancreas. A firm rubbery mass was felt in the mid portion of the body of the gland. On further mobilization of the pancreas, two other masses were noted, one in the tail and another in the body near the first. The duodenum was Kocherized and the head of the pancreas was inspected carefully. No masses could be felt or seen. A distal pancreatectomy-splenectomy was performed. Pathologic examination of this specimen revealed eight discrete pancreatic adenomas, six located in the body and two in the tail. The largest was a 13 mm. adenoma of the body, a 12 mm. adenoma was closely located to this, and a third adenoma measuring 10 mm. in diameter was located in the tail. There were four more small adenomas of the body and one small adenoma of the tail which measured from 2 to 4 mm. in diameter. Histologically, all were beta cell islet adenomas. The day following removal of the adenomas, diabetic urines were 4+ for sugar. By the second postoperative day blood sugar was 116 mg./100 ml. and thereafter remained in the range of normal. He did well postoperatively. By the tenth postoperative day all drains and sutures had been removed, he had made an excellent recovery and was eating well. Further evaluation showed persistently elevated serum calciums with low serum phosphate. The diagnosis of primary hyperparathyroidism was made and on 11/30/62, he had excision of a large parathyroid adenoma. He had a good recovery and was discharged on 12/7/62. The patient has enjoyed good health with no recurrence of hypoglycemia, hyperparathyroidism or pulmonary tumor during the past 9 years.

Case 8. P. M., a 24-year-old Vanderbilt graduate student, was admitted on July 29, 1963 to the Psychiatric Service of Vanderbilt Hospital following a grand mal seizure. He had been followed for several months in the Psychiatric Clinic. For almost a year he had had seizures, episodes of slurred speech, ataxia and paresthesias. He also drank excessively and had been seen in the emergency room on several occasions for intoxication. After admission to the hospital he was belligerent and required constant surveillance. After a fasting blood sugar level of 30 mg./100 ml. and relief of symptoms by glucose, he was transferred to the Medical Service for study. Multiple and repeated studies of fasting blood sugars, glucose tolerance, tolbutamide tolerance and leucine stimulation were carried out. Fasting, tolbutamide and leucine tests showed profound hypoglycemia and suggested hyperinsulinism due to an islet tumor. On 8/14/63 he underwent exploratory laparotomy and careful examination of the pancreas. There was no palpable adenoma in the head, body or tail. Exploration of the peritoneal cavity for aberrant pancreatic tissue also revealed no tumor. A distal pancreatectomy-splenectomy was performed leaving a small segment of head and uncinate process. The cut edge of remaining pancreas was oversewn and the area drained. Pathologic examination of serial sections of the specimen showed a 4 mm. adenoma deeply embedded in the proximal end of the tail of the pancreas (Fig. 1). Histologic study showed this to be a beta cell islet adenoma. Insulin levels drawn from the portal vein immediately before and after excision of the adenoma were 164 microunits per milliliter and 35 microunits per milliliter, respectively.

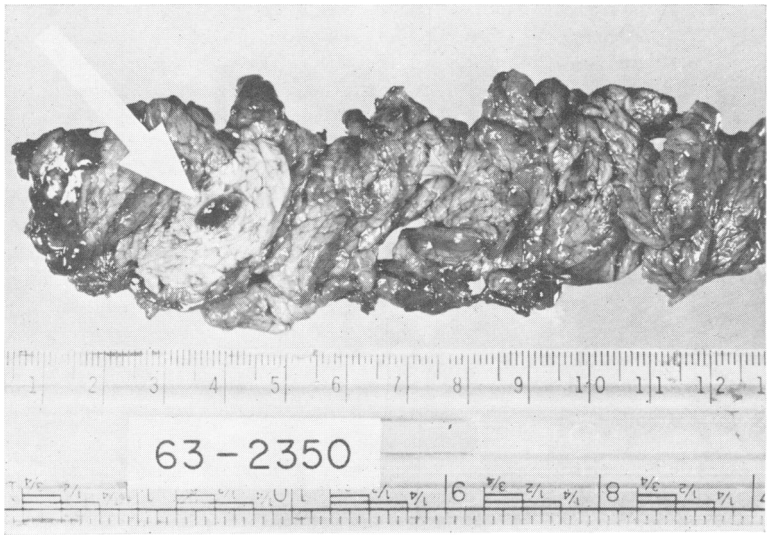

FIG. 1. (Case 8) Empiric resection of body and tail of pancreas: 4 mm. beta cell adenoma found on serial sectioning of specimen.

Blood sugar approximately 1 hour after excision was 360 mg./100 ml. Five per cent dextrose was being infused at constant rate during this time. Postoperative course was complicated by development of a pancreatic fistula and a wound infection. He was discharged on the eighteenth postoperative day. Blood sugars returned to normal values by the eighth postoperative day. The pancreatic fistula healed spontaneously within a few weeks. Follow-up to the present time has showed him to be completely asymptomatic. He is working regularly and has had no seizures or other evidence of hypoglycemia or diabetes during the past 8 years.

Case 9. C. M., a 55-year-old man, was initially seen on March 25, 1967 complaining of "weakness and falling out spells" for approximately 6 months. He had been treated during this time for hypoglycemia which was thought by his local physician to be due to alcoholism and liver disease. He gave a history of excessive alcohol ingestion and was believed to have cirrhosis. There had been no improvement in his condition after several months of treatment with high protein, low carbohydrate diet. There was no family history of diabetes. Glucose tolerance test, tolbutamide tolerance test and prolonged fast with concomitant measurements of glucose and insulin levels (Fig. 2) were indicative of hyperinsulinism. On 3/31/67 an exploratory laparotomy was performed through an upper abdominal "bucket handle" incision. A tumor was found in the body of the pancreas. It was rubbery firm in consistency and reddish-brown in color. A distal pancreatectomy-splenectomy was performed. The cut edge of the remaining pancreas was oversewn and the area drained. Pathologic examination showed the tumor to be a beta cell islet adenoma of the pancreas. Blood sugar drawn on the operating table approximately 30 minutes after resection of the distal pancreas with the tumor was 263 mg./100 ml. After operation the patient responded well except for superficial wound infection which cleared with local drainage. He was discharged on the twenty-seventh postoperative day. He has subsequently returned to normal activities. He has been followed for 4 years with no recurrences of hypoglycemia or tumor.

Case 10. R. K., a 67-year-old man, collapsed while doing heavy work and was brought to the Emergency Service of St. Thomas Hospital on 6/3/67 disoriented and agitated. Blood sugar level at the time of admission was 30 mg./100 ml. He was given orange juice and his condition promptly improved. He gave a history of spells of dizziness, nervousness, ataxia and frontal headaches of one year's duration. Family history was negative for diabetes. There was no history of serious illnesses. Systemic review and physical examination showed no significant abnormalities. A glucose tolerance test, tolbutamide test and prolonged fast with measurement of concomitant glucose and insulin levels were diagnostic of hyperinsulinism (Fig. 2). Celiac arteriogram and upper gastrointestinal x-ray were negative. On 6/20/67 an exploratory laparotomy was performed. A large tumor of the pancreatic tail was discovered. Distal pancreatectomy-splenectomy was performed. The cut edge of the remaining pancreas was oversewn and the area drained. On pathologic examination of the specimen there was a fairly discrete tumor which was 43 mm. in diameter and dark yellow in color. On histologic examination it was a beta cell adeno-

carcinoma. There were no positive lymph nodes in the area of resection. Postoperatively the patient responded well. Blood sugar rose to a high of 222 mg./100 ml. on the first postoperative day and gradually returned to normal by the 8th day and thereafter remained normal. He was discharged on the 17th postoperative day. During follow-up to the present time the patient has been completely asymptomatic. He has returned to full-time work and is functioning well except for mild angina.

Case 11. J. B., a 26-year-old woman was admitted to Vanderbilt Hospital on May 21, 1968 with episodes of peroral and digital paresthesias, diplopia, sweating and irritability for 9 months. The symptoms were relieved by ingestion of sugar. A few days prior to admission she had sustained a major clonic seizure and responded to treatment with intravenous glucose at another hospital. Past history and family history were non-contributory. Physical examination on entry showed no abnormalities. Fasting blood sugar level on admission to Vanderbilt Hospital was 30 mg./100 ml. She underwent a glucose tolerance test, prolonged fast, and tolbutamide tolerance test, all with concomitant serum insulin assays. A diazoxide response test was also performed. All were indicative of hyperinsulinism (Fig. 3). A celiac arteriogram was interpreted as compatible with tumor of the pancreatic head. Upper gastrointestinal x-rays were normal. Diagnosis was hyperinsulinism due to islet tumor of the pancreas. On May 29, 1968 she underwent exploratory laparotomy and a firm tumor in the anterior surface of the head of the pancreas was found. It was enucleated and the area drained by a sump suction catheter. Blood samples for insulin and glucose determination were drawn from the portal vein on the operating table just prior to excision of the tumor and 30 minutes after excision. The pre-excision values were glucose 429 mg./100 ml. and insulin 92 μU/ml. Thirty minutes after excision of the tumor the values decreased to glucose 252 mg./100 ml. and insulin 37 μU/ml. The unusually high pre-excision glucose level was caused by an injection of 20 cc. of 50% glucose which had been given by the anesthesiologist a few minutes earlier. The blood sugar level 8 hours after excision of the tumor was 234 mg./100 ml. and the serum insulin concentration was 27 μU/ml. Histologically the tumor was a beta cell islet adenoma 16 mm. in diameter. The patient's postoperative course was uncomplicated. A repeat glucose tolerance test, tolbutamide test and prolonged fast with serum insulin levels were entirely normal. She was discharged on the ninth postoperative day. Follow-up in the last 3 years to the present time has shown that she has returned to full normal activities with no recurrence of hypoglycemia or tumor.

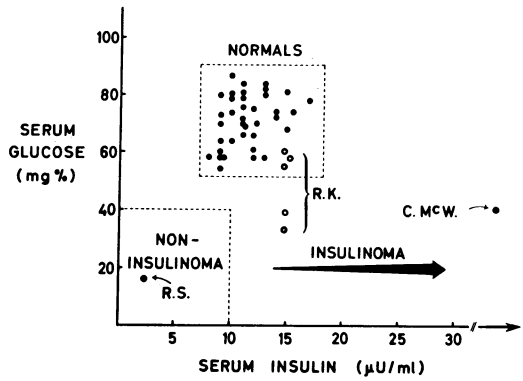

FIG. 2. (Cases 9, 10) Data in two patients with proven beta cell tumors (C. M. and R. K.) compared with normals and hypoglycemic patient (R. S.) without insulin secreting tumor.

Case 12. L. G., a 63-year-old man, was admitted to Baptist Hospital on 6/13/69 with episodes of loss of consciousness, profound weakness and psychotic behavior for 3 months. There was a history of excess ethanol intake and hypertension. He had undergone vagotomy and antrectomy for a bleeding ulcer 9 years prior to admission. He had had three further laparotomies for lysis of adhesions and small bowel obstruction. At the last procedure, pancreatic exploration for adenoma was done at Nashville General Hospital and none was found. Physical examination showed no significant abnormalities except for the scars of the previous abdominal operations. Fasting blood sugar level on admission was 35 mg./100 ml. A glucose tolerance test, tolbutamide tolerance, and prolonged fast with concomitant insulin levels were all positive for hyperinsulinism. A celiac and superior mesenteric arteriogram was normal. Upper GI x-rays

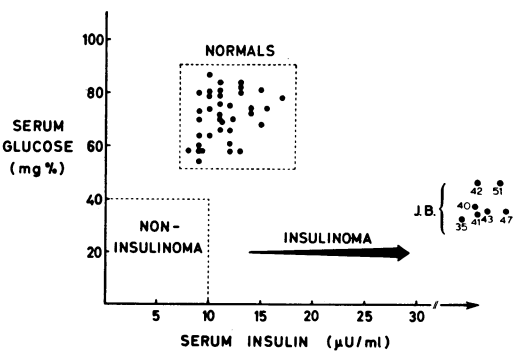

FIG. 3. (Case 11) "Inappropriately" high insulin levels in patient (J. B.) with fasting hypoglycemia due to proven beta cell adenoma.

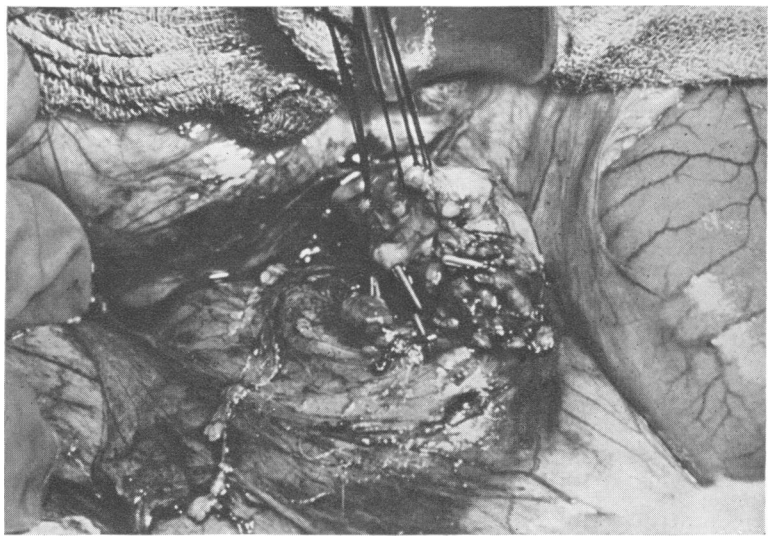

FIG. 4 (Case 11) Photograph taken during enucleation of 16 mm. beta cell adenoma from anterior surface of head of pancreas. Traction sutures were used to elevate the encapsulated tumor.

were also normal. A pancreatic scan was abnormal and indicative of pancreatitis. He remained hypoglycemic. On 6/27/69 exploratory laparotomy was performed. The pancreas was fully mobilized and inspected and no tumor could be found. Exploration of the abdomen for aberrant pancreatic tissue was also negative. After a distal pancreatectomy-splenectomy the area was drained. Gross examination of the serially sectioned specimen showed no tumor. Histologically, the specimen showed mild chronic pancreatitis but no adenoma was found. Postoperatively there was no blood sugar rise. The patient consistently maintained blood sugar levels less than 100 mg./100 ml. with D5W infusion. Postoperative serum insulin levels were somewhat decreased from preoperative values but still abnormally high. The patient's early postoperative course was uncomplicated. He was discharged on the 12th postoperative day. He responded well for several months but the symptoms of hypoglycemia gradually returned. A low carbohydrate high protein diet was employed. However, the persisting hypoglycemic symptoms were poorly controlled. Alcoholism, weight loss and physical deterioration continued to be major problems and follow-up on this patient was sporadic. Eighteen months after operation he died in another hospital emergency room in a coma. Autopsy was refused and no blood sugar was drawn at the time of death.

Case 13. D. G., a 55-year-old man, first came to the emergency service at Vanderbilt Hospital on May 13, 1970. He was unconscious and had a blood sugar level of 40 mg./100 ml. He responded promptly to intravenous glucose. He had had "weak spells" for 1 year but had not previously lost consciousness. He frequently ate between meals to counteract the "weak spells." His family stated that he had had bizarre behavior for at least a year. He had been treated with Librium and Vivactil during this time. He had undergone hemigastrectomy and gastrojejunostomy for peptic ulcer disease in 1957. A half sister had died of diabetes, otherwise there was no family history of diabetes. There was a questionable past history of rheumatic fever. He was a thin man and had a loud diastolic murmur consistent with aortic insufficiency. Except for the surgical scar in the abdominal wall there were no other significant findings. The patient underwent a prolonged fast, tolbutamide and glucose tolerance tests with measurements of serum insulin and glucose. All tests showed hypoglycemia with inappropriately high insulin levels (Fig. 5). A diazoxide test resulted in a blood glucose rise from 112 to 168 mg./100 ml. in 2½ hours. Selective celiac and superior mesenteric arteriogram showed no abnormalities. Upper GI x-rays demonstrated the previous partial gastrectomy but no other abnormality. A diagnosis of hyperinsulinism due to pancreatic islet tumor was made. On 5/25/70 exploratory laparotomy was performed. The pancreas was carefully examined and no adenoma could be seen or palpated. A distal pancreatectomy-splenectomy was performed; the cut edge of remaining pancreas was oversewn and the area drained. Pathologic examination of serial sections of the specimen revealed a 6 mm. beta cell adenoma located 5 cms. from the proximal margin of resection in the tail of the pancreas. Blood glucose drawn in the recovery room shortly after excision of the adenoma was 276 mg./100 ml. Blood sugar level returned

to normal in 4 days. The patient made an uneventful recovery. Repeat postoperative IV glucose tolerance test, tolbutamide tolerance test and 72-hour fast and insulin assays were normal. He was discharged on the 24th postoperative day. He has been asymptomatic during follow-up to the present time with no recurrence of hypoglycemia and no evidence of diabetes.

Case 14. B. O., a 22-year-old nurse, was admitted to Vanderbilt Hospital July 23, 1970 with episodes of weakness, lightheadedness and hunger. Her first attack had occurred during pregnancy. Blood sugar had been drawn on one occasion at Nashville Metropolitan General Hospital and found to be 45 mg./100 ml. The patient spontaneously aborted her pregnancy at 6 months' gestation. The attacks of hypoglycemia became more frequent and were associated with palpitations and sweating. She was allegedly seen at another hospital emergency room on one occasion before her admission to Vanderbilt Hospital where the blood sugar level was reported to be 18 mg./100 ml. She was treated by her physician with low carbohydrate, high protein diet and improved somewhat. Her only medication was birth control pills. She had had several urinary tract infections in the past. There was no family history of diabetes. Physical examination showed no abnormalities. Fasting blood sugar level on admission was 50 mg./100 ml. A prolonged fast led to a blood sugar of 19 mg./100 ml. in 13 hours at which time serum insulin was 125 μU/ml. Tolbutamide tolerance tests showed prompt and severe hypoglycemia. Celiac and superior mesenteric arteriograms were normal. Serum insulin concentrations were elevated to very high levels. Upper GI x-rays were normal. Certain features of her illness raised the possibility of factitious hypoglycemia. Blood levels for sulfonylurea compounds were normal. Self administration of insulin was considered but was unsubstantiated. A diagnosis of hyperinsulinism due to islet adenoma was finally made. On 8/30/70 she underwent exploratory laparotomy. The pancreas was thoroughly explored and no tumor could be found. There was no aberrant pancreatic tissue within the peritoneal cavity. A distal pancreatectomy with splenectomy was performed. The cut edge of pancreas was oversewn and drains were inserted. Pre- and post-resection portal vein sugar and insulin levels from samples drawn at the time of operation showed no significant change in either glucose or insulin following distal pancreatectomy. In addition blood sugar levels in the early postoperative period ranged in the 80 to 100 mg./100 ml. zone. There was no postoperative hyperglycemia. Histologic examination of the resected specimen showed normal pancreas. Recovery was slow with much nausea and vomiting which prolonged her hospital stay. Parenteral glucose was gradually withdrawn and after resumption of diet there were no further episodes of hypoglycemia; multiple fasting blood sugar levels remained in the low normal range. The drains were removed on the 12th postoperative day and she was discharged on the 23rd postoperative day.

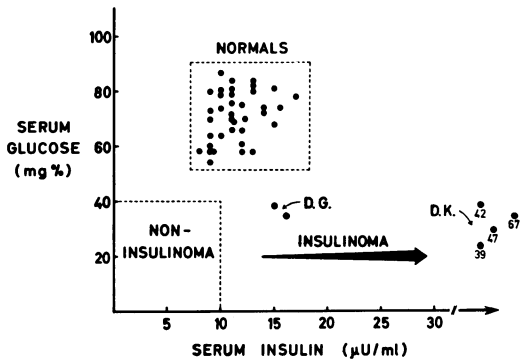

FIG. 5. (Cases 13, 15) Data in two patients (D. G. and D. K.) with inappropriately high serum insulin levels with fasting hypoglycemia due to proven beta cell adenoma.

During the last year and half she has resumed her occupation and has had no further hypoglycemic episodes. Neither diet or medication have been necessary since operation.

Case 15. D. K., a 41-year-old housewife, was admitted on January 28, 1971 to Vanderbilt Hospital. She had had attacks of numbness, blurred vision, nervousness and personality changes for 4 years and had been under psychiatric care for several years. She had learned to rely on orange juice frequently as a means of aborting attacks. Prior to admission she had had an automobile accident in which she had lost consciousness while driving. Family history and past history were noncontributory. Physical examination showed a very healthy woman with no abnormalities. She underwent a glucose tolerance test, tolbutamide test and prolonged fast with concomitant insulin (Fig. 5) assays. All were positive for hypoglycemia and inappropriately high insulin levels. At 22 hours of fasting blood glucose was 24 mg./100 ml. and serum insulin was 51 μU/ml. A selective celiac and superior mesenteric arteriogram and upper gastrointestinal x-rays showed no abnormalities. On 2/16/71 she underwent exploratory laparotomy. A large adenoma was palpated in the head of the pancreas on the anterior surface of the uncinate process. The remainder of the pancreas was normal. The common duct was opened and a #3 Bakes dilator was passed in order to determine the duct's location in the head. Approximately 2

TABLE 1. *Summary of Data in*

Patient	Age	Sex	Adm Date	Clinical Manifestations	Duration	Whipple's Triad	Admission FBS (mg./100 ml.)	Pre-op Fasting (6 to 72 hours) Blood Sugar (mg./100 ml.)	Pre-op Fasting (6 to 72 hours) Serum Insulin (μU/ml.)
1. M. R.	33	F	(1) 1952	Episodes of coma, sweats, paresthesias	3 yrs.	Yes	32	42 (at 12 hrs.)	—
			(2) 1963	Persistence of Sx	>10 yrs.	Yes	40	28 (at 12 hrs.)	—
2. H. B.	54	M	1958	Syncopal attacks, ataxia, weakness, psychotic behavior	3 yrs.	Yes	30	37 (at 5 hrs.)	—
3. L. M.	68	F	1960	Episodes of confusion, ataxia, psychotic behavior and coma	8 yrs.	Yes	36	36 (at 6 hrs.)	—
4. D. P.	18	M	1961	Episodes of confusion, sweats, coma, fits, ataxia, paresthesias	7 yrs.	Yes	59	35 (at 5 hrs.)	—
5. A. O.	72	F	1962	Episodes of weakness, slurred speech, confusion, syncope	5 yrs.	Yes	36	29 (at 6 hrs.)	—
6. P. P.	10	F	1962	Convulsions and episodes of coma	5 yrs.	Yes	30	23 (at 12 hrs.)	—
7. H. P.	40	M	1962	Comatose episodes, trembling, paresthesias aborted by sweets	13 mos.	Yes	37	33 (at 12 hrs.)	—
8. P. M.	24	M	1963	Convulsions, ataxia, paresthesias, slurred speech	1 yr.	Yes	30	—	—
9. C. M.	55	M	1967	Episodes of weakness, syncope; heavy alcohol intake	6 mos.	Yes	—	40	>30
10. R. K.	67	M	1967	Dizzy spells, ataxia, nervousness	1 yr.	Yes	30	34 (at 16 hrs.)	14
11. J. B.	26	F	1968	Paresthesias, sweats, irritability, diplopia one seizure	9 mos.	Yes	30	35 (at 3 hrs.)	41
12. L. G.	63	M	1969	Episodes of coma, weakness, psychotic behavior, heavy alcohol intake	3 mos.	Yes	35	48 (at 12 hrs.)	183
13. D. G.	55	M	1970	Weak spells, previous vagotomy, antrectomy, admitted in coma	1 yr.	Yes	40	30 (at 19 hrs.)	17
14. B. O.	22	F	1970	Episodes of weakness, hunger, light headedness	6 mos.	Yes	50	19 (at 13 hrs.)	>125
15. D. K.	41	F	1971	Spells of paresthesias, nervousness, blurred vision personality changes syncope→auto wreck	4 yrs.	Yes	50	24 (at 22 hrs.)	51

15 Patients with Hyperinsulinism

Tolbutamide Test	Operative Findings	Operative Procedure	Pathologic Dx	Result	Follow-Up
−	(1) No tumor found	Distal pancreatectomy, splenectomy	Normal pancreas	Unchanged	Cortisone & diet for >10 years
+	(2) 15 mm. tumor in head	Enucleation	Beta cell adenoma	Excellent (mild diabetes)	8 years
−	8 mm. tumor in tail	Wedge resection	Beta cell adenoma	Poor	Died 6 mos. postop with complication of pancreatitis no hypoglycemia
−	13 mm. tumor in body	Distal pancreatectomy, splenectomy	Beta cell adenoma	Excellent	11 years
−	4 cm. tumor in head	Whipple operation	Beta cell adenoma	Excellent	10 years
+	9 mm. tumor in tip of tail	Excision	Beta cell adenoma	Excellent	9 years
+	19 mm. tumor in head	Enucleation	Beta cell adenoma	Excellent	9 years
+	Multiple tumors in body and tail	Distal pancreatectomy, splenectomy	Multiple beta cell adenomas	Excellent*	9 years
+	No tumor found	Distal pancreatectomy, splenectomy	Beta cell adenoma (4 mm.)	Excellent	8 years
+	22 mm. tumor in body	Distal pancreatectomy, splenectomy	Beta cell adenoma	Excellent (mild diabetes)	4 years
+	43 mm. tumor in tail	Distal pancreatectomy, splenectomy	Beta cell adenocarcinoma	Excellent	4 years
+	16 mm. tumor in head	Enucleation	Beta cell adenoma	Excellent	3 years
+	No tumor found	Distal pancreatectomy, splenectomy	Mild chronic pancreatitis	Poor	Died 18 mos. postop No autopsy
+	No tumor found	Distal pancreatectomy, splenectomy	Beta cell adenoma (6 mm.)	Excellent	1½ years
+	No tumor found	Distal pancreatectomy, splenectomy	Normal pancreas	Good	1½ years
+	16 mm. tumor in head	Enucleation	Beta cell adenoma	Excellent	10 months

mm. of normal pancreatic tissue lay over the tumor. The pancreatic capsule was incised, the adenoma carefully exposed and enucleated. The area was drained. On pathologic examination the tumor was 16 mm. in diameter, well encapsulated and dark brown in color. Microscopic examination showed it to be a beta cell adenoma. Blood sugar and insulin levels were obtained from the portal vein just prior to and 30 minutes following excision of the adenoma during a constant infusion of 5% Dextrose. The pre-excision values were sugar 120 mg./100 ml., insulin 146 μU/ml.; 30 minutes post-excision sugar was 282 mg./100 ml., insulin 6 μU/ml. The blood sugar level returned to normal by the third postoperative day. Postoperative glucose tolerance test, tolbutamide test, prolonged fast for 72 hours, and insulin levels were entirely normal. The patient made an uneventful recovery and was discharged on the 17th postoperative day. There have been no further hypoglycemic attacks and she has remained well during the 10-month period since operation.

Clinical Aspects

Among the 13 patients in this group who had confirmed functioning beta cell islet tumors there were seven men and six women. The average age at onset of symptoms was 47 years; the range was from 5 years in the youngest patient to 66 years in the oldest. In the three patients of the same family (Cases 4, 6, 7), the father (Case 7) is an example of multiple endocrine adenomatosis.

The principle features of the clinical courses of this group are summarized in Table 1. The duration of hypoglycemic symptoms averaged 49 months with a range of 3 months to almost 14 years. Symptoms varied from those usually caused by very rapid decreases in blood sugar levels with epinephrine release (e.g., weakness, sweating, hunger, tachycardia, "inward trembling") to the cerebral manifestations which are attributable to more gradual decreases over a period of hours (e.g., headache, blurred vision, diplopia, mental confusion, incoherent speech, ataxia, psychotic behavior).[1] Episodes of syncope, with and without convulsive seizures, occurred in 12 (92%) patients. Six patients had undergone psychiatric therapy or consultation and one had been incarcerated in the state prison.

Symptoms occurred most commonly after overnight fasting and after exertion. Morning lethargy with difficulty in arousal was a prominent feature in each patient's history. More than half of the group had had symptoms for 3 or more years before the diagnosis of functioning beta cell islet tumor was made.

In this series there were no significant findings on physical examination which contributed to the diagnosis of beta cell islet tumors.

Laboratory Data and Diagnostic Studies

After fasting the overnight blood sugar levels were 50 mg./100 ml. or lower in each patient in this small series on one or more occasions during diagnostic evaluation. Further, in each patient the clinical criteria of Whipple's Triad were validated.

Glucose tolerance tests were done as a screening procedure in all patients in an effort to exclude reactive or functional hypoglycemia. In this series, glucose tolerance tests were not particularly helpful in establishing a diagnosis of hyperinsulinism due to functioning islet tumor.

Prolonged fasting with evaluation of the patient's symptomatic responses and blood glucose concentrations has been used in the diagnosis of beta cell islet tumors for many years. In most patients with islet tumor hypoglycemic symptoms develop within the first 24 hours with concomitant reduction in blood sugar levels to concentrations of 40 mg./100 ml. or lower.[8] Relief by oral or intravenous glucose fulfills Whipple's criteria. Less frequently it is necessary to prolong fasting to 48 or 72 hours before severe hypoglycemia occurs. Since the advent of accurate methods of measuring serum immuno-reactive insulin (IRI),[7] more precise information can be obtained by documenting both glucose and insulin levels during the deprivation test. Figures 2, 3 and 5

illustrate the relationship between serum glucose and insulin concentration in normal patients and in several with beta cell islet adenomas in this series. In our opinion prolonged fasting with simultaneous measurements of serum, glucose and insulin levels is the single most useful test for evaluating patients suspected of having insulin producing tumors.

The tolbutamide tolerance test developed for clinical usage by Fajans *et al.*[2] has been employed in the effort to diagnose beta cell tumors in most patients in this series since 1961. Patients with functioning beta cell tumors usually respond to the rapid intravenous injection of 1 Gm. of sodium tolbutamide which promptly reduces and sustains blood glucose to hypoglycemic levels. The test was positive in each patient in whom it was used in this series.

The L-leucine sensitivity test, the glucagon test, and the administration of diazoxide[1, 16] were used in several patients in this series as adjuvants to diagnosis of beta cell tumors but provided little additional information of value above that provided by the other tests.

Radiologic studies which were used in many of these patients to identify and localize a pancreatic tumor included upper GI x-rays, selective celiac and superior mesenteric arteriography and pancreatic scan. These studies with the addition of chest x-rays and intravenous pyelograms were useful chiefly in excluding the existence of large extra pancreatic tumors as a cause for hypoglycemia. In one of six patients selective arteriography correctly indicated the location of a beta cell tumor in the head of the pancreas. None of the other tumors, including the largest (43 mm.), were demonstrated by radiologic studies.

Pathologic Findings

Among the 15 patients in this study who underwent operation for preoperative diagnosis of hyperinsulinism, 13 had functioning beta cell islet tumors. There were 19 adenomas and one adenocarcinoma removed from these 13 patients. One patient had eight separate, discrete adenomas located in the body and tail of the pancreas. The remaining 12 patients had single tumors (Table 2). All adenomas were discrete and approximately spherical in configuration. The adenocarcinoma was also spherical in configuration and fairly discrete. The average diameter of the tumors was 13.3 mm.; the range was from 2 to 43 mm. All tumors were intrapancreatic except for one which was attached to the uncinate process by a small pedicle. Five were located in the head of the pancreas, ten in the body and five in the tail (Fig. 6). Of the ten tumors located in the body of the pancreas, six were in the one specimen containing eight adenomas. The color of the tumors ranged from reddish-brown to yellow or tan. Histologic examination showed the cellular characteristics of beta cell islet adenoma in each of the 19 benign tumors. In the single instance of malignant islet tumor the 43 mm. lesion was well localized

TABLE 2. *Pathologic Findings*

Adenoma, single	11
Adenoma, multiple	1
Adenocarcinoma	1
Normal pancreas	2
	15

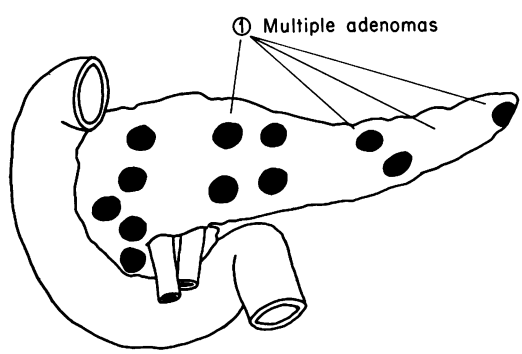

FIG. 6. Diagram of approximate location of solitary beta cell islet tumors in 12 patients. One patient had multiple beta cell adenomas in body and tail.

TABLE 3. *Summary of Operative Findings and Procedures*

Tumor Identified at Primary Exploration (10 Patients)	
Distal pancreatectomy—splenectomy	4
Excision or enucleation of tumor	4
Whipple operation	1
Wedge excision	1
Tumor Not Identified at Primary Exploration (5 Patients)	
Distal pancreatectomy—splenectomy	5
Tumor found in specimen	2
Tumor not found in specimen	3*
Tumor Identified at Secondary Exploration (1 Patient)*	
Enucleation of Tumor	1

but showed many mitotic figures, pleomorphism and perineural invasion. There were no metastases. No correlation between the size of the tumors and the duration of the symptoms or the severity of symptoms was found.

In the two patients with hyperinsulism in whom no beta cell tumor was identified either at the time of operation or in the excised body and tail of pancreas, pathologic examination of the specimen showed minimal changes in chronic pancreatitis in one and normal pancreas in the other. There was no evidence of islet hyperplasia in either specimen.

Surgical Treatment

After functioning beta cell islet tumors were diagnosed in this group of patients, operation was performed with dispatch.

There was a total of 16 exploratory laparotomies in 15 patients. Fourteen laparotomies were performed through bilateral subcostal or upper abdominal "bucket-handle" incision and two through a midline incision. In each instance the abdominal contents, pancreas and the common sites of aberrant pancreatic tissue were thoroughly explored. As previously emphasized by Laroche, Ferris, Priestley *et al.*,[8] pancreatic exploration for functioning beta cell islet tumor requires inspection and palpation of the entire gland. The pancreatic head can be assessed and palpated bimanually after mobilization of the duodenum and head by the Kocher maneuver. The body and tail are visualized and palpated bimanually by dividing the gastrocolic ligament and the posterior peritoneal reflexion from the body and tail of the pancreas to the root of the transverse mesocolon.

A summary of findings at operation and the surgical procedures employed in the management of this series of 15 patients with hyperinsulinism is presented in Table 3.

A tumor was detected in 10 patients at initial exploratory laparotomy among whom was the patient who had multiple adenomas of the body and tail (Case 7). This patient and three others with solitary tumors which could be visualized and palpated in body or tail underwent distal pancreatectomy and splenectomy. Simple excision or enucleation of the tumor was performed in four other patients (Fig. 4). One patient had a Whipple procedure for removal of a deeply seated tumor of the pancreatic head. Another had wedge resection of a tumor of the inferior portion of the mid portion of the pancreatic tail.

Five patients in whom no tumor could be identified at primary exploration underwent distal pancreatectomy-splenectomy. In two of these patients serial section of the excised body and tail by the surgical pathologist disclosed a small adenoma (Fig. 1). In the three other patients serial sections and microscopic study failed to show either gross or microscopic evidence of beta cell tumor or of islet hyperplasia. One (Case 1) was reoperated on more than 10 years later and an adenoma was found in the residual head of the pancreas and enucleated.

Results

All of the patients who were operated upon recovered and survived the immediate postoperative period. Postoperative

courses in 11 patients were without complication.

One patient had a superficial wound infection which did not prolong hospital stay. Another patient, who had undergone distal pancreatectomy-splenectomy with drainage of the area developed a pancreatic fistula in the drain sinus. This occurred shortly after discharge from the hospital and healed spontaneously after a few weeks. Another patient had prolonged ileus after distal pancreatectomy which delayed recovery.

In each of the 12 patients in whom beta cell tumors were removed at primary exploration there was immediate relief of hypoglycemia and hyperinsulinism. Transitory hyperglycemia was characteristically present in the first few days after operation. Eleven patients have been cured of hyperinsulinism and have had excellent results with no recurrence of hypoglycemia or tumor in follow-up period of 10 months to 11 years.

One of the 12 (Case 2) in whom beta cell islet adenoma had been wedged out of the mid portion of the pancreatic tail returned 2 months after operation with severe pancreatitis. After a long illness complicated by pseudocyst formation, massive bleeding episodes and sepsis, he died 6 months after the original operation. It seems clear that the "wedge excision" of the beta cell tumor obstructed the pancreatic duct in the mid portion of the tail.

In the three patients in whom no tumor was found at primary exploration or at pathologic examination of the resected distal pancreas, symptoms and laboratory evidence of hyperinsulinism persisted in two (Cases 1, 12) and cleared in one (Case 14). In patient M. R. (Case 1) symptoms of hyperinsulinism were controlled fairly well by high protein, low carbohydrate diet and cortisone for over 10 years. As detailed in the case summary, this patient finally agreed to return for re-evaluation and at re-operation in 1963 a beta cell adenoma was enucleated from the residual head of the pancreas which relieved hyperinsulinism. She has had an excellent result over the last 8 years. Mild diabetes, controlled by diet and oral hypoglycemics, has developed in this patient and in one other in this series. In patient L. G. (Case 12) manifestations of hyperinsulinism apparently persisted until the patient's death 18 months after distal pancreatic resection. Follow-up was inadequate and no autopsy was done. It is possible that a beta cell tumor was missed at the two pancreatic exploratory operations.

TABLE 4. *Results of Surgical Treatment*

Removal of Beta Cell Tumor(s) by Local Excision or Pancreatic Resection (13 Patients)	
Excellent	12
Late death	1
Pancreatic Resection (Distal)—No Tumor Found (2 Patients)	
Good	1
Late death	1

In patient B. O. (Case 14) although postoperative recovery was slow, manifestations of hypoglycemia and hyperinsulinism have disappeared since the distal pancreatic resection. In the last 18 months she has resumed her work as a nurse and has remained healthy. Follow-up studies have shown no evidence of endogenous hyperinsulinism. Factitious hyperinsulinism as the explanation of her illness cannot be excluded.

Comment and Summary

This report emphasizes the importance of recognition of the clinical syndrome and of precise laboratory data in the diagnosis of endogenous hyperinsulinism[6] due to beta cell tumors of the pancreatic islets. Whipple's Triad is as valid today as it was when first described in 1935.[13] A recent review by Conn and Pek[1] has summarized the many sophisticated laboratory methods available today in differentiating endogenous hyperinsulinism from the other causes

of hypoglycemia. Although many of these newer diagnostic studies were used in the present series, it is our opinion that prolonged fasting with simultaneous measurements of serum glucose and insulin levels is the single most useful test for evaluating patients suspected of having insulin producing tumors. As indicated by the data in Figures 2, 3 and 5, serum insulin levels are extremely low (<10 μU/ml.) in patients with profound hypoglycemia due to causes other than insulin secreting tumors. When profound hypoglycemia is accompanied by an "inappropriately" elevated endogenous serum insulin level, a diagnosis of functioning beta cell islet tumor is established.

When endogenous hyperinsulinism is proven by these criteria, surgical exploration for functioning beta cell islet tumor is indicated.

Operative experience with the patients of this series parallels that of Miller,[10] Williams, Bryson and Hume[16] and is similar to the large experience of Laroche, Ferris, Priestley *et al.*[8] Usually beta cell islet tumors are benign and solitary. They can be identified easily and removed safely if the pancreas is carefully and thoroughly explored according to the precepts emphasized by Laroche,[8] ReMine[12] and their associates. Excellent long-term results are obtained in a majority of patients.

When no tumor can be grossly identified in the pancreas or in the sites of aberrant tissue, it is our preference to do an empiric resection of the body and tail of the pancreas. Serial sections of the specimen by the surgical pathologist can be expected to identify a small beta cell tumor in 40 to 50% of patients.[8] If no tumor can be found in the sectioned specimen and portal vein blood sugar remains unchanged, the surgeon must seriously consider further excision of the pancreatic head. Under these circumstances in patients with proven endogenous hyperinsulinism it is most probable that a beta cell islet tumor exists in the head of the pancreas. Although experience is minimal, the 90 to 95% subtotal pancreatectomy procedure of Fry and Child[4] as suggested by Williams *et al.*[16] seems to be the next logical step in these unique circumstances, rather than completion of total pancreatectomy.

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