Islet Cell Tumors and Hypoglycemia

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The clinical course of hypoglycemia resulting from hyperinsulinism, first reported by Wilbur in 1927,[51] is characteristic and usually related to insulin-secreting tumors of the pancreatic islets of Langerhans. Other conditions can also produce the symptom complex associated with islet cell tumors and must be recognized in considering patients for surgical treatment (Table 1). Although it is not difficult to distinguish between functional and organic hypoglycemia, it is challenging to distinguish between the various causes of organic hypoglycemia.[23, 28, 40, 52] The present paper describes eleven patients who were operated upon and discusses the diagnostic tests and surgical management of organic hypoglycemia in adults and infants.

Clinical Course

The syndrome produced by islet cell tumors is well known and was presented in 1963 by Longmire.[19] In spite of awareness of this condition, many islet cell tumors are not diagnosed for months or years. Since repeated attacks of hypoglycemia may result in permanent brain damage, it is imperative to establish the diagnosis early and to alleviate the condition surgically. Patients with islet cell tumors (also known as insulinomas or islet adenomas) have bizarre symptoms which often lead to hospitalization on neurological or psychiatric services. Confusion, headache, convulsions and unconsciousness are due to anoxia of the brain, since there is little storage of glucose in the brain substance, while tremulousness, sweating, tachycardia, nervousness, etc., result from epinephrine release in response to hypoglycemia. The symptom complex varies with the levels of insulin production and can be promptly relieved by carbohydrates administered orally or parenterally. Obesity is characteristic in hypoglycemic individuals who control attacks by eating frequently and whenever symptoms begin.

Causes of Organic Hypoglycemia

Although islet cell tumors are the most frequent cause for organic hypoglycemia in adults, some large mesodermal tumors elaborate an insulin-like substance which produces the characteristic picture.[11, 48] Plasma immuno-reactive insulin (IRI) is not elevated with mesenchymal tumors, however.[48] In children, hyperplasia and hypertrophy of the islets are more common than tumors, and in some adults idiopathic hypoglycemia is seen without insulinomas.

The treatment of organic hypoglycemia unrelated to other endocrine disturbances is surgical, but the procedure depends upon the cause of the hypoglycemic state. Since individuals with various types of organic hypoglycemia fulfill Whipple's Triad[49] (symptoms of hypoglycemia, blood sugars below 50 mg./100 ml., and relief of symptoms by administration of glucose), it is important to evaluate each instance satisfying these criteria by accurate laboratory means.

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TABLE 1. *Causes of Hypoglycemia*

Increased Secretion Insulin

1. insulinomas
2. islet cell carcinoma
3. nesidioblastosis
4. fibrosarcomas and other tumors (insulin-like)
5. newborn infants of diabetic mothers
6. idiopathic familial (McQuarrie's syndrome)
7. early diabetes
8. dumping syndrome
9. leucine sensitivity

Inadequate Supply Glucose

1. starvation
2. excess loss (milk, urine, stools)
3. excess utilization (fever, neoplasms, exercise)

Hepatic Disorders

1. liver cell damage (cirrhosis, hepatitis)
2. glycogen storage disease
3. galactosemia
4. hereditary fructose intolerance
5. familial galactose and fructose intolerance
6. maple syrup urine disease and others

Hormone Deficiency

1. hypopituitarism (growth hormone and ACTH)
2. Addison's disease (glucocorticoids)
3. hypothyroidism
4. catecholamine deficiency (congenital or sympathectomy)
5. glucagon deficiency

Drug Administration

1. insulin-factitious or overdose
2. sulfonylureas
3. ethanol
4. other agents

Patient Evaluation

The following plan should be pursued in patients presumed to have organic hypoglycemia.

1. History and Physical Examination. Since the symptoms of hypoglycemia are characteristic, these should be elicited completely. Physical examination should detect an intra-abdominal tumor of mesodermal origin since these must be large to cause symptoms of hypoglycemia. The absence of a mass does not exclude islet cell or mesodermal tumor.

2. Fasting Blood Sugars. These are consistently below 50 mg./100 ml. in organic hypoglycemia.

3. Other Laboratory Studies. Specific tests for other endocrinopathies or for various forms of hepatic disease are indicated when suspected of causing hypoglycemia.

4. Glucose Tolerance Test. The usual glucose tolerance test is of no real help, since results with islet cell tumors are variable and unreliable (Fig. 1). However, if the test is continued for 6 to 8 hours, extremely low blood sugar may be demonstrated in organic hypoglycemia.

5. Prolonged Fasting. One of the most valuable measures to establish organic hypoglycemia is a fast for 24 to 72 hours, during which exercise is encouraged.[23, 40, 45] In islet cell tumors blood sugars fall to low levels during prolonged fast, and the picture is accentuated by exercise which further reduces blood glucose. In contrast, patients with functional hypoglycemia usually develop symptoms post-prandially and are not affected by exercise. In most cases of islet cell tumors, the fast has to be terminated within 24 hours because of severe symptoms and dangerously low blood sugars.

6. Tolbutamide Test and Plasma Insulin Levels. Tolbutamide was first used as a test for insulinoma in 1959,[13, 22, 39] and was developed for clinical usage by Fajans *et al.*[14] The best studies for specific diagnosis are blood glucose levels and plasma immuno-reactive insulin content (IRI)[53] after fasting[46] and after administration of certain drugs, such as tolbutamide and leucine[18, 47] (Fig. 2). As shown by Samols,[42] fasting plasma insulin levels may be normal in some patients with proven insulinoma, although on repeated testing high levels are usually found. A normal person after fasting has almost no detectable insulin, so that a level of 10–15 microunits per ml. is a significant elevation. Fajans *et al.*[14] first utilized the tolbutamide test for the diagnosis

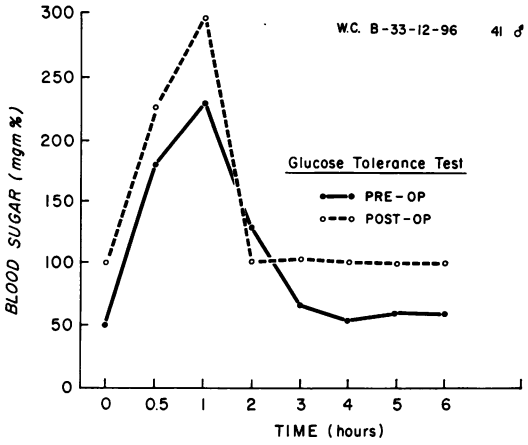

FIG. 1. Case 2. The glucose tolerance test before and after excision of islet cell tumor. The test showed a similar pattern in both instances and was not helpful in the diagnosis.

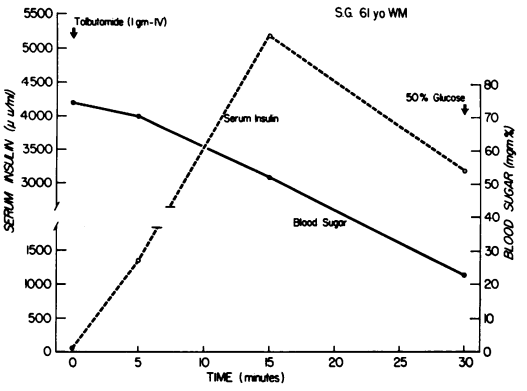

FIG. 2. Case 6. Simultaneous blood sugar and serum insulin levels during tolbutamide test in patient with islet cell tumor. There is a marked rise in insulin and fall in glucose.

of insulinoma. With the development of the immuno-reactive insulin (IRI) determination, a combination of these tests has proven of great help in the diagnosis of insulinoma. The patient is given 1 gram of sodium tolbutamide dissolved in 20 ml. of 0.9% saline intravenously over a 2-minute period. Blood specimens are taken at 10-minute intervals for the first 30 minutes for measurement of IRI, and blood sugar is measured every 15 minutes for an hour and every 30 minutes for the next 2–3 hours. The test is terminated if hypoglycemic symptoms are encountered. The secretion of insulin from the tumor as a result of tolbutamide stimulation occurs maximally during the first 20–30 minutes of the test. A level greater than 150 microunits per ml. is considered significant. The magnitude of rise of the serum insulin is related to insulin content of the tumor.[18] It is significant when blood glucose is reduced (less than 66% of the fasting glucose) to a greater degree than in the normal, but of more significance is the fact that the glucose level tends to remain low for 2–3 hours or longer, while the serum insulin levels return to the fasting level.[14] If the tolbutamide test is positive, the diagnosis is confirmed and a prolonged fast may be avoided.

7. *L*-leucine Sensitivity Test. The test was first used in 1961[17, 50] and has become a valuable aid in the study of hypoglycemia.[15] Administration of leucine more consistently produces hypoglycemia in children with idiopathic hypoglycemia of infancy and childhood[10] than in the adult. The test is performed by giving 150 mg./Kg. leucine in a 2% aqueous solution orally over a 5-minute period. A control blood sample for glucose is drawn, after which samples are obtained at 10, 15, or 30-minute intervals up to 180 minutes. Although serum insulin does not rise as significantly, nor blood glucose drop as markedly with leucine as with tolbutamide, in some cases it may be positive when the tolbutamide test is negative.[17] It should be considered in patients suspected of having tumor who have repeatedly negative responses to tolbutamide.[15]

8. Glucagon Test. One milligram of glucagon is given intramuscularly and blood sugars are determined at 15-minute intervals. A sharp rise in blood sugar occurs if hepatic glycogen stores are not depleted, and is followed in patients with insulinomas by a rapid fall after the first hour to severe hypoglycemic levels.[32]

TABLE 2

Case Hospital	Age Sex	Symptoms	Duration	Whipple's Triad	FBS	GTT	Tolbutamide Test
H. McN/ MCV	52/M	Psychosis, disorientation	2 yrs.	+	31 25		
W. C./MCV	41/M	Disorientation, headache, seizure	2 mos.	+	31 38		
S. G./St.L	61/M	Seizures	20 yrs.		75 83	±	+
B. P./MCV	36/M	Confusion, disorientation	6 mos.	+	44 33 25	32 5 hrs.	+
T. S./SCH	35/M	Confusion, unconsciousness	1½ yrs.	+	19	Diabetic curve	
E. C./SCH	71/F	Dizziness,	2 yrs.	+	Normal to 22	22 6 hrs.	
D. P./SCH	54/M	Nervousness, irritability	6 mos.	+	50	28 8 hrs.	+
L. H./SCH	82/F	Weakness, confusion	1 mo.	+	Repeatedly low		
C. K./St.L	63/M	Confusion, agitation, diabetes	1 mo.	+	15		+ 9.1 mg./ 100 ml.
D. W./MCV	9 mo. M	Convulsions, lethargy	1 mo.	+	47 37		
G. B./MCV	Newborn M	Convulsions	2 days	+	12 27 20		

Insulin Levels	Pathology	Location Pathology	Type of Surgery	Follow Up	Pertinent Findings	Pre-op. Fast
	Benign islet cell tumor	Tail	75% resection	FBS 78 mg./ 100 ml.	Found in pathology specimen	
	Benign I.C.T.	Junction body & head	75% resection	FBS 85 Diabetic GTT	Seen grossly at operation	19 hrs. BS 31 mg./100 ml.
+	Benign I.C.T.	Tail	Distal pancreatectomy	FBS 104	Seen grossly	18 hrs. 39 & 25 mg./ 100 ml.
	Benign I.C.T.	Tail	Distal pancreatectomy	Hyperglycemic 10 days	Seen grossly	30 hrs. 38 mg./100 ml.
	Benign I.C.T.	Tail	Enucleation	Transient hyperglycemia	Seen grossly	
	Benign I.C.T.	Body	Enucleation	FBS 146 Insulin 3 days	Seen grossly	10 hrs. 14 mg./100 ml.
	Islet cell carcinoma	Diffuse liver metastases	Liver biopsy	Lived 34 mos. post-op	Seen grossly	12 hrs. 30 mg./100 ml.
	Islet cell carcinoma	Tail liver metastases	Liver biopsy	Lived 7 mos.	Felt and seen grossly	
	Diffuse hyalinisation of islets—no tumor		Neg. Expl. 75% resection	Normal 2 wks. diabetic oral Rx	No findings	
	Normal pancreas & liver		Neg. Expl. 75% resection liver biopsy	Persistent hypoglycemia-N response steroids	No findings	
	Nesidioblastosis	Diffuse	90% resection	Persistent hypoglycemia, pancreatic insuff. brain damage	Sensitive to leucine—+ glucagon stimulation test No drug response	

TABLE 3. *Criteria for Diagnosis*

1. Whipple's triad	10/11
2. FBS	10/11
3. Tolbutamide	4/4
4. Serum insulin	1/1
5. Effect of fasting	5/5

9. X-ray Studies. Chest x-rays are necessary to rule out bulky intrathoracic tumors similar to non-pancreatic abdominal tumors. Gastrointestinal x-rays are of questionable assistance in demonstrating pancreatic lesions but may disclose displacement by large tumors. Selective pancreatic angiography first done by Olsson[38] is capable of demonstrating islet-cell tumors. Unlike pancreatic adenocarcinomas which are relatively avascular and are diagnosed by invasion and destruction of the normal pancreatic blood vessels by tumor ingrowth,[1, 35] islet-cell tumors of the beta-cell type (insulinomas) show neovascularization or recognizable tumor "stains" or "blushes."[1, 4, 31, 35, 38] Non-beta islet cell carcinomas[9] and glucagon-secreting alpha cell carcinomas,[33] have also been identified. Tumors as small as 1.0 cm.[4, 7] and 1.5 cm.[30, 38] in diameter have been identified by this technic. Identification of the tumor depends upon its vascularity and Loeb[30] estimated from a histological study that only 20% have dilated blood filled sinusoids which would be expected to visualize. Bookstein[4] identified only two of six on angiography. Failure to identify the tumor by angiography because of poor vascularity or small size (none under 1.0 cm. has been found) should not mitigate against use of this technic, since it may provide valuable information in certain instances. Pancreatic scanning has not been of significant help in diagnosis.

The diagnostic criteria utilized in the present series are shown in Table 2.

Hypoglycemia in Infants and Children

Hypoglycemia in infants and children is more involved. There are many causes. The onset is usually before 2 years of age and rarely after four. Evaluation is based chiefly on clinical history. Provocative tests may be harmful if the infant or child has significant fasting hypoglycemia. Functional hypoglycemia is easily differentiated from organic hypoglycemia, but differentiation of functioning islet cell tumor from idiopathic hypoglycemia is difficult. In normal children tolbutamide tests and serum insulin levels are similar to those in adults, but children with idiopathic hypoglycemia respond to tolbutamide as do adults with islet cell adenomas.[44] Serum insulin levels after fasting and after tolbutamide and *L*-leucine administration are likewise elevated.[12] Thus these tests are of no value in differentiating islet cell adenoma from idiopathic hypoglycemia in infants and children. Islet cell tumors are more common beyond age 4, while idiopathic hypoglycemia is more common under this age. Only five islet cell tumors have been reported in children under 12 months of age.[2, 21, 24, 41, 43]

Case Reports

An outline of the findings in the cases reported here is shown in Table 3.

Benign Islet Cell Tumors

Case 1. H. McN., a 52-year-old man was admitted to the Psychiatric Service, Medical College of Virginia, on 6–30–52 after he was found wandering on the street unclothed from the waist down except for a pair of socks. On examination there were under-productive speech, aphasia, and disorientation. Blood pressure was 180/100, pulse 76. He had an old convergent strabismus, and rhonchi were present throughout both lung fields. Abdominal examination was negative and reflexes were hypoactive bilaterally. Following blood sugar determination, he responded to intravenous 50% glucose with lessening of disorientation and disappearance of aphasia. He had a history of episodes of bizarre behavior associated with tremulousness, relieved by eating for years. Fasting blood sugar levels were 31 mg./100 ml. and again 25 mg./100 ml. Intravenous glucose tolerance test showed a peak at 103 mg./100 ml. at 30 minutes, with a fall to 37 mg./100 ml. On 7–18–52 he un-

derwent abdominal operation at which no pancreatic tumor was seen grossly. Seventy-five per cent pancreatectomy was performed and a 1.5 cm. lesion in the tail proved to be islet adenoma. Postoperatively, blood sugars were between 200 and 300 mg./100 ml., which gradually decreased. One month postoperatively fasting blood sugar was 78 mg./100 ml.

Case 2. W. C., a 41-year-old man was admitted to the Medical College of Virginia Hospital on 9–19–59 with a history for one year of headaches and severe sweating, and for two months of awakening in the early morning hours disoriented, confused, and with severe headache. He had eight such attacks over this period. The evening prior to admission after a 19-hour fast he had a grand mal seizure and remained confused, irrational and violent until 12 hours later, when he responded rapidly to carbohydrate ingestion. Physical examination was unremarkable. Hemoglobin was 14.8 Gm./100 ml., blood sugar on admission, 31 mg./100 ml. at one test and 38 mg./100 ml. on another. Fasting sugars ranged from 50–65 mg./100 ml. Glucose tolerance test showed fasting sugar 50 mg./100 ml., ½ hour 180, 1 hour 230, 2 hours 129, 3 hours 65, 4 hours 54, 5 hours 60, and 6 hours 60. At operation a 2 cm. lesion was found at the junction of the body and head of the pancreas and subtotal pancreatectomy was carried out. Pathological report was benign islet cell tumor. Blood sugar prior to removing the tumor was 77 mg./100 ml., and was 360 mg./100 ml. soon after removal. Postoperatively he required insulin for 4 days and fasting blood sugar at time of discharge was 85 mg./100 ml.

Case 3. T. S., a 35-year-old man had symptoms of hypoglycemia which progressed for 18 months until admission to the hospital in October, 1963. At that time he became unconscious during the course of overnight fast prior to a blood sugar determination. On admission fasting blood sugar was 19 mg./100 ml., and it was believed that he had an islet cell tumor. Glucose tolerance test produced a diabetic curve and tolbutamide test was considered too hazardous because of low fasting blood sugar. Operation was performed on November 8, 1963 and a single islet cell tumor was excised from the tail of the pancreas. Pathological examination disclosed benign islet cell tumor, and recovery has been complete.

Case 4. B. P., a 36-year-old housewife first noticed early morning confusion in May, 1965 and was subsequently studied on the neurosurgical service of another hospital with negative neurological findings. Later, hypoglycemia was suspected but prolonged fast failed to confirm the diagnosis. Symptoms progressed and in September, 1965, a tolbutamide test and prolonged fast were strongly positive. At operation on November 11, 1965 splenectomy and resection of the distal 6 cm. of the pancreas were performed. A solitary tumor in the tail could be demonstrated. Histological diagnosis was benign islet cell tumor, and recovery has been complete.

Case 5. E. C., a 71-year-old woman, complained for 2 years of episodic confusion and dizziness which was relieved by eating, and in December, 1967 she fell unconscious from a parked automobile. In April, 1968 she was referred to a neurologist for evaluation of seizures, and hypoglycemia was suspected. Initial blood sugars were normal but a blood sugar level was 22 mg./100 ml. during a 6-hour glucose tolerance test. Fasting produced blood sugar of 14 mg./100 ml. after 10 hours, and symptoms of hypoglycemia were promptly relieved by carbohydrates. Operation was carried out on April 23, 1968 and a 2 cm. tumor was removed from the inferior portion of the body of the pancreas. Benign islet cell tumor was the pathological diagnosis and recovery has been complete.

Case 6. S. G., a 61-year-old man was admitted to St. Luke's Hospital on 4–17–68 for further evaluation of seizures. He had convulsions in childhood and for the past 20 years had 1–2 seizures a week for several weeks at a time, after which a month or so would elapse without an attack. The attacks were described as being typical grand mal seizures at times and at other times loss of consciousness with no convulsive movements.[16] He had been taking anticonvulsive medication, but for several weeks prior to admission he had an increased number of seizures, particularly in the early morning. Glucose tolerance test prior to admission showed fasting blood sugar of 80 mg./100 ml., ½ hour 66 mg./100 ml., 1 hour 46 mg./100 ml., 2 hours 34 mg./100 ml., 3 hours 32 mg./100 ml., 4 hours 40 mg./100 ml., and 5 hours 70 mg./100 ml. Since the glucose tolerance test, he had been able to abort seizures by ingesting carbohydrate. He was well developed, slightly obese, temperature 98.6 and pulse 72. There were no significant physical findings. Hemoglobin was 14.4 Gm./100 ml., one fasting blood sugar was 75 mg./100 ml. and another 83 mg./100 ml. After fasting 18 hours he had symptoms of hypoglycemia with a blood sugar of 39 mg./100 ml. and another of 25 mg./100 ml. Several 3-hour postprandial blood sugars were in the range of 30 to 47 mg./100 ml. Intravenous tolbutamide test was carried out and showed fasting sugar of 74 with a drop to 23 after 30 minutes, at which time the test was terminated because of symptoms. Serum insulin levels during this test were: fasting 62

μU/cc., 5 minutes—1,350 μU/cc., 15 minutes—5,200 μU, and 30 minutes—3,200 micro-units. On 4–26–68 at operation a 3 × 3 × 2 cm. mass was found in the tail of the pancreas densely adherent to the hilum of the spleen. The spleen and distal pancreas were resected. The final pathologic report was islet cell adenoma of the pancreas. Postoperatively the patient did well. His fasting blood sugar two months postoperatively was 104 mg./100 ml.

These six cases illustrate features of benign islet cell tumors, particularly the variability in duration of symptoms (from 2 months to 20 years) and the frequency of admissions to neurologic or psychiatric services. It is sometimes difficult to confirm the presence of a tumor. In one case with normal fasting blood sugars, the diagnosis was established by serum insulin levels after tolbutamide stimulation. In this case, the criteria of Whipple's Triad were not fulfilled since fasting blood sugars were normal. It was possible, however, to make a diagnosis with the tolbutamide test and measurement of plasma insulin levels. Fasting produced positive results in four instances in which it was used. In unusual instances it may be necessary to employ fasting, tolbutamide tests, measurements of plasma insulin levels and other studies.

Malignant Islet Cell Tumors

Case 7. D. P., a 54-year-old retired British Army general entered Union Theological Seminary in Richmond in September, 1962. At this time he first noticed nervousness and irritability, and within 6 months he developed classical symptoms of early morning hypoglycemia. After having lost 12 lbs. and serious difficulties with hypoglycemic attacks, he was hospitalized in April, 1963. The diagnosis of organic hypoglycemia was established by repeated blood sugar determinations, positive fasting test, and strongly positive tolbutamide test. At operation on May 7, 1963, an islet cell carcinoma of the pancreas with diffuse hepatic metastases was confirmed by biopsy of a metastatic liver nodule. Postoperative management included dietary measures to control hypoglycemia and a regimen of medications consisting of steroids, diazoxide, regular glucagon and a repository zinc glucagon which carried him through the night. He was able to perform normal functions for many months and lived for 34 months after operation, dying March 19, 1966—3½ years after the onset.

Case 8. L. H., an 82-year-old widow was hospitalized in April, 1963 because of weakness, weight loss, lapses of memory, and incoordination on arising. An epigastric mass was palpated and laboratory tests suggested islet cell tumor. After a brief attempt at home management, operation was performed on June 4, 1963. Inoperable islet cell carcinoma arising in the tail of the pancreas and large metastases in the liver were found, and biopsies confirmed the diagnosis. She was managed postoperatively by frequent feedings to control hypoglycemic symptoms. After four months she developed strictures from peptic esophagitis secondary to hiatal hernia and a feeding gastrostomy was carried out. Subsequently hypoglycemia became more difficult to control and she died January 3, 1964 of massive hemorrhages from ulcerative esophagitis. Autopsy confirmed the diagnosis of pancreatic islet cell carcinoma with extensive hepatic metastases.

With malignant islet cell tumors, clinical and laboratory findings may be identical to those of benign tumors. At operation the tumor should be resected if possible, since the levels of insulin production vary with the extent of the tumor. In advanced lesions, prolongation of life may be possible with drug therapy designed to elevate blood sugar levels and to halt growth of the tumor.

Idiopathic Hypoglycemia

Case 9. C. K., a 63-year-old man was admitted to St. Luke's Hospital on 5–12–67 because of confusion, disorientation, and agitation in the early morning hours. He was diabetic for 10 years, initially treated with diet and oral hypoglycemic agents, but the latter were unnecessary for 4 years because diabetes was in good control. He had an episode of confusion approximately one month prior to admission, which was relieved by eating breakfast, and 2 weeks prior to admission he had numbness of his tongue and extremities relieved by eating candy. He ate fruit prior to retiring each evening but had not the night before admission. He was obese and afebrile, weight 171 lbs., blood pressure 130/80, pulse 96, and he was not confused. Hemoglobin was 13.6 Gm./100 ml., ESR 48, Fasting Blood Sugar 34, BUN normal. Without supplemental feedings, he developed severe symptoms of hypoglycemia and during several episodes fasting blood sugars were 15 mg./

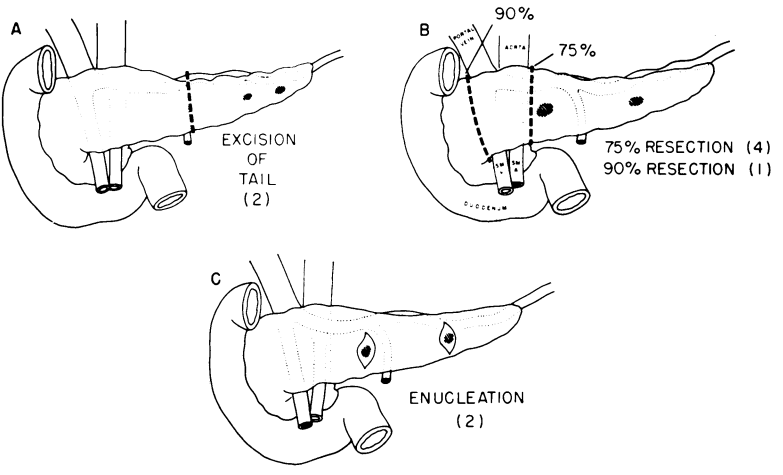

FIG. 3. Distribution of islet cell tumors in present series and type of surgery performed. Only liver biopsy done in two malignant cases not shown. In three patients with no islet cell adenoma found, 75% resection was done in two and 90% resection in one.

100 ml. On intravenous tolbutamide test fasting sugar was 15 mg./100 ml. and after 30 minutes dropped to 9.1 mg./100 ml., at which time the patient became unconscious and the test was terminated. On 5–19–67, at operation the entire pancreas was mobilized and no islet cell tumor was found. Seventy-five per cent pancreatectomy was carried out and careful pathologic examination showed no tumor. There was hyalinization of approximately 75% of the islet cells, compatible with the diagnosis of diabetes mellitus. Postoperatively blood sugar rose to the range of 235 mg./100 ml. By the second week postoperatively, however, fasting sugars were normal, then gradually increased and he was given oral hypoglycemic agents. Fasting blood sugar obtained one year postoperatively was 142 mg./100 ml. The patient has had no further episodes of hypoglycemia.

Case 10. D. W., a nine-month-old boy was admitted to the Medical College of Virginia Hospital on 2–23–59 having been well until one month previously when he developed vomiting, diarrhea, and dehydration with twitching of the face. At this time he was admitted to another hospital in a moribund state. He improved rapidly with treatment but developed viral pneumonia and soon became lethargic and unresponsive, in spite of clearing of the pneumonia. On physical examination he responded only to painful stimuli, and his eyes were fixed in a stare. Abdominal examination was negative. Neurologic examination showed hyperactive deep tendon reflexes and mild spasm of the extremities with sustained ankle clonus. Hemoglobin was 12.6 mg./100 ml., fasting blood sugar 47 and 37 mg./100 ml., CSF sugar was 25 mg./100 ml. and 2-hour post-prandial blood sugar 37 mg./100 ml. Constant infusion of glucose was required to keep the blood sugar elevated but the neurologic status did not improve. ACTH and hydrocortisone administration were ineffective in elevating blood sugar. At operation no abnormality was found and a 75% pancreatectomy was performed. Microscopic examination showed no abnormality in the pancreas and a biopsy of the liver was normal. Postoperatively his status was unchanged and blood sugar remained in the range of 36–44 mg./100 ml., with no response to ACTH or Cortisone. He was discharged from the hospital without improvement and has been lost to follow-up.

Case 11. G. B., a boy was born at the Medical College of Virginia on 7–13–67, the third child of a 24-year-old mother who had no family history of diabetes. The birth weight was 10 lb., 3 oz. Routine blood sugar 2 hours after birth was 12 mg./100 ml. with repeated values of 27 and 20 mg./100 ml. The child had no symptoms, but 2 days after birth developed repeated generalized seizures controlled by intravenous glucose. Physical examination was unremarkable. Laboratory tests showed persistent severe hypoglycemia. Glucagon stimulation test indicated intact liver stores of glycogen and a leucine sensitivity test showed an initial blood sugar of 87, 15 minutes 42, 30 minutes 50 mg./100 ml., 45 minutes 35 mg./100 ml. Other endocrine tests were normal. He was treated with ACTH and Cortisone and later Susephrine and Diazoxide in addition to a low leucine diet. Hypoglycemia persisted. On 10–11–67 he underwent 95% pancreatectomy. Postoperatively blood sugars were elevated but after several days it was necessary to resume drug therapy. Blood sugars have remained in the range of 40–50 mg./100 ml. in spite of drugs, and he requires Phenobarbital to control seizures which are thought to be due to brain damage as confirmed by a diffusely abnormal E.E.G. He has evidence of pancreatic exocrine insufficiency (less than 5% activity with duodenal

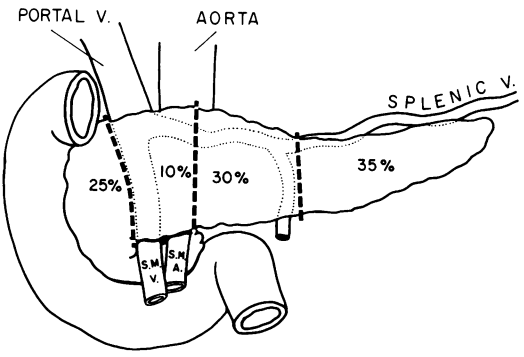

FIG. 4. Distribution of islet cell tumors based on review of Howard [27] and series of Laroche.[29] (493 cases.) Ectopic and multiple tumors not included.

samples) and requires supplemental oral enzymes. The pathologic diagnosis was diffuse nesidioblastosis,[5] centroacinar cell hyperplasia and tubuloislet neoformation of pancreas.

Although islet-cell tumors are rare in infants they may occur in the neonate [2, 21, 24, 41, 43] and an attempt should be made to establish this diagnosis, as permanent brain damage can be caused by severe hypoglycemia.

When hyperplasia of the islets is responsible for hypoglycemia, 75% resection may be adequate with supplementary drugs, and sometimes is curative. Medical management should always be tried, and postoperative medical management is simplified by major resection of the pancreas.

Hyperplasia of islets has been suggested as the cause of hypoglycemia in infants with hypersecretion of insulin and in patients with the Zollinger-Ellison syndrome when no tumor is found. Recently nesidioblastosis has been reported in adults with the Zollinger-Ellison syndrome.[3, 5] Nesidioblastosis may also produce hypoglycemia, as in Case 11 which is being reported in detail elsewhere.[6] This condition consists of new islet-cell formation from pancreatic acinar cells, and occurs in animals and patients stimulated chronically with tolbutamide, corticosteroids, or glucose. In the neonate the condition is thought to be a hyperresponsiveness of islets to some stimulus in utero—possibly glucose or amino acids. It is postulated that this condition may progress to diffuse islet cell hyperplasia or adenoma formation.

Hypoglycemia persisted in Case 11 despite 90% resection and therapy with drugs. Permanent brain damage resulted from prolonged hypoglycemia in spite of vigorous medical management. Reoperation

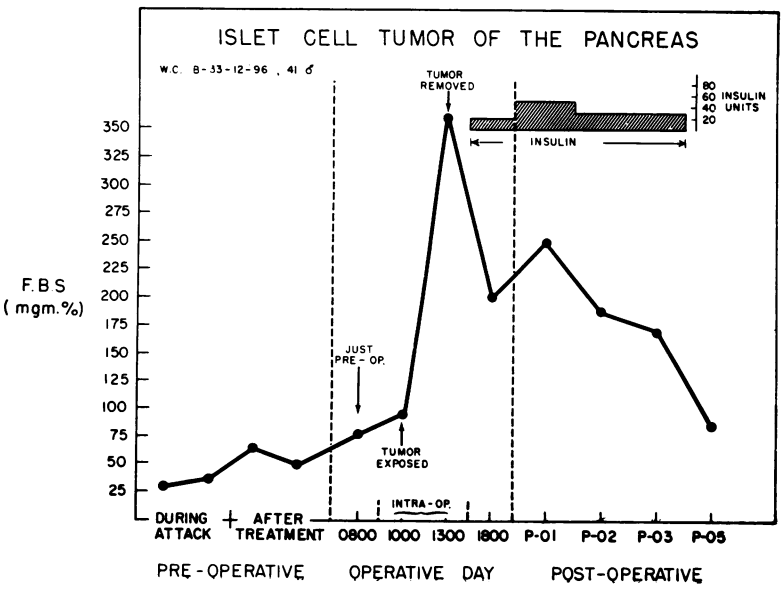

FIG. 5. Case 2. Hyperglycemic response to excision of islet cell tumor. There was an immediate sharp rise in blood glucose upon excision of the tumor which required insulin for control over 4-day period.

with resection of all but 2 to 3% of the pancreas would probably be the best procedure in these patients, since production of diabetes by total pancreatectomy in the neonate would probably be difficult to manage. The adult with idiopathic hypoglycemia (Case 9) initially had diabetes, later became hypoglycemic, and finally reverted to the diabetic state after 75% resection.

Surgical Approach

The surgical approach in organic hypoglycemia is straightforward. In adults, islet cell tumors are the most common cause, and are usually readily found. The pancreas must be completely exposed and mobilized for palpation by the Kocher maneuver and by opening the gastro-colic omentum. Benign islet cell tumors are usually single, measure up to 4 cm. in size, are reddish brown, covered by a thin capsule and may be in any part of the pancreas. The location of the tumors reported here and the operation are shown in Figure 3. Simple enucleation is adequate for accessible adenomas, but more extensive resection may be necessary when a tumor is not palpable. Distal blind pancreatectomy has been recommended [8, 27, 29] when the tumor

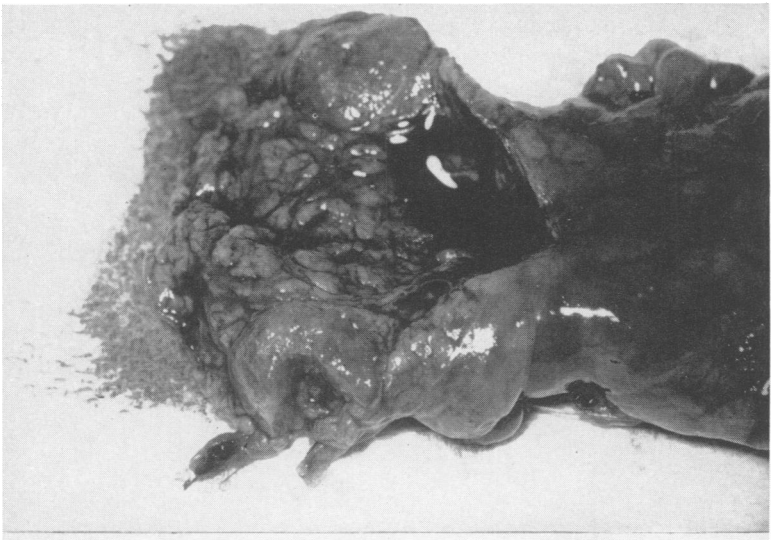

FIG. 6. A. Resected specimen Case 2 illustrating relatively small size of tumor. (Tumor bisected.)

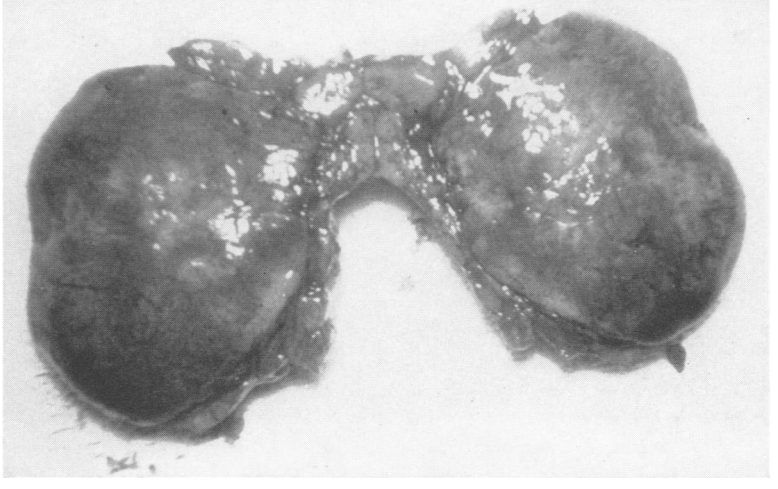

FIG. 6. B. Resected specimen Case 6 illustrating large tumor bisected with normal pancreas in center.

TABLE 4. *Pathology*

1. Adenoma	6
2. Carcinoma	2
3. Nesidioblastosis	1
4. Normal pancreas	2
	11

is not found on the assumption that this removes about ⅔ of adenomas (Fig. 4). The drawback is that tumors in the head of the pancreas are not in the resected specimen, and the condition is not relieved. In a series of blind distal (75%) pancreatectomies,[29] the cure rate was 55%, and in some instances even though no tumor was identified symptoms were relieved, suggesting that idiopathic hypoglycemia similar to that of childhood occurs also in adults. Pancreatico-duodenectomy has been suggested as a primary procedure when a tumor cannot be found in instances of hypoglycemia.[19, 36, 37] Because of difficulties with the Whipple procedure, 95% resection as advocated by Childs for chronic pancreatitis may be more acceptable.

Measurement of the blood sugar during operation is an excellent way to assure complete removal of the tumor[25, 34] (Fig. 5). A simple method for accomplishing this has been advocated, using the dip stick testing of blood glucose levels.[25] Successful removal of a small tumor by segmental resections beginning at the tail and extending toward the head is indicated by hyperglycemic rebound, and the dip stick method furnishes an easy and quick method of measuring blood sugars sequentially.

Although tumors are usually small (Fig. 6A), they may be easily seen and felt (Fig. 6B).

In idiopathic hypoglycemia in infants and children, medical management should

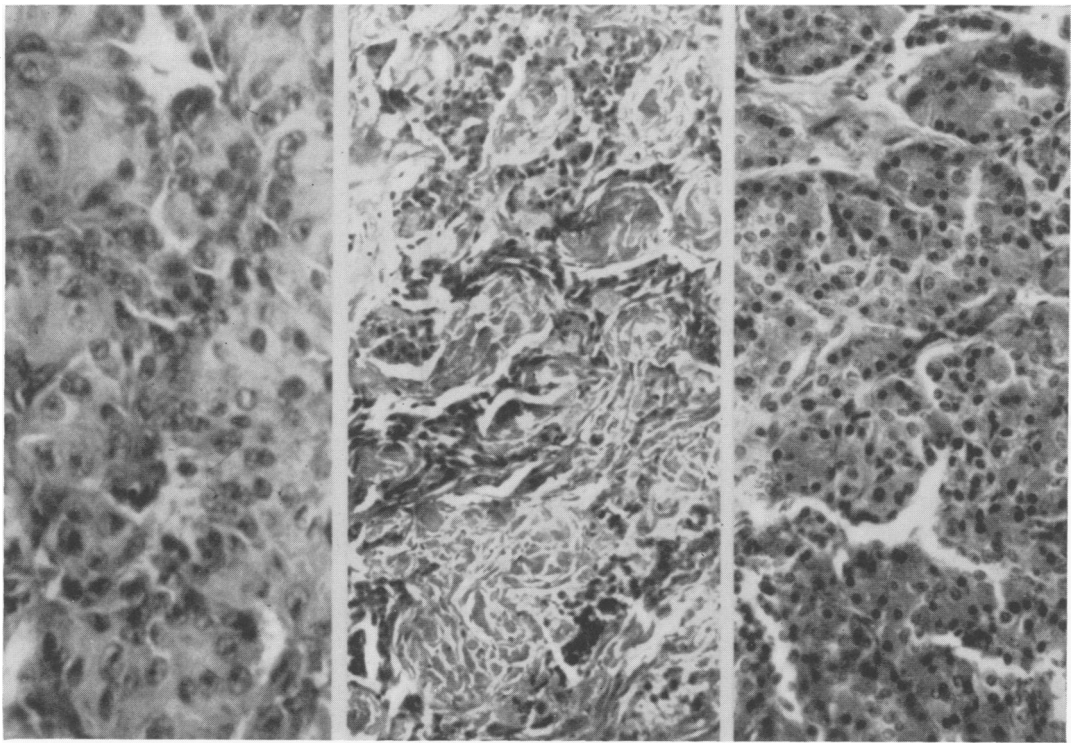

FIG. 7. Photomicrographs showing (L to R) (a) Benign islet cell tumor (Case 4), (b) Malignant islet cell tumor (Case 7) and (c) nesidioblastosis (Case 11).

be attempted initially and surgical operation considered when medical management fails or there are serious side effects.[20] Resection of 75% or more of the pancreas is the procedure of choice in these cases and may be curative, if islet cell hyperplasia is present, or at least permit more successful medical management when no tumor is found.[26] Re-resection of all but 2–3% of remaining pancreatic tissue, should be carried out if the infant cannot be controlled after the initial operation.

Summary and Conclusions

Hypoglycemia produces symptoms which may simulate neurological or psychiatric conditions, and the diagnosis may be delayed for months or years after onset of symptoms. Organic hypoglycemia can be distinguished from functional hypoglycemia by careful tests. These include sophisticated laboratory studies to reinforce clinical evaluation. The criteria of Whipple's Triad are nearly always met. The best diagnostic tests include prolonged fasting, intravenous tolbutamide test, and plasma insulin immuno-assay. The tolbutamide test is of particular value and more specific for islet cell tumor when combined with simultaneous measurement of serum insulin levels. Serum insulin levels are valuable in prolonged fasting, since in lesions other than islet cell tumors, there should be practically no measurable serum insulin. Angiography may be useful to localize tumors. When organic hypoglycemia has been proven, operation is carried out, and in the majority benign islet cell tumors are found.

When no tumor is found the tail should be resected up to the left border of the superior mesenteric vessels. Blood sugars should be measured during operation, and if sugar fails to rise within 30 minutes after removing the tail, 90% resection of the pancreas should be carried out as shown in Figure 3. If the sugar fails to rise after this, a 95% resection may be carried out. If the patient is not cured by this procedure total pancreatectomy may have to be done at a subsequent operation, but this seems preferable to beginning total resection as advocated by some authors.[19, 36, 37]

Less commonly, islet cell carcinomas are problems in long-term treatment, as the cure rate is low. In children, under the age of 4 and occasionally in adults, a form of idiopathic hypoglycemia (without islet cell tumor) may be encountered. These require extensive pancreatic resection, and results are inferior to those in islet cell tumors. Attempts at medical management should be undertaken before surgical operation, especially in children under 4 years of age.

Eleven cases are reported illustrating various types of surgically treated organic hypoglycemia.

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Discussion

Dr. Kenneth W. Warren (Boston): Dr. Williams has covered this subject so nicely, there's very little that needs to be said. He has pointed out the diagnostic methods, and they accumulate and increase every few years, but I would like to warn you that, the more exotic the tests are, the less reliable they are.

As far as the glucose tolerance test is concerned, if you run this test to 6 hours, it is not a glucose tolerance test, it's a starvation test. And I think you can make this diagnosis in every patient by prolonged starvation and exercise under very careful supervision.

I was very happy to hear Dr. Williams emphasize that many of these patients are studied by neurologists and psychiatrists, and, indeed, many of them have been institutionalized. This is a problem that one should depend primarily upon a very careful history, and then starvation until you have produced the symptoms, and then relieve the symptoms immediately by the administration of glucose.

In a selected series of these patients suspected of having adenomas or hypoglycemia and who have been operated upon, in 75 per cent an adenoma will be found. In 10 per cent the adenoma will be multiple. In 10 per cent the tumor will be malignant, with metastases, and in 10 per cent the adenoma itself will show microscopic evidence of malignancy, but will behave as a relatively benign tumor. We still prefer to call them malignant tumors, and watch them very carefully.

The other thing I would like to emphasize is that I think x-ray will have a place, not so much in diagnosis, but in localization of these tumors. I would also agree that a ductal pancreatectomy is better than enucleation, when a tumor is there; and then wait the interval. We have been very reluctant to do a 95 per cent resection or a total pancreatectomy. We have done it, but we have always done it in stages, so that maybe this 30-minute wait will have a great effect.

It should be borne in mind that 3 per cent of these adenomas are barren, and this is a likely place to look with very careful exploration of the pancreas at that time.

More recently we have used FUDR in some of the patients who had liver metastases, and we think it has a real but a very selective place. We had one very remarkable patient who had good response to FUDR. Infusion is continuous, through the hepatic artery. The patients developed recurrent symptoms, and on reexploration the catheter had been displaced, and it was reinserted, and the patient again had a good response.

Dr. Edward Horgan (Winchester): My interest in the islet cell tumor goes back to the thesis for my Master of Science degree in surgery, which was entitled "The Histogenesis of Carcinoma in the Islets of the Pancreas."

In that study for the thesis I found what Carrington referred to (slide), that we have hypertrophy of islets and sometimes a number of them in the pancreas.

(Slide) Here is an adenoma, a hypertrophied islet (slide), and here is another (slide), and here is one which Dr. Kenneth Warren spoke about, a microscopic carcinoma, and when we find that the cells have broken through the capsule (slide), we find the appearance under high power is that of a malignancy.

Islet cell tumors have been found in accessory pancreatic tissue very recently, but accessory pancreatic tissues have been found on many occasions. On one occasion I reported two (slide), and here is one accessory pancreatic, in the posterior wall of the greater curvature of the stomach.

(Slide) And here is one in the duodenum.

These accessory pancreatic tissues (slide) are independent of the pancreas. They function independently (Slide). They have all of the histologic structures of the pancreas, and it is possible that some of these tumors will become malignant.

We have recently had one large tumor of the pancreas which we knew existed for 6 years. It was first found on exploration in a patient who was being operated upon for massive bleeding from the uterus in 1962.

One year later the patient was readmitted to the hospital for acute cholecystitis, and at operation I found that the tumor was still present, but we thought it was larger; I'd like to say too that the diagnosis then was mild diabetes.