Hypothesis: Nesidioblastosis is an important cause of adult hyperinsulinemic hypoglycemia, and control of this disorder can often be obtained with a 70% distal pancreatectomy.

Design: The records of all adult patients operated on for hypoglycemia between 1974 and 1999 were reviewed retrospectively. Patients with the pathologic diagnosis of nesidioblastosis were contacted for follow-up (1.5-21 years) and are presented. Patients’ results were compared with those of 36 other individuals with this disorder who were previously reported in the literature.

Setting: The University of Chicago Medical Center (Chicago, Ill), a tertiary care facility.

Patients: A consecutive sample of all patients operated on for hypoglycemia.

Interventions: Seventy percent distal pancreatectomy for all patients with nesidioblastosis, and maintenance therapy with verapamil hydrochloride for 2 patients.

Main Outcome Measures: Achievement of normoglycemia with and without medication, development of insulin-dependent diabetes mellitus, pancreatic exocrine insufficiency, and need for reoperation.

Results: Of 32 adult patients who underwent surgical exploration for hyperinsulinemic hypoglycemia at our institution, 27 (84%) were found to have 1 or more insulinomas, and 5 (16%) were diagnosed with nesidioblastosis. Each patient with nesidioblastosis underwent a 70% distal pancreatectomy. Follow-up duration for the 5 patients ranged from 1.5 to 21 years, with 3 patients (60%) asymptomatic and taking no medications, and 2 patients (40%) experiencing some recurrences of hypoglycemia. The 2 patients with recurrences are now successfully treated with a calcium channel blocker, an approach, to our knowledge, never before reported for adult-onset nesidioblastosis.

Conclusions: Nesidioblastosis is an uncommon but clinically important cause of hypoglycemia in the adult population, and must always be considered in a patient with a presumptive preoperative diagnosis of insulinoma. This study indicates that a 70% distal pancreatectomy is often successful in controlling hypoglycemia, and rarely results in diabetes mellitus. However, the optimal treatment of this disorder remains to be determined.

Arch Surg. 2001;136:656-663
PATIENTS AND METHODS

The medical records of all adult patients operated on for hypoglycemia at the University of Chicago Medical Center between 1974 and 1999 were reviewed. Of 32 cases identified, 27 (84%) were diagnosed with 1 or more insulinomas, and 5 (16%) were diagnosed with nesidioblastosis without an accompanying insulinoma. The patients with nesidioblastosis were contacted for follow-up, and appropriate laboratory testing was performed when possible.

Reports of adult-onset nesidioblastosis in the literature were found by a search of MEDLINE, and these patients were analyzed by symptoms, extent of pancreatectomy, and outcome. Outcome was measured by control of hypoglycemia and hypoglycemic symptoms with and without medication, need for reoperation, evidence of pancreatic exocrine insufficiency, and development of insulin-dependent diabetes mellitus.

RESULTS

In each of the following 5 cases of hyperinsulinism, no islet cell tumor was found in multiple sections of the 60% to 80% distal pancreatectomy specimens examined. All cases showed a diffuse increase in islet tissue, forming islets that varied in size (Figure 1). Some pancreatic sections showed that nearly 50% of the cross-sectional area was made up of islet tissue. Many small- and medium-sized islets were present in close association with small and proliferating pancreatic ductules (Figures 2, 3, 4, and 5). Four of the 5 cases did exhibit foci of dilated pancreatic ducts or ductules, suggesting focal areas of duct obstruction (Figure 6), which might be a factor in stimulating islet hyperplasia and nesidioblastosis. Many medium- and large-sized islets showed irregular non-oval outlines. Scattered islets of varying size contained large hyperchromatic islet cell nuclei (dysplasia, Figure 7). Some of these were 6 to 8 times larger than smaller adjacent nuclei. Immunohistochemical staining showed that the increased number of islet cells still contained the usual ratios of insulin-, glucagon-, somatostatin-, and polypeptide-secreting cells.

CASE 1

In 1979, a 22-year-old man was admitted to the University of Chicago Medical Center, having experienced dizziness, lightheadedness, and headaches for 3 months. His
blood glucose level was 2.3 mmol/L (42 mg/dL), and at that time, his insulin levels were inappropriately high. A 70% distal pancreatectomy was performed, removing all pancreatic tissue to the left of the superior mesenteric vessels. Pathological examination results were consistent with nesidioblastosis (Figure 5), and no insulinoma was found grossly or microscopically.

At 21 years’ follow-up, the patient was found to be normoglycemic and generally asymptomatic, without evidence of pancreatic exocrine insufficiency. At times of heavy alcohol use when he did not eat, he stated that he had symptoms of hypoglycemia.

CASE 2

In 1985, a 37-year-old woman was referred to the University of Chicago Medical Center for evaluation of hypoglycemia and symptoms of lethargy and anxiety. She had a low blood glucose level (1.9 mmol/L [35 mg/dL]) and an elevated serum insulin level (158 pmol/L). A 72-hour fast resulted in insulin values of 51 to 92 pmol/L during periods of severe hypoglycemia. An exploratory laparotomy was performed, and no insulinoma was found at the time of operation. A 70% distal pancreatectomy was performed, removing all pancreatic tissue to the left of the superior mesenteric vessels. Pathological analysis was consistent with nesidioblastosis (Figure 3), and no insulinoma was found grossly or microscopically.

Postoperatively, the patient was initially asymptomatic and normoglycemic, and she was discharged without any complications. Soon afterwards, she developed recurrence of symptomatic hypoglycemic episodes. She was begun on a regimen of verapamil hydrochloride and has remained asymptomatic and normoglycemic, taking 80 mg by mouth, 3 times daily for the last 15 years without evidence of pancreatic exocrine insufficiency.

CASE 3

In 1990, a 42-year-old woman had 1½ years of diaphoresis, shaking, palpitations, confusion, dysphagia, dysarthria, diplopia, lightheadedness, and a 9.07-kg weight gain. Her symptoms usually occurred while awakening and during exercise, and they were usually relieved by eating. She had undergone a glucose tolerance test at an outside hospital that demonstrated a glucose level of 1.1
mmol/L (20 mg/dL), but no further workup was pursued for the next year. In October 1990, the patient developed severe hypoglycemia during a 72-hour fast (glucose, 1.7 mmol/L [30 mg/dL]; insulin, 105 pmol/L). Magnetic resonance imaging, computed tomographic (CT) scan images, and results of an abdominal ultrasonography all demonstrated a nonspecific thickening in the tail of the pancreas. The patient underwent an exploratory laparotomy in December 1990. A 1-cm nodule found near the tail of the pancreas was excised and interpreted as consistent with diffuse islet cell hyperplasia during frozen section examination. No other masses were palpated, but results of an intraoperative ultrasound demonstrated a 1-cm hypoechoic lesion in the head of the pancreas. This region was explored surgically, but no discrete mass was found. A biopsy of this region also yielded the diagnosis of islet cell hyperplasia. At this point, a 70% distal pancreatectomy was performed. The pathologic diagnosis was consistent with nesidioblastosis (Figure 4 and Figure 6), and no insulinoma was found grossly or microscopically.

The patient experienced no complications postoperatively, and she was discharged normoglycemic and asymptomatic. The patient has remained asymptomatic and normoglycemic (blood glucose, 3.3-5.4 mmol/L [60-97 mg/dL]) after 9 years of follow-up; she is taking no medications and is without evidence of pancreatic exocrine insufficiency.

CASE 4

In 1993, a 45-year-old man experienced diaphoresis and chills and was found to have a blood glucose level of 1.7 mmol/L (30 mg/dL) at an outside hospital. A 72-hour fast was performed, but the blood glucose level never fell below 2.8 mmol/L (50 mg/dL), and no further workup was attempted at that time. During the next 3 years, he intermittently experienced diaphoresis and forgetfulness, and gained 34 kg. In April 1996, the patient was found at the side of the road in his car and could not remember how he had gotten there. He was taken to a hospital, where he was found to have a blood glucose level of 1.3 mmol/L (24 mg/dL), an insulin level greater than 1910 pmol/L, a C-peptide level of 9.92 nmol/L (normal, <1.3 nmol/L), and a proinsulin level 360 pmol/L (normal, <21 pmol/L). Test results for insulin antibodies and oral hypoglycemic agents were normal.

An abdominal CT scan was negative for a tumor, and an abdominal ultrasound was suggestive of a 1-cm hypoechoic lesion at the junction of the head and body of the pancreas that was consistent with a possible insulinoma. He underwent an operation in June 1996 for a presumed insulinoma, and though a thorough inspection of the pancreas showed it to be diffusely nodular, palpation and intraoperative ultrasound results failed to demonstrate a tumor. A 70% distal pancreatectomy was performed, removing all of the pancreatic tissue to the left of the superior mesenteric vessels. Pathological features were consistent with nesidioblastosis (Figure 7), and no insulinoma was found grossly or microscopically.

Immediately postoperatively, the blood glucose level rose to 9.2 mmol/L (165 mg/dL), and returned to normal levels without treatment throughout the following several days. At 3 months’ follow-up, the patient had normal fasting blood glucose and insulin levels (6 mmol/L [112 mg/dL] and 69 pmol/L, respectively). At 3 years’ follow-up, he remained asymptomatic and normoglycemic (blood glucose, 5-6.7 mmol/L [90-120 mg/dL]), taking no medications, and with no evidence of pancreatic exocrine insufficiency.

CASE 5

In February 1999, a 48-year-old woman began experiencing dizziness and occasional night sweats. In April 1999, she was hospitalized after having a seizure and was found to have a blood glucose level of 0.9 mmol/L (16 mg/dL). A 72-hour fast resulted in hypoglycemia, and the patient had a glucose level of 1.7 mmol/L (31 mg/dL), an insulin level of 49 pmol/L, and a nonsuppressed C-peptide level. Test results for oral hypoglycemic agents were normal. A CT scan, an abdominal ultrasound, and an octreotide scan were performed in an attempt to localize a possible insulinoma, but the results for all 3 tests were normal. A calcium-stimulated arteriogram (Figure 8) demonstrated a rise in insulin level when calcium was injected into both the splenic and gastroduodenal arteries, suggesting abnormal islet cells throughout multiple vascular territories of the pancreas. SMA indicates superior mesenteric artery. To convert insulin values from microunits per milliliter to picomoles per liter, multiply the given value by 7.175.

Calcium-stimulated arteriogram in patient 5. Note that in this patient, the calcium-stimulated arteriogram resulted in a rise of insulin when calcium was infused into both the splenic and gastroduodenal arteries, suggesting abnormal islet cells throughout multiple vascular territories of the pancreas. SMA indicates superior mesenteric artery. To convert insulin values from microunits per milliliter to picomoles per liter, multiply the given value by 7.175.
of the total pancreatic tissue (Figure 1). No insulinomas were found grossly or microscopically.

In the immediate postoperative period, the patient had a benign course with mild hyperglycemia (quickly returning to normal values), with no episodes of hypoglycemia (blood glucose, 3.5-8.3 mmol/L [63-149 mg/dL]). During the first postoperative year, the patient experienced intermittent recurrences of hypoglycemic symptoms, with blood glucose levels ranging from 2.5 to 3.3 mmol/L (45-60 mg/dL) at the time of her symptomatic episodes. Of note, her symptoms often occurred postprandially after having consumed large, carbohydrate-rich meals. During studies while the patient was eating 6 meals per day, she was asymptomatic, with blood glucose levels higher than 4.4 mmol/L (80 mg/dL). A fasting test was performed, during which the patient remained asymptomatic, with normal blood glucose levels for the first 24 hours. She became hypoglycemic (blood glucose, 2.7 mmol/L [48 mg/dL]) 26 hours into the fast, and she had neuroglycopenic symptoms at that time. Given her tolerance for a prolonged fast, she was discharged and was administered 80 mg of verapamil hydrochloride by mouth, to be taken 3 times daily, she was advised to continue eating 6 small low-carbohydrate meals daily. To date, she has remained normoglycemic and asymptomatic on this regimen.

Hypoglycemia of infancy is caused by nesidioblastosis of the pancreatic islet cells, and finding an insulinoma in this age group is virtually unknown. On the other hand, in the adult, hypoglycemia characterized by a Whipple triad with hyperinsulinemia and increased C peptide levels is almost always owing to an insulinoma. These tumors are single in most patients; however, in the case of patients with MEN-1 syndrome, multiple insulinomas of the pancreas are the rule.

In 1975, nesidioblastosis was first described in an adult hypoglycemic patient. The peptide testing was done at the University of Chicago Medical Center. Since that time, 35 other cases of this entity have been reported in the English-language literature. In this article, we add reports of 5 new patients, who were treated at the University of Chicago Medical Center throughout the last 21 years (Table 1). While adult nesidioblastosis is still uncommon, it certainly is not rare. Previous studies have estimated that this entity accounts for 0.5% to 7% of all cases of adult hyperinsulinemic hypoglycemia. Adult nesidioblastosis occurred in 16% of patients who were operated on for hypoglycemia at our institution during the last several decades.

The preoperative differentiation of adult nesidioblastosis from an insulinoma is difficult. Most patients, including our 5 individuals, had hypoglycemia that occurred with fasting or exercise, just as happens in a patient with insulinoma. Thus, a fasting test result is usually abnormal. Service et al. on the other hand, reported the cases of 5 adults (Table 1, patients 32-36) who suffered from severe postprandial or “reactive” hypoglycemia, and who were found to have nesidioblastosis of the pancreas when they were operated on. At the time of hypoglycemia, patients with nesidioblastosis or an insulinoma have shown inappropriately high insulin and C peptide levels. Our last patient had nondetectable proinsulin values, and this may perhaps be a clue to the diagnosis of nesidioblastosis.

Conventional radiologic testing is not reliably helpful in differentiating an insulinoma from nesidioblastosis. While the diagnosis of nesidioblastosis should be considered when imaging studies (CT, magnetic resonance imaging, ultrasonography, and angiography) do not localize a discrete lesion of the pancreas, it should not be relied on. Most insulinomas are small (<1 cm), and even in experienced hands, the sensitivity of these radiologic studies for an insulinoma is only 50% to 80%, and false-positive results occur as well.

The most promising imaging technique for localization of an insulinoma is transgastric ultrasonography of the pancreas. In the absence of detecting an insulinoma using this technique, the suspicion of a diagnosis of adult nesidioblastosis should be heightened. One should then proceed to percutaneous transhepatic portal venous sampling, or better yet, to a calcium-stimulated arteriogram of the pancreas. In this latter test, a selective arteriogram is performed of the gastroduodenal artery, splenic artery, superior mesenteric artery, and hepatic artery. After dye is injected into a given artery, a bolus of calcium is then injected. Insulin is sampled from a catheter placed in a hepatic vein. When an insulinoma is present, calcium injection results in the release of insulin only if the specific artery that feeds the area of the pancreas that contains that tumor is tested. On the other hand, in the presence of nesidioblastosis, calcium injection into all of the pancreatic vessels may result in insulin release from the entire pancreas, as the abnormal islets are usually found throughout the entire pancreas (Figure 8). This finding would be highly suggestive of nesidioblastosis in the absence of the MEN-1 syndrome, in which multiple insulinomas are often present.

While pancreatic resection represents the definitive treatment for an insulinoma, patients often require medication to control their hypoglycemia preoperatively or postoperatively. Diazoxide is the most frequent medication used, but its use is accompanied by troublesome adverse effects, including fluid retention, hypotension, hypertrichosis, and bone marrow suppression. Other medications that have been used with varying success include somatostatin analogs and glucocorticoids.

There have been reports regarding the use of calcium–channel–blocking agents to treat patients with insulinoma, neonatal nesidioblastosis, and reactive hypoglycemia. To our knowledge, cases 2 and 5 in this study represent the first reported use of calcium-channel–blocking agents in patients with adult nesidioblastosis.

The extent of surgical resection for adult-onset nesidioblastosis remains controversial. As presented in Table 2, most surgeons have performed a distal pancreatectomy, thus removing the part of the pancreas to the left of the superior mesenteric vein. A few patients have been treated by 90% to 95% (near-total) pancreatectomy, while others were treated by small distal resections. Near-total pancreatectomy would seem logical...
because of the diffuse nature of the islet cell disease. This procedure has resulted in the resolution of hypoglycemia; however, 40% of patients developed insulin-dependent diabetes mellitus. Exocrine pancreatic insufficiency occurs with some frequency as well. A 60% to 80% distal pancreatectomy results in a cure in about half of the patients, with no need for medication; an additional 19% of patients were normoglycemic with medication. Of note is the fact that insulin-dependent diabetes mellitus occurred in only 8% of this group. Smaller distal resections seem to be of only limited value therapeutically.

In our 5 patients, each of whom was treated by distal pancreatectomy, all are alive with follow-up durations up to 21 years. Three are normoglycemic and using no medication, while 2 others are normoglycemic following treatment with a calcium channel blocker. None developed diabetes mellitus. Thus, we have found this surgical approach to be satisfactory but not perfect. At the Mayo Clinic (Rochester, Minn), most patients with adult nesidioblastosis have had resections of the distal

Table 1. Cases of Adult Nesidioblastosis With Hypoglycemia From the Literature*

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>Px, %</th>
<th>Outcome (Drug)</th>
<th>Follow-up, y</th>
<th>Study Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>59/M</td>
<td>&quot;Hypoglycemic stupor&quot;</td>
<td>67</td>
<td>IDDM</td>
<td>1</td>
<td>1975</td>
<td>2</td>
</tr>
<tr>
<td>57/M</td>
<td>None (abnormal lab value)</td>
<td>95</td>
<td>NG</td>
<td>3</td>
<td>1981</td>
<td>3</td>
</tr>
<tr>
<td>28/F</td>
<td>&quot;Symptoms of hypoglycemia&quot;</td>
<td>33</td>
<td>HG/IDDM after 100% Px</td>
<td>5</td>
<td>1981</td>
<td>3</td>
</tr>
<tr>
<td>49/M</td>
<td>Dizzy/sweats/blurry vision</td>
<td>60</td>
<td>NG</td>
<td>3</td>
<td>1981</td>
<td>3</td>
</tr>
<tr>
<td>37/F</td>
<td>Syncope</td>
<td>50</td>
<td>NG (high insulin)</td>
<td>1</td>
<td>1981</td>
<td>3</td>
</tr>
<tr>
<td>20/M</td>
<td>Convulsions/syncope/sweats</td>
<td>95</td>
<td>IDDM</td>
<td>0.25</td>
<td>1981</td>
<td>3</td>
</tr>
<tr>
<td>21/M</td>
<td>Dizziness/HA/palpitations</td>
<td>70-75</td>
<td>NG</td>
<td>. . .</td>
<td>1987</td>
<td>5</td>
</tr>
<tr>
<td>84/F</td>
<td>Syncope/convulsions/sweats</td>
<td>80</td>
<td>IDDM</td>
<td>2</td>
<td>1995</td>
<td>6</td>
</tr>
<tr>
<td>66/N</td>
<td>NA</td>
<td>80</td>
<td>Slight HG (diazoxide)</td>
<td>. . .</td>
<td>1984</td>
<td>7</td>
</tr>
<tr>
<td>69/N</td>
<td>Sweats/coma/coma</td>
<td>70</td>
<td>NG</td>
<td>. . .</td>
<td>1997</td>
<td>8</td>
</tr>
<tr>
<td>32/M</td>
<td>Confusion/sweats/syncope</td>
<td>50</td>
<td>NG</td>
<td>0.25</td>
<td>1986</td>
<td>9</td>
</tr>
<tr>
<td>48/N</td>
<td>NA</td>
<td>95</td>
<td>NG</td>
<td>. . .</td>
<td>1976</td>
<td>10</td>
</tr>
<tr>
<td>15/M</td>
<td>NA</td>
<td>70-90</td>
<td>HG/NG after 2nd operation</td>
<td>. . .</td>
<td>1980</td>
<td>11</td>
</tr>
<tr>
<td>58/F</td>
<td>Dizziness/lethargy/sweats</td>
<td>75</td>
<td>NG</td>
<td>2</td>
<td>1981</td>
<td>12</td>
</tr>
<tr>
<td>56/F</td>
<td>Weakness/palpitations/syncope</td>
<td>Body/tail</td>
<td>Continued syncope</td>
<td>. . .</td>
<td>1983</td>
<td>13</td>
</tr>
<tr>
<td>29/F</td>
<td>Blurry vision/clammy skin</td>
<td>75</td>
<td>HG refractory to drugs</td>
<td>. . .</td>
<td>1983</td>
<td>13</td>
</tr>
<tr>
<td>53/M</td>
<td>Confusion/vertigo/gait changes</td>
<td>Partial</td>
<td>NG</td>
<td>. . .</td>
<td>1983</td>
<td>13</td>
</tr>
<tr>
<td>47/F</td>
<td>Dizziness/lethargy</td>
<td>60</td>
<td>NG (diazoxide)</td>
<td>1.3</td>
<td>1983</td>
<td>14</td>
</tr>
<tr>
<td>26/N</td>
<td>NA</td>
<td>75</td>
<td>HG (diazoxide)</td>
<td>. . .</td>
<td>1984</td>
<td>15</td>
</tr>
<tr>
<td>36/N</td>
<td>Confusion/numbness/sweats</td>
<td>Distal</td>
<td>NG</td>
<td>0.3</td>
<td>1985</td>
<td>16</td>
</tr>
<tr>
<td>43/F</td>
<td>Hunger</td>
<td>75</td>
<td>NG</td>
<td>2.5</td>
<td>1988</td>
<td>17</td>
</tr>
<tr>
<td>46/M</td>
<td>Dizziness/syncope</td>
<td>80</td>
<td>HG/IDDM after 100% Px</td>
<td>6</td>
<td>1989</td>
<td>18</td>
</tr>
<tr>
<td>24/M</td>
<td>Confusion/HA</td>
<td>90</td>
<td>IDDM</td>
<td>11</td>
<td>1989</td>
<td>18</td>
</tr>
<tr>
<td>29/F</td>
<td>Syncope/seizure/HA/sweats</td>
<td>50</td>
<td>HG/NG after 95% Px</td>
<td>5</td>
<td>1989</td>
<td>19</td>
</tr>
<tr>
<td>63/F</td>
<td>Dizziness/lethargy/confusion</td>
<td>95</td>
<td>NG</td>
<td>8</td>
<td>1989</td>
<td>19</td>
</tr>
<tr>
<td>42/F</td>
<td>Seizure/confusion/weakness</td>
<td>50</td>
<td>HG/NG after 95% Px</td>
<td>2</td>
<td>1989</td>
<td>19</td>
</tr>
<tr>
<td>80/M</td>
<td>Dizziness/weakness</td>
<td>70</td>
<td>HG/NG (octreotide)</td>
<td>7</td>
<td>1990</td>
<td>20</td>
</tr>
<tr>
<td>52/M</td>
<td>NA</td>
<td>75</td>
<td>NG</td>
<td>10</td>
<td>1995</td>
<td>21</td>
</tr>
<tr>
<td>50/M</td>
<td>Syncope/dizziness/sweats</td>
<td>70†</td>
<td>HG (diazoxide)</td>
<td>1.25</td>
<td>1996</td>
<td>22</td>
</tr>
<tr>
<td>24/F</td>
<td>Amnesia/lethargy/hunger</td>
<td>70</td>
<td>HG (diazoxide)</td>
<td>2.5</td>
<td>1997</td>
<td>23</td>
</tr>
<tr>
<td>66/F</td>
<td>Syncope</td>
<td>Distal</td>
<td>NG (diazoxide)</td>
<td>. . .</td>
<td>1998</td>
<td>24</td>
</tr>
<tr>
<td>37/M</td>
<td>Seizures</td>
<td>70</td>
<td>NG</td>
<td>0-3</td>
<td>1999</td>
<td>25</td>
</tr>
<tr>
<td>16/M</td>
<td>Sweats/irritability</td>
<td>70</td>
<td>NG</td>
<td>0-3</td>
<td>1999</td>
<td>25</td>
</tr>
<tr>
<td>72/M</td>
<td>Blurry vision/sweats/dystarthish</td>
<td>70</td>
<td>NG</td>
<td>0-3</td>
<td>1999</td>
<td>25</td>
</tr>
<tr>
<td>72/M</td>
<td>Sweats/diplopia/light-headed</td>
<td>70</td>
<td>NG</td>
<td>0-3</td>
<td>1999</td>
<td>25</td>
</tr>
<tr>
<td>78/F</td>
<td>Flushing/blurry vision/confusion</td>
<td>Limited</td>
<td>HG</td>
<td>0.25</td>
<td>1999</td>
<td>25</td>
</tr>
<tr>
<td>22/M</td>
<td>Dizziness/HA/lightheadedness</td>
<td>70</td>
<td>NG</td>
<td>21</td>
<td>2000</td>
<td>Current</td>
</tr>
<tr>
<td>37/F</td>
<td>Lethargy/anxiety</td>
<td>70</td>
<td>HG/NG (verapamil hydrochloride)</td>
<td>15</td>
<td>2000</td>
<td>Current</td>
</tr>
<tr>
<td>42/F</td>
<td>Sweats/palpitations/confusion</td>
<td>70</td>
<td>NG</td>
<td>9</td>
<td>2000</td>
<td>Current</td>
</tr>
<tr>
<td>45/M</td>
<td>Sweats/chills/numbness</td>
<td>70</td>
<td>NG</td>
<td>3.5</td>
<td>2000</td>
<td>Current</td>
</tr>
<tr>
<td>46/M</td>
<td>Dizziness/HA/seizure</td>
<td>70</td>
<td>HG/NG (verapamil)</td>
<td>1.5</td>
<td>2000</td>
<td>Current</td>
</tr>
</tbody>
</table>

* Only 36 cases of adult-onset nesidioblastosis have been reported in the English-language literature prior to this study. Px indicates pancreatectomy; IDDM, insulin-dependent diabetes mellitus; NA, not available; NG, normoglycemic; HG, hypoglycemic; HA, headache.
† Pancreatectomy was proximal, as part of a Whipple procedure.

Table 2. Outcome vs Extent of Operation*

<table>
<thead>
<tr>
<th>90%-95% Px</th>
<th>60%-89% Px</th>
<th>&lt;60% Px</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 5)</td>
<td>(n = 26)</td>
<td>(n = 6)</td>
</tr>
</tbody>
</table>

Normoglycemic (no medication) 60 50 33
Normoglycemic (with medication) 0 19 0
Hypoglycemic 0 23 67
IDDM 40 8 0

* All data are percentages. According to a summary of all reported cases in the literature (including the cases from this article), patients are more likely to be cured of hypoglycemia with larger pancreatic resections, but they are also more likely to develop insulin-dependent diabetes mellitus (IDDM). Px indicates pancreatectomy.
pancreas to the right of the superior mesenteric vessels. This has resulted in an 80% cure rate with operation alone (Jon van Heerden, MD, oral communication, 2000). At the University of Michigan, Ann Arbor (Norman Thompson, MD, oral communication, 2000), each patient is tested preoperatively with diazoxide. Those who respond favorably receive a distal pancreatectomy while others who do not do well taking this medication undergo subtotal pancreatectomy.

In summary, adult nesidioblastosis resulting in hypoglycemia is an important entity that should be understood by all surgeons who operate for an insulinoma. The optimal treatment of this condition requires further study. Whether or not a nonoperative approach to this disease will ever be practical remains to be determined.

**Supported in part by the Nathan and Frances Goldblatt Society for Cancer Research, Chicago, Ill.**

Presented at the 108th Scientific Session of the Western Surgical Association, Dana Point, Calif, November 14, 2000.

**Corresponding author:** Edwin Kaplan, MD, Department of Surgery, the University of Chicago Medical Center, 5841 S Maryland Ave, MC 5031, Chicago, IL 60637.

**REFERENCES**

2. Sandler R, Horvitz DL, Rubenstein AH, Kuzuya H. Hypoglycemia and endo¬

**DISCUSSION**

Jon A. van Heerden, MD, Rochester, Minn: The University of Chicago, and Dr Kaplan in particular, have long been recognized for their contributions and expertise in the field of endogenous hyperinsulinism. This presentation of a rare, yet import¬ant, facet of hyperinsulinism is another wonderful example of their many contributions.

Almost 20 years ago, in 1981 to be exact, 2 distinguished members of our association, Norman Thompson, who is with us currently, and Jay Harrnes, who is not at this meeting, pre¬sented to the members of the Western Surgical Association their early experience with adult nesidioblastosis. Although there has been a great deal of skepticism about the existence of an adult nesidioblastosis over the last 2 decades, sufficient data are currently available to refute any doubting Thomases.

Our surgical group has now operated on 11 patients with adult nesidioblastosis; 1 for hypergastrinemia or the Zollinger-Ellison syndrome, which required a Whipple operation and is...
now cured and normoglycemic 14 years later, and 10 for hyperinsulinism treated by distal pancreatectomy, a la the Kaplan group. Nine of these 11 patients have had an excellent response rate to their subtotal pancreatectomies.

I would like to ask Dr Kaplan and his coauthors to educate all of us a little bit more on this rare entity by expanding perhaps on some of the following queries: (1) Were all specimens carefully looked at and ‘bread-loafed’ to exclude the presence of a small occult insulinoma? We know that insulinomas can be very small, and are we sure that none were missed in these 5 patients? (2) Is calcium stimulation arteriography now performed at the University of Chicago if all preoperative localizing modalities are negative in the patient with definite endogenous hyperinsulinism? (3) The extent of pancreatic resection was somewhat arbitrary in the authors’ experience since section was somewhat arbitrary in the authors’ experience since calcium channel blocker before an operation is considered? Certainly if we can diagnose this entity preoperatively with certainty, then a trial of medical therapy is appropriate. (1) Were all specimens carefully looked at and ‘bread-loafed’ to exclude the presence of a small occult insulinoma? We know that insulinomas can be very small, and are we sure that none were missed in these 5 patients? (2) Is calcium stimulation arteriography now performed at the University of Chicago if all preoperative localizing modalities are negative in the patient with definite endogenous hyperinsulinism? (3) The extent of pancreatic resection was somewhat arbitrary in the authors’ experience since it makes more sense teleologically to me that nesidioblastosis should involve the entire pancreas, and is this perhaps the reason for failures in basically 40% of your patients and in approximately 20% of our patients? I think we need to ask the question: is true localized nesidioblastosis in fact an entity? It makes more sense teleologically to me that nesidioblastosis should involve the entire gland. (4) Should all patients with this diagnosis (i.e., nesidioblastosis) have a trial of calcium-channel antagonist therapy prior to, or instead of, pancreatic resections?

Norman W. Thompson, MD, Ann Arbor, Mich: Dr van Heerden recalled that we did present a paper with 6 patients with this entity almost 19 years ago. We have had 4 or 5 since, and our current way of evaluating patients with organic hypoglycemia is to do endoscopic ultrasound. If their results are negative in demonstrating an insulinoma, that is the group that we do selective pancreatic arterial stimulation with calcium. That is the way one can diagnose this disease preoperatively. It doesn’t mean that every patient with hypoglycemia requires the study; in fact, only about 5% of insulinoma suspects do. If results are positive, then we pretreat these patients as we have for the last 15 years with diazoxide. If they respond to diazoxide, then the 70% resection seems to be adequate. If they don’t respond to diazoxide, then we do an 85% resection. During the last 15 years, we have only had one recurrence after a 70% resection, and that was a patient, a young woman, who did require an 85% resection. We haven’t had any experience with calcium-blocking agents, but those drugs could be substituted, I think, for diazoxide in pretesting. I think the diagnosis can routinely be made preoperatively. I don’t think we have to say that it’s really that difficult to make that diagnosis ahead of time and thus avoid the possibility of being forced to consider a possible “blind distal pancreatectomy at operation.”

My question is, how do you separate hyperplasia from nesidioblastosis? As I looked at those slides, several looked like islet cell hyperplasia rather than nesidioblastosis.

Clive S. Grant, MD, Rochester: As Dr van Heerden alluded to previously, we have had experience, almost exclusively over the last 3 years, with nesidioblastosis, but we think that it represents the pathologic counterpart of a new syndrome reported by Dr John Service, of noninsulinoma pancreaticogenous hypoglycemia [NIPH]. Patients with NIPH almost all have had a negative 72-hour fast, but when they are symptomatic, they have hypoglycemia documented biochemically with concomitantly elevated insulin and C peptide levels, and a negative screen for sulfonylurea. What remains difficult is distinguishing patients with NIPH from those with insulinomas. This is particularly relevant in deciding which localization studies to obtain preoperatively. Dr Thompson just indicated that he uses endoscopic ultrasound, and we have recently enjoyed good success with this as well. However, I doubt that the quality of endoscopic ultrasound is universally good enough to rely on across the entire country. If the authors can suggest a reliable method to distinguish these patients preoperatively, either biochemically or by imaging techniques, I would be most interested.

Richard C. Thirlby, MD, Seattle, Wash: In your last patient, did you obtain an octreotide scan, and do you have any experience with efficacy of octreotide in these patients? If it works, the long-acting octreotide will be available quite soon on compassionate use. It might be a preferable alternative to a three-times-a-day pill.

Dr Kaplan: Dr. van Heerden, we agree that it is critical to examine the pathologic specimens very carefully to be certain that a small insulinoma is not missed. It is also true that nesidioblastosis can occur in some patients who have an insulinoma. Thus, it is critical intraoperatively to be certain that an insulinoma is not present. By the way, Dr Thompson, the term nesidioblastosis includes what was called islet cell hyperplasia in the past.

The best studies of calcium-stimulated arteriography have been done by Dr John Doppman at the NIH [National Institutes of Health, Bethesda, Md]. He has shown that this test is excellent in regionalizing the area of the pancreas that contains the insulinoma. More studies must be done on patients with nesidioblastosis to determine whether or not the entire pancreas is stimulated to release insulin by this technique. If so, this will add to the possibility that nesidioblastosis can be diagnosed preoperatively. Dr Thompson’s suggestion that this test be done when transgastric ultrasonography is negative is a good one.

How radical should the operation be? Drs van Heerden and Thompson have great experience in this field, and thus far, no perfect operation has been described. Perhaps Dr Thompson’s idea of using diazoxide, or a calcium channel blocker first, and then judging the size of the operation by the response, may have merit.

Should all adult nesidioblastosis patients have a trial of a calcium channel blocker before an operation is considered? Certainly if we can diagnose this entity preoperatively with certainty, then a trial of medical therapy is appropriate.

Drs Service and Grant have described a new syndrome in which patients with nesidioblastosis had postprandial or reactive hypoglycemia, while insulinomas are present with fasting hypoglycemia. One of our patients had post prandial hypoglycemia, but the others had fasting hypoglycemia. At the Mayo Clinic, those patients with reactive hypoglycemia are not being operated on. That is our practice as well.

A question was asked about octreotide scanning. Octreotide scanning is much better for the diagnosis of a gastrinoma than it is for insulinoma. We tried an octreotide scan on our last patient, and it was negative.

In summary, there is no question in my mind that adult nesidioblastosis does exist as a distinct entity. I am cautiously enthusiastic that calcium channel blockers may be of value. If we can diagnose this entity preoperatively, and know that an insulinoma is not present, I would be enthusiastic in trying medical therapy first, and not operating on patients with this condition.