Insulinoma and other Hypoglycemias

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INTRODUCTION

Hypoglycemia is the medical condition in which the blood glucose is abnormally low, and has many symptoms (Table 1). The reason for these symptoms involve excessive glucose utilization, inadequate production, excessive insulin levels, deficient counterregulatory hormones, and abnormal target tissue responses. Frequently, as in sepsis, multiple factors contribute. Glucose levels below normal are typically responsible for signs or symptoms of neuroglycopenia. Whipple's triad is comprised of a serum glucose less than 50 mg/dL, symptoms of neuroglycopenia, and relief of symptoms by administration of food or glucose [1]. Preferably, the episode should be documented during spontaneous development of symptoms, but dynamic testing during observed fasting may be necessary. In most circumstances, hypoglycemia represents a serious condition and its cause must be identified and treated in order to avoid serious neurologic complications.

Table 1. Classification of symptoms of hypoglycemia	
ADRENERGIC	**NEUROGLYCOPENIC**
Diaphoresis Hunger Tingling Tremulousness Palpitations Anxiety	Visual changes Confusion Unusual behavior Weakness Warmth Lethargy Dizziness Seizures Coma

A venous plasma glucose obtained in an adult after an overnight fast that is below 50 mg/dL suggests the diagnosis of hypoglycemia (Table 2). Whole blood values are approximately 10% below plasma values, and capillary samples can be 30-40 mg/dL lower than plasma values after either ingestion of a meal or glucose infusion [2]. In addition, alterations in the peripheral circulation may lead to pseudohypoglycemia [3]. These discrepancies can indicate a hypoglycemic state when in fact arterial values are in the normal range. Vigorous physical activity in a healthy patient can produce glucose levels in the range of 30-50 mg/dL [4]. For these reasons, blood glucose levels for determination of hypoglycemia should be obtained after an overnight fast to assure accuracy in measurement.

Table 2. Classification of hypoglycemic disorders	
Healthy patient	**Ill patient**
Drug-induced Tumors Islet Cell Non-islet cell Nesidioblastosis Factitious hypoglycemia Malnutrition Autoimmune-induced Miscellaneous Pregnancy Exercise Reactive hypoglycemia	Drug-induced Sepsis, Trauma and Burns Cardiac Failure Renal Disease Liver Disease Hormone Deficiencies TPN with insulin therapy Status post removal of a pheochromocytoma

Low glucose values can very rarely also be due to errors in sample handling. If not immediately processed, samples should be collected in tubes with glycolytic inhibitors, as glycolysis by red and white blood cells may result in a 10-20-mg/dL drop in blood glucose level per hour at room temperature. Samples with excessive amounts of cells, such as those obtained from patients with polycythemia vera or leukemia, may also reveal an artificially low glucose level even with glycolytic inhibitors [5][6]. Hypertriglyceridemia may reduce plasma glucose levels as much as 15% below the actual value.

NORMAL GLUCOSE HOMEOSTASIS

To understand hypoglycemia, one must first understand normal glucose homeostasis. Plasma glucose levels vary over a relatively narrow range (55-165 mg/dL) during the course of 24 hours despite wide fluctuations in supply and consumption. Impaired glucose control may have detrimental effects at either end of the spectrum. Hyperglycemia has been demonstrated to be a direct etiologic factor in vascular occlusive disease and even mild elevations in postprandial glucose, as seen in patients with impaired glucose tolerance, results in a significant increase in cardiovascular risk [7]. Hypoglycemia results in cognitive dysfunction, as glucose is the solitary source of energy for the brain except in prolonged fasting [8]. The brain during such fasting can utilize the elevated levels of ketone bodies present in the fasting state. In the non-fasting state they are limited. The brain has no capacity to store or produce glucose and therefore relies on plasma levels to function. In the hypoglycemic state, uptake across the blood-brain barrier becomes the rate-limiting step.

As plasma glucose levels fall, there is a typical progression of physiologic responses and symptoms [9]. A drop of 20 mg/dL to approximately 72 mg/dL reduces brain uptake and pancreatic insulin secretion and initiates release of counterregulatory hormones. This typically restores normoglycemia and avoids further reduction in plasma glucose concentration. Adrenergic symptoms appear at levels of 60 mg/dL (Table 1), and these usually motivate a person to eat in order to avoid a further decrement in blood glucose. When the glucose level drops below 55 mg/dL, neuroglycopenic signs and symptoms ensue, with electroencephalographic changes [10] (Table 1). Decreases below 40 mg/dL produce somnolence and behavioral aberrations such as belligerence, and prolonged levels below 30 mg/dL lead to coma, seizures, permanent neurologic deficits and death. Severe hypoglycemia can also trigger arrhythmia, myocardial infarction and stroke in patients with underlying cardiovascular disease [11][12].

Most young healthy patients can maintain blood glucose levels in the hypoglycemic range for up to 8 hours without any permanent neurologic damage [13] and patients with insulinoma have been documented to have normal cognitive function with chronic hypoglycemia and blood glucose levels as low as 24 mg/dL [14]. This experience of hypoglycemia unawareness also occurs in diabetic patients that have had recurrent episodes of hypoglycemia and results in a greater degree of hypoglycemia required to initiate counterregulatory hormone release and trigger the typical autonomic and neuroglycopenic symptoms and signs. A diminished sensitivity to beta-adrenergic stimulation in peripheral tissues [15] is responsible, as is increased transport of glucose across the blood-brain barrier [16]. In poorly controlled diabetics, the opposite can happen, with higher than usual glucose levels causing signs and symptoms of hypoglycemia [17]. Other factors, such as age, gender, body fat, medications such as beta blockers that block the adrenergic response to hypoglycemia and co-existent medical conditions are also known to decrease the signs and symptoms of hypoglycemia [18][19][20][21][22].

In the post-absorptive state, occurring during the period of overnight fasting, glucose levels are maintained at approximately 90 mg/dL. For this to happen, glucose utilization must be equal to glucose release. Although without major effect in the short-run, glucose removal slightly exceeds release, so that by 24 hours of fasting, there is a 10-20% decrease in measurable levels. By 72 hours, these may be as low as 50 mg/dL in a normal individual [23]. Most of the glucose removed by tissues in the post-absorptive state is determined by tissue requirements and glucose transport activities of specific tissues, and insulin plays more of an accommodating role. The counterregulatory hormones such as cortisol, glucagon, growth hormone and epinephrine act to temper tissue sensitivity to insulin.

Glucose release into the circulation by glycogenolysis or gluconeogenesis is more closely regulated than glucose consumption. Only the liver and kidney produce significant amounts of free glucose for release, although many tissues contain the necessary enzymes for these processes. The liver is responsible for the vast majority (80-85%) [24], and half of glucose released is due to glycogenolysis [25]. By 48 hours of fasting, when glycogen stores in the liver are diminishing, gluconeogenesis takes over and is responsible for 80% of glucose production, nearing 100% at 72 hours [26][27]. The kidneys are capable only of gluconeogenesis, as they have no appreciable glycogen stores [28].

In order to prevent hypoglycemia, counterregulatory processes produce insulin suppression and counterregulatory hormone stimulation. With exogenous insulin administration, decreased blood glucose levels suppress endogenous insulin secretion and cause elevated glucagon, epinephrine, growth hormone and cortisol levels. Stimulation of the autonomic nervous system causes elevated levels of norepinephrine and pancreatic polypeptide [29]. Glucagon and epinephrine are the principal counterregulatory hormones [30]. Glucagon acts by stimulating glycogenolysis and gluconeogenesis, thus increasing hepatic glucose release [31]. Type 1 diabetics and pancreatectomized patients are much more likely to develop severe hypoglycemia [32]. Epinephrine and norepinephrine stimulate hepatic glycogenolysis, renal gluconeogenesis, augment lipolysis, and inhibit insulin release and insulin-stimulated glucose uptake [33][34]. Growth hormone and cortisol suppress insulin-mediated glucose uptake and augment glucose release [35][36].

NON-TUMOR HYPGLYCEMIC DISORDERS

The best system of classification is based on clinical characteristics. Healthy patients will usually have different etiologies than those who are ill. Hospitalized patients often have risks associated with iatrogenic factors. Drug-induced hypoglycemia can be seen in both populations, although in healthy patients this is most commonly due to an accidental ingestion (sulfonylureas) or deliberate injection (insulin), the latter seen in cases of factitious hypoglycemia. In seriously ill patients, drug-induced hypoglycemia is most often an idiosyncratic reaction to an appropriately prescribed drug. Insulinomas are more likely to be encountered in healthy patients. Asymptomatic or symptomatic hypoglycemia may be caused by leukemia, severe hemolysis, glycogen-storage disease with adaptation, status post operations for morbid obesity, rarely after resection of pheochromocytoma or minimally functioning insulinomas.

Drug-induced (Table 2)

Overdoses of insulin, both intentional and unintentional, and drug-induced hepatic failure or dysfunction are the most common causes or hypoglycemia. Insulin, sulfonylureas and alcohol account for over 70% of cases in one large series [37]. The mechanism by which insulin and sulfonylurea overdoses cause hypoglycemia is obvious. Alcohol can result in plasma glucose levels as low as 5 mg/dL in the otherwise healthy patient during an overnight fast [38], with mortality rates of 10% in adults [39]. Alcohol-induced hypoglycemia is seen in glycogen-depleted states, whether the fast has occurred before or after alcohol ingestion. Alcohol inhibits gluconeogenesis by impairing counterregulatory hormone responses [40], by reducing uptake of gluconeogenic precursors [41], and by inhibiting oxidation of lactate and glutamate in the liver and kidney [42]. Plasma insulin levels are appropriately low, however, counterregulatory mechanisms to restore euglycemia are inadequate, and glucose ingestion or infusion is necessary [43].

Of the remaining cases of drug-induced hypoglycemia, propanolol [44], sulfonamides [45] and salicylates [46] are most common. Non-selective beta-blockers, including propanolol, inhibit hepatic and renal release of glucose, augment sensitivity of peripheral tissues to insulin, and more importantly, obscure the signs and symptoms of hypoglycemia [47][48]. The exact mechanism why salicylates cause hypoglycemia is unclear, but may involve inhibition of hepatic release of glucose and stimulation of insulin secretion [49]. Sulfonamides may also increase insulin release in a similar manner to sulfonylureas. With the increasing use of pentamidine in AIDS patients, its unusual mechanism bears mention. This agent is cytotoxic to beta islet-cells and the release of stored insulin from dying cells causes hypoglycemia, usually followed by a permanent state of diabetes [50].

Many other medications have been reported to cause hypoglycemia, usually in association with insulin or sulfonylureas, and these are listed in Table 3. In evaluating the hypoglycemic diabetic patient, one should recognize all the factors that may have precipitated the event, including dietary habits, dosage errors, other medications, age, physical activity, and comorbid conditions. In non-diabetic patients, one of the initial investigations should involve medication evaluation with actual observation of the patients medications.

Table 3. Drugs that have been reported to induce hypoglycemia	
Acetaminophen Acetazolamide Acetohexamide Acetylsalicylic acid Aluminum hydroxide Bishydoroxycoumarin Chloroquine Chlorpromazine Chlorpropamide Cimetidine Diphenhydramine Disopyramide Doxepin Glimepiride Glipizide Glyburide Haloperidol Imipramine Lidocaine	Lithium Metoprolol Nadolol Oxytetracycline Pentamidine Pindolol Propoxyphine Propranolol Quinine Ranitidine Sulfadiazine Sulfamethoxazole Sulfisoxazole Terbutaline Tolazamide Tolbutamide Trimethoprim-sulfamethoxazole Warfarin

Sepsis, Trauma and Burns

The physiologic responses seen with trauma and significant infection cause a hypermetabolic state with increased resting energy expenditure, catabolism of protein and fats with negative nitrogen balance and high glucose turnover [51][52]. Stimulation of secretion of stress hormones, which also happen to be counterregulatory hormones include glucagon, epinephrine, growth hormone and cortisol, sympathetic activation and release of cytokines and other molecules cause increased glucose utilization by non-insulin-sensitive tissues [53][54]. This in turn increases anaerobic glycolysis. Hypoglycemia can result when the liver and kidney are unable to compensate for this increased utilization, but rarely occurs without infection as a catayst [55]. In the early stages of infection, hyperglycemia is mediated primarily by glucagon and is due to high glucose turnover and a relative excess of production compared to utilization [56]. In later stages with impaired tissue oxygenation and anaerobic glycolysis prevailing, glucose utilization exceeds release due to failure of hepatic gluconeogenesis [57][58].

Cardiac failure

Hypoglycemia due to cardiac failure, although rarely seen in adults, is more prevalent in the pediatric population [59]. This may be related to a relative paucity of gluconeogenic precursors in affected patients with insufficient adipose and muscle tissue. The most accepted theory explaining the relationship between heart failure and hypoglycemia involves the Pasteur effect, where inadequate oxygen supply leads to an increase in anaerobic glycolysis. This causes a lower level of NAD, which is essential for several steps in gluconeogenesis [60]. Other factors include diminished delivery of gluconeogenic precursors secondary to low cardiac output, increased glucose utilization for anaerobic glycolysis and higher energy requirements.

Liver disease

While the liver is essential for glucose homeostasis, hypoglycemia will not occur unless at least 80% of the liver is destroyed or removed. [61]. The destruction must be extensive or there must be widespread injury. There is not any correlation between liver function tests and hypoglycemia. [62]. In most instances, due to the interruption of gluconeogenesis, the hypoglycemia of liver disease manifests as fasting hypoglycemia.

Renal disease

Hypoglycemia is one of the most serious sequelae from renal failure, as it may lead to death or severe complications in an already ill patient. Up to 50% of hospitalized patients with hypoglycemia have renal failure [63]. The hypoglycemia may be secondary to decreased clearance of oral hypoglycemic medications or insulin, or may be spontaneous. There may be underlying chronic malnutrition and decreased renal gluconeogenesis. Uremic hypoglycemia generally presents with neuroglycopenic symptoms and the patients may have gradual onset of drowsiness and confusion or may present with a neurologic event such as coma or stroke. The hypoglycemia may be either transient or intractable [64].

Counterregulatory hormone deficiencies

Although theoretically, deficiencies in any of the hormones that normally maintain euglycemia may cause hypoglycemia, this is unusual in the absence of diabetes mellitus. Deficiencies of these hormones are rare, and when one does occur, the other counterregulatory hormones usually compensate for the one that is lacking.

Glucagon deficiency can occur with long-standing diabetes, after pancreatectomy, and with chronic pancreatitis. These patients can develop severe and prolonged episodes of hypoglycemia related to insulin administration [65]. Hypoglycemia associated with a primary glucagon deficiency is rare, with few case reports in the literature.

In patients following bilateral adrenalectomy or removal of a pheochromocytoma and those with long-standing diabetes or autonomic neuropathy, insulin-induced hypoglycemia can be associated with an impaired catecholamine response [66].

The evaluation of the ill patient or a patient following resection of a pheochromocytoma with altered mental function should include an immediate blood glucose evaluation and an investigation for iatrogenic etiologies, including known adverse effects of prescribed medications and possible medication administration errors (one patient receiving another patient’s hypoglycemic agents, or inadvertent or excessive addition of insulin to nutrition formulations).

The evaluation of the healthy patient should document the presence of symptoms and exclude factitious hypoglycemia due to insulin injection or sulfonylurea ingestion. Whereas symptoms associated with genuine causes of hypoglycemia are relatively predictable and consistent, symptoms associated with factitious hypoglycemia occur erratically and independent of food ingestion.

Symptoms of hypoglycemia fall into two categories, adrenergic (neurogenic or autonomic) and neuroglycopenic (Table 1) [67]. A work-up for tumor-associated hypoglycemia should be initiated once hyperinsulinemic hypoglycemia is confirmed.

TUMOR-INDUCED HYPOGLYCEMIA

Nesidioblastosis

Laidlaw coined the term “nesidioblastosis” in 1937 [68], and since then the terms endocrine cell dysplasia, islet cell hyperplasia, islet cell hypertrophy, microadenomatosis and islet hypertrophy have been used to describe this condition [69]. This is the most commonly reported cause of neonatal hyperinsulinemia. In adults, however, it accounts for only 0.5 – 7% of all cases hyperinsulinemic hypoglycemia [70], and some authors even dispute the diagnosis. The entity is thought to be due to proliferation of abnormal beta cells throughout the pancreas, and in neonates is associated with genetic mutations, which appear to be absent in adults with the disease [71]. Preoperative differentiation from insulinoma may be quite difficult. Conventional radiographic tests are not diagnostic, as small (<1cm) insulinomas may be missed, but negative studies may suggest nesidioblastosis as the diagnosis. Suspicion is even higher when transgastric ultrasound (EUS) fails to identify a discrete lesion consistent with an insulinoma. Intra-arterial calcium stimulation with hepatic vein insulin sampling tests can be highly suggestive (in absence of MEN) when insulin levels rise with injection in all sites. Control of hypoglycemia preoperatively or after a failed operation can be accomplished with diazoxide, however, adverse side effects such as fluid retention, hypotension, hypertrichosis and bone marrow suppression may make this therapy unacceptable to some patients. Other options for medical therapy include somatostatin analogs [72], glucocorticoids, and calcium channel blockers. The latter have been used successfully without significant adverse effects [73]. The extent of pancreatic resection is controversial. In a review of all reported cases in the literature, Witteles et al [74] found that some authors recommend distal pancreatectomy only, while others chose a near-total resection. Although most patients had resolution of their hypoglycemia after near-total pancreatectomy, up to 40% became insulin-dependent diabetics either immediately or at adolescence, and a significant number also developed exocrine insufficiency. Resection of 60-80% of pancreatic parenchyma resulted in only a 50% cure rate, but an additional 19% were normoglycemic with medication, with only an 8% incidence of insulin-dependent diabetes [75].

Non-islet cell tumors

Since the first reported case of hypoglycemia due to a non-islet cell tumor in 1930, many different types of tumors have been causally linked to hypoglycemia, the most common in the western hemisphere being of mesenchymal origin [76], but primary hepatic tumors are the most common etiologies in other countries [77]. Location of mesenchymal tumors is nearly equally distributed between intrathoracic, retroperitoneal and intraabdominal sites. These tumors tend to be large, indolent and malignant [78]. In general, insulin and C-peptide levels are suppressed, a possible exception seen with small cell cancer of the cervix, which may demonstrate ectopic insulin production [79]. Improvement or resolution of the hypoglycemia may occur after surgical debulking, which supports the theory of increased glucose utilization as an etiology in these patients [80][81]. In most instances, however, it is excessive production of IGF-like molecules by the tumor that leads to suppression of glucose production and reduction in counterregulatory hormone secretion as well as increased glucose utilization [82][83][84][85].

Insulinomas

Incidence

Although rare in the overall population, with an incidence of only 4 per 1 million person-years [86], insulinoma is the most common cause of hyperinsulinemic hypoglycemia in the adult population. Nesidioblastosis, as mentioned above, is another rare cause. Insulinomas must be strongly considered in the hypoglycemic patient, particularly one that is young and otherwise healthy. The median age at diagnosis is 47 years, with a slight female predominance (59%). Only 6% of all insulinomas are malignant, and 8% are associated with multiple endocrine neoplasia type I (MEN-1) [87][88]. These tumors are usually single, except when associated with MEN-1. In the latter patients, multiple tumors are the rule (about 85%) instead of the exception. Most patients with insulinomas are amenable to surgical cure [89].

History

The major landmarks in the history of insulinomas span over a century (Figure 1). Paul Langerhans first described pancreatic islet cells in 1869 while he was a medical student under Virchow [90], which was followed 33 years later by Nichols' discovery of islet cell tumors [91]. Banting and Best discovered insulin in 1922 [92] and were eventually awarded the Nobel Prize, followed the same year by the recognition of hyperinsulinism as a clinical entity [93]. William J. Mayo attempted the first surgical resection in a patient with an insulinoma in 1926; however this malignant islet cell tumor proved to be unresectable [94]. Whipple's classic triad of hypoglycemic symptoms, low serum glucose and relief of symptoms with glucose administration, previously mentioned, was described in 1935 [95].

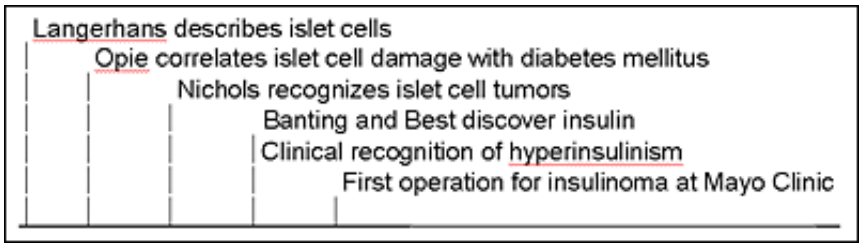

Figure 1. Historical Landmarks of isnulinomas

Biochemistry of Insulin

The genetic material responsible for insulin production is located on chromosome 11, and it is synthesized as a polypeptide chain called proinsulin by beta cells of the pancreas [96]. Enzymatic cleavage produces equimolar amounts of C-peptide and the active molecule insulin, however the relative abundance of C-peptide is higher due to a longer half-life (11-14 minutes vs. 4-6 minutes for insulin) and a slower elimination. Whereas the liver rapidly degrades insulin, C-peptide is excreted by the kidneys [97]. C-peptide is not found in commercially prepared injectable insulin; therefore undetectable levels of C-peptide indicate an exogenous source and

thus a patient with factitious hypoglycemia. Proinsulin accounts for only 25% of total insulin in serum from normal patients, but is higher in >85% of patients with insulinomas [98].

Diagnosis

Symptoms of insulinoma are the same as those seen with any cause of hypoglycemia, and may progress to loss of consciousness, coma and even permanent neurological damage. The neurological findings are typically global, but some patients may manifest focal symptoms including seizures or those resembling a cerebrovascular accident [99]. Although specific symptomatology may vary between patients, individual patients will usually have little variation between episodes. Patients or their family members usually describe symptoms upon wakening or several hours after a meal. Active patients may become symptomatic during exercise, and observant ones will learn to adapt by eating frequent small meals to avoid the onset of symptoms.

Due to the numerous etiologies of hypoglycemic symptoms, insulinoma patients frequently have long delays in diagnosis, with a mean duration of 15 to 36 months of symptoms before the diagnosis is considered [100][101].

The definitive diagnosis of hyperinsulinemic hypoglycemia requires that several criteria be met. When appropriate diagnostic tests are performed, the diagnosis is seldom uncertain. The patient must first be observed to have appropriate symptoms with documented blood glucose levels of 40 mg/dL (2.2 mM) or lower. Concomitant insulin levels at or above 6 mU/mL (43 pmol/L) with elevated C-peptide levels of at least 2 nmol/L are necessary, with absence of sulfonylurea in the plasma. If these criteria are met, the diagnosis is made; however if borderline values are encountered, further testing will be necessary.

A history of neuroglycopenic symptoms or confirmed low plasma glucose warrants further work-up. Relying on patient glucometer use during symptoms is flawed for multiple reasons. The test is difficult for the patient to perform while symptomatic, and it is inaccurate in the lower (hypoglycemic) range of values.

Diagnostic Tests

Patients who meet the above criteria are given the diagnosis of insulinoma. One method of achieving this is by performing a “minifast” as described by Fajans and Vinik [102]. Patients are observed for symptoms during a morning visit to the physician’s office, having fasted since 6 PM the previous evening. Blood glucose, insulin, C-peptide and sulfonylurea levels are checked in the office. The high success rate of this test is based on the fact that about 75% of patients will develop symptoms within 18 hours of beginning a fast [103].

The 72-hour fast

The 72-hour fast with testing for blood glucose and insulin is the most reliable diagnostic test. The patient is observed in a hospital setting under a standardized protocol for signs and

symptoms of hypoglycemia [104][105][106]. Some argue that the fast can be terminated at 48 hours, as it rarely requires the full 72 hours. Forty-three percent of patients will become hypoglycemic and symptomatic in 12 hours, 67% within 24 hours, 95% by 48 hours and 100% within 72 hours [107]. Patients are hydrated without calories and participate in daily exercise. Blood is drawn every 6 hours for plasma glucose, C-peptide and insulin levels, and at 1 to 2 hour intervals when glucose levels fall to 60 mg/dL. The fast is concluded when glucose falls to 40 mg/dL and the patient demonstrates signs or symptoms of hypoglycemia. Hypoglycemia alone is insufficient for diagnosis, as some young healthy women may have plasma glucose levels < 40 mg/dL and will not have symptoms and therefore do not have a hypoglycemic disorder. Beta hydroxybutyrate (BHB) levels should be checked on such patients and 1 mg glucagon injected intravenously with subsequent blood glucose monitoring in 10, 20 and 30 minutes. A diminished beta hydroxybutyrate level and/or a vigorous plasma glucose response to intravenous glucagon suggest hypoglycemia due to insulin or an insulin-like factor [108][109]. It should be noted that there are reports of low insulin levels in hypoglycemic patients with surgically confirmed tumors [110]. In addition, if severe symptoms occur before the onset of hypoglycemia, the fast must be terminated. BHB levels and the plasma glucose response to glucagon are useful in providing additional support of the diagnosis in this situation. Insulin is lipolytic, antiketogenic and glycogenic. For this reason, when plasma glucose is below 50 mg/dL, a concomitant BHB level of 2.7 mmol/L or less or an elevation in glucose of 25 mg/dL or more in response to glucagon facilitates the diagnosis of insulinoma [111].

Plasma sulfonylurea levels will distinguish between the insulinoma and sulfonylurea-induced hypoglycemia. All (beta-cell polypeptides) levels will be reduced in non-insulin or insulin-like mediated hypoglycemia.

[112]

Supplementary tests

When results of the 72-hour fast are indeterminate, additional tests can be performed to support or refute the diagnosis of insulinoma. These include the C-peptide suppression test and the Tolbutamide tolerance test. During the former, exogenous beef or pork insulin infusion suppresses the release of insulin from normal pancreas but not from insulinomas. Measurement of C-peptide will reveal elevated levels upon completion of the test within 2 hours [113]. Tolbutamide is a secretagogue that elicits an exaggerated release of insulin from insulinomas when compared to normal beta islet cells. A plasma glucose level of <47 mg/dL or a plasma insulin level by radioimmunoassay of 20 mU/mL during the first 3 hours after administration is highly suggestive of an insulinoma [114][115].

Localization studies

One thing is certain in the controversial area of localization: the ideal localizing test does not yet exist. This test would be inexpensive, non-invasive, 100% accurate, widely available and easy to perform. If such a test existed, the question of localization would be an easy one. However, in lieu of this, recommendations about whether localization tests should be used and, if so, which tests are widely variable. Two things that are agreed upon are that, firstly, the biochemical

diagnosis must be assured before embarking on potentially time consuming and expensive tests, and secondly,, the focus should be on the pancreas, as extrapancreatic insulinomas are exceedingly rare. The decision to perform any type of preoperative localization is controversial. Some authors avoid preoperative testing [116][117] while others justify it with reports of 10-27% of tumors being undetectable intraoperatively [118][119]. Preoperative localization of tumors also enables laparoscopic removal in some patients. Most would agree that localization studies should be done prior to reoperation [120].

Ultrasound

Transabdominal ultrasound, although inexpensive, readily available and non-invasive is extremely operator dependent and difficult to perform in obese patients. Success is reported over a wide range, from 9-67%, for tumor localization [121][122]. Endoscopic ultrasound (EUS), although somewhat invasive, has been used extensively for localization of islet cell tumors. Success rates are variable with 57-93% of tumors localized in the hands of experienced endoscopists [123][124][125]. It, has become the preferred preoperative localization study in many medical centers including ours. It is, however, an invasive test requiring heavy sedation, not without significant risk and lacks wide scale availability with adequate experience.

Intraoperative ultrasound (IOUS) is perhaps the greatest advancement in the localization of pancreatic islet cell tumors over the past two decades. It is labor intensive and operator dependent, but it can usually successfully localize even small tumors; it can also demonstrate relevant anatomy to avoid the pitfalls of pancreatic surgery including ductal injury during enucleation [126]. Reports in the literature quote a sensitivity of 86-100% in experienced hands [127][128][129], and suggest that increasing use of IOUS will minimize the need for extensive preoperative localization in initial operations. The routine use of IOUS can also change intraoperative management, including identification of non-palpable lesions and resection instead of enucleation for malignant features seen on IOUS [130]. IOUS is especially useful for tumors in the head of the pancreas, where palpation of small tumors is limited due to the thickness of the gland [131]. IOUS, unfortunately, often fails to identify small insulinomas on the tail of the pancreas near the hilum of the spleen.

Selective arterial calcium stimulation

Selective arterial calcium stimulation with hepatic venous sampling (Imamura-Doppman test) is performed on the basis that secretion of insulin from insulinomas is stimulated by a rise in serum calcium [132]. Its use has classically been described for patients with established hyperinsulinemia (or hyperproinsulinemia) without adequate localization of the lesion on routine preoperative tests. However, with the increasing use of IOUS, its application may be limited to reoperative cases. The procedure is initiated by performing subselective angiography of the splenic, superior mesenteric and gastroduodenal arteries, with a venous catheter in the right hepatic vein. Calcium gluconate (dosage) is then injected as a bolus into each individual branch and venous samples are drawn. Venous samples are taken prior to injection and at 30 second intervals for 150 seconds after injection. Insulin, glucose and calcium measurements are made on each sample. A step-up in insulin concentration signals successful regionalization of the tumor. This procedure is invasive and expensive, and has reported success rates ranging from

91-94% [133][134].

Trans-hepatic portal venous sampling

Trans-hepatic portal venous sampling (TPVS) involves obtaining samples from the superior mesenteric, portal and splenic veins for measurement of insulin levels. This test has been reported to be 55-100% accurate in regionalizing the tumor [135][136], however regionalization is all that it is capable of. It is expensive, invasive and technically difficult to perform, and for these reasons is not routinely used in most centers including ours. Its use has been reported for differentiation between nesidioblastosis and insulinoma, but it has generally been replaced by the Imamura-Doppman test.

Arteriography was formerly the “gold standard.” Its sensitivity was about 60%, but was touted by some to be upwards of 90% [137][138]. Recent studies suggest a sensitivity ranging from 29 to 50% [139][140][141]. This may be attributed to less frequent utilization and radiographers that are less experienced in interpreting the distinctive blush produced by these well-vascularized tumors. It is also invasive, expensive, and identifies the largest and thus easiest to find tumors. It has some value in patients with persistant problems after a failed exploration. It may also be useful when difficulties with imaging via intraoperative ultrasound or palpation are anticipated, or as the step preceding intraarterial calcium stimulation to distinguish discrete insulinoma from nesidioblastosis. We rarely use this test today.

Other studies

Other modalities include MRI, with 40-100% sensitivity [142][143][144], octreotide scanning [145], and intraoperative gamma probe. Computed tomography (CT) has made dramatic advances in the quality of abdominal imaging over the past decade with the advent of the spiral scanner. It has the advantage of being non-invasive, relatively inexpensive, readily available and interpretable by the surgeon. However, its utility in localization of small insulinomas remains limited, with a sensitivity ranging from 17-33% [146][147][148][149]. Perhaps the most compelling argument for CT scanning prior to operative resection is for identifying large tumors or hepatic metastases so that appropriate preoperative planning can be done.

Surgical Management

Patients with a confirmed diagnosis of insulinoma, with or without successful preoperative localization are candidates for surgical exploration. Patients are either admitted the night prior to surgery or on the morning of surgery and are administered intravenous glucose solution while they are NPO. Some surgeons remove glucose from IV fluids a few hours before surgery to avoid confusion during intraoperative glucose monitoring, but this is not our practice. We continue glucose infusion and monitor blood sugars, as hyperglycemia can be managed with removal of glucose or insulin, and is less detrimental in the short term than hypoglycemia. Glucose levels usually rise within minutes of resection of the tumor, but may take 60 minutes or longer especially in very thin patients. Once the abdomen is opened, the liver should be assessed for metastatic disease using inspection, palpation (if open procedure) and/or IOUS.

Pancreatic mobilization is performed using standard surgical techniques and thorough palpation performed, which will identify 42-88% of all tumors [150][151][152][153]. IOUS, with or without a radiologist depending upon the surgeon's experience in performing and interpreting ultrasound is able to identify nearly all tumors as well as their relationship to relevant anatomic structures. Enucleation is the procedure of choice, with dissection performed in a plane between the normal pancreatic parenchyma and the pseudocapsule composed of compressed tumor cells. Approximating the edges of the pancreatic capsule if easily done closes the remaining defect, otherwise the defect is left open with a drain placed in proximity. Formal pancreatic resection should be performed if there is any suspicion of malignancy, including hard consistency, puckering of the surrounding tissue, nodal or hepatic metastasis or proximal ductal dilatation. In cases where resection is necessary, the spleen should be preserved when appropriate and feasible, and the duct ligated when visible. The cut edge of the pancreas is closed with staples or sutures and a drain is left in place. Pancreaticoduodenectomy is rarely necessary for benign insulinoma [154]. It, however, can be completed by experienced surgeons with low morbidity and mortality [155].

Success of surgical treatment is reported at 77-100% in the literature [156][157][158][159] with higher success rates recently with the increasing use of IOUS, as previously mentioned.

When no tumor is found during the initial operation, reoperative surgery is necessary and more challenging. Blind distal pancreatectomy is no longer advocated as most of the tumors that fit into this category are located in the head or uncinate process of the pancreas and not the distal portion [160][161]. Completion pancreatectomy can have serious consequences including mortality and situations, such as blind distal pancreatectomy, that might mandate this should be avoided. One large series reports a 33% incidence of iatrogenic diabetes mellitus following reoperative surgery [162]. These patients should be referred to an experienced endocrine or pancreatic surgeon, and the diagnosis reconfirmed. Although we do not advocate extensive localization studies prior to initial operation for patients with insulinomas, we do recommend them for reoperative patients, as postoperative scarring in the pancreatic bed and position or size of the tumor often makes palpation of tumor or tumors abnormalities more challenging. Some authors advocate medical therapy such as Diazoxide until localization is successful, however, IOUS has improved success rates significantly in reoperative insulinoma surgery [163].

Perioperative complications do occur, and fall into the realm of both non-pancreatic complications and those that are directly related to tumor resection. Non-pancreatic causes include myocardial infarction or other dysrhythmias, stroke, and other medical morbidities related to general anesthesia, as well as surgical etiologies such as wound complications, bowel injury, bleeding and intraabdominal infection. Pancreatic complications include abscess, pseudocyst and fistula formation that occur in 16-43% of these patients [164][165]. The incidence of pancreatic complications is expected to decrease with the increasing use of IOUS for identification of tumors and relevant anatomy, including relationship to the pancreatic ductal system [166][167]. Overall postoperative morbidity and mortality rates are 14 and 0% respectively in most large series [168].

Postoperative management centers on management of hyperglycemia and anticipation of

potential complications. Glucose levels will increase rapidly within hours of tumor resection and may surpass levels of 200 mg/dL, depending on the extent of pancreatic resection. Patients should be administered glucose-free fluids, and may require small amounts of intermittent insulin. Regular (TID) glucose monitoring with a glucometer is continued until morning fasting levels are in the normal range. Somatostatin use is debated, but is most commonly used only if drain output is high in pancreatic amylase. The drain is removed when output is minimal and the patient is tolerating a low fat diet. Splenectomized patients should receive trivalent vaccine, preferably preoperatively for hemophilus influenza B, meningococcus and pneumococcus.

Multiple Endocrine Neoplasia

This subset of patients, as noted previously, differs from those with sporadic disease in a few features. Although benign disease still prevails in MEN patients, it is almost always multicentric, and disease recurrence is virtually guaranteed if all tumors are not resected. There is limited advantage of preoperative localization other than to rule out metastatic or invasive tumors and possible coexisting adrenal tumors, as routine distal pancreatectomy with enucleation of lesions in the head identified by IOUS is the recommended procedure to avoid incomplete treatment [169][170].

Malignant Insulinomas

Malignant tumors comprise only 5-10% of all insulinomas [171], but present a difficult situation. These patients present with the same symptoms as patients with benign disease. Malignancy is defined only by local invasion into surrounding tissue or the presence of metastatic disease. Cytologic changes and DNA analysis are not particularly helpful in distinguishing benign from malignant cells [172]. The primary tumors tend to be single and can be quite large (>6cm) as compared to most benign tumors, which are usually smaller (<2cm) [173]. Some studies have demonstrated higher serum proinsulin levels in patients with malignant lesions [174], however this has been shown in patients with benign lesions as well [175][176]. There are reports in the literature that suggest an allelic loss of chromosome 3p25 as a potential molecular marker to differentiate benign from malignant insulinoma [177]. Median disease-free survival following curative resection is 5 years, and about 65% of patients recur, with a median interval to recurrence of 2.8 years. Median survival after disease recurrence is only 19 months. Unlike the more virulent ductal adenocarcinoma, aggressive attempts of palliative resection should be pursued, as survival can be extended to a median of 4 years [178]. Ten-year survival rates of up to 29% have been reported with aggressive therapy [179]. Ninety-six percent of patients will achieve symptomatic improvement with a mean duration of 22 months following resection [180].

The best recognized treatment of liver metastases is resection, which provides extremely effective palliation when at least 90% of the tumor perioperative bulk can be removed [181]. This likely leads to prolonged survival as well, and low mortality rates (< 3%) [182][183].

Some patients, however, will not be candidates for resection based on extent and multifocal disease, alternatives have been explored, including the use of radiofrequency thermal ablation

of hepatic neuroendocrine metastases, including insulinomas. Our experience in 34 patients with 234 tumors over a period of 5 years has demonstrated substantial success, with symptoms ameliorated in 95%, significant or complete control of symptoms in 80% for a mean period of over 10 months. In addition, 41% of patients had no progression of disease during the follow-up period. Morbidity and mortality is low with this laparoscopic procedure (5% and 0% respectively) and patients had a mean hospital stay of 1.1 days [184].

Medical Management

Patients who are not candidates for resection, because of either bulky malignant or metastatic disease have a few options for management. Dietary modifications can be successful in mild cases, with intake of frequent meals and snacks, taking care to avoid prolonged periods of fasting. High-sugar products should be readily available for when symptoms develop. In the case of functional metastases (many are non-functional), refractory hypoglycemia may require treatment with Diazoxide or continuous infusion of glucose via implantable pumps.

Adriamycin and streptozocin provide regression of disease in about 70% of patients, with a remission from symptoms for eighteen months [185]. Toxic side effects limit their usefulness, however, as often the effects are worse than the hypoglycemia.

Diazoxide, known for its hyperglycemic side effects when used as an antihypertensive, is useful in patients with unresectable disease, those who have undergone unsuccessful operations, or those who are not operative candidates for other reasons, such as medical comorbidities. This drug suppresses insulin secretion by both a direct action on beta cells as well as the extrapancreatic effect of enhanced glycogenolysis [186]. The administered oral dose is 200-600 mg daily. Half of patients will have good control of hypoglycemia [187], but the same percentage will develop adverse side effects such as edema, weight gain and hirsutism. More than 10% will also have significant nausea. Some authors recommend a trial of diazoxide therapy prior to surgical exploration when localization tests fail to identify the tumor [188].

Calcium channel blockers have been used successfully, especially in patients with nesidioblastosis [189], but somatostatin analogues (octreotide) have been shown to provide only temporary or at best modest relief of symptoms [190]. Angiographic embolization is reported [191][192] but has limited applications due to the rich blood supply that is characteristic of these lesions.

SUMMARY

There are many diverse causes of hypoglycemia, and medications, comorbidities and factitious causes should be investigated. Of all the potentially curable causes, insulinoma may be the most important diagnosis to make in the otherwise healthy patient. Most insulinomas are solitary and benign, but when present in patients with MEN1 multiple tumors are usually present. Hypoglycemia and endogenous hyperinsulinemia are diagnostic, but preoperatively may sometime require extensive testing to confirm the diagnosis. Localization of these tumors, is improving. Preoperative transabdominal ultrasound or CT may be sufficient prior to an initial

operation for insulinoma, the former to localize the tumor and the later to identify potentially malignant or metastatic tumors. Reoperative cases may require extensive localizing tests to avoid further operative failure or the significant morbidity associated with completion pancreatectomy. Intraoperative ultrasound has so far proven to be unrivaled for localization of insulinoma as well as delineating anatomy, thus improving the success rate and possibly decreasing the already low postoperative complication rate for resection of these tumors. Excision of benign insulinomas leads to long-term cure.

References

1. Whipple AO, Frantz VK. Adenoma of islet cell tumors with hyperinsulinism. Am Surg 1935; 101: 1299-1335. ▲
2. Marks V. Hypoglycemia—real and unreal, lawful and unlawful: The 1994 Banting Lecture. Diabet Med 1995; 12: 850-64. ▲
3. Rushakoff RJ, Lewis SB: Case of Pseudohypoglycemia. Diabetes Care 2001 24: 2157-2158. ▲
4. Felig P, Cherif A, Minegawa A, et al. Hypoglycemia during prolonged exercise in normal man. N Engl J Med 1982; 306: 895-900. ▲
5. Billington C, Casciato D, Choquette D, et al. Artifactual hypoglycemia associated with polycythemia vera. JAMA 1983; 249: 774-75. ▲
6. Goodenow T, Malarkey W. Leukocytosis and artifactual hypoglycemia. JAMA 1977; 237: 1961-62. ▲
7. Jarrett R. The cardiovascular risk associated with impaired glucose tolerance. Diabet Med 1996; 13(suppl): 15-19. ▲
8. Owen O, Morgan A, Kemp H, et al. Brain metabolism during fasting. J Clin Invest 1967; 46: 1589-95. ▲
9. Mitrakao A, Ryan C, Veneman T, et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. Am J Physiol 1991; 260: E67-E74. ▲
10. Towler D, Havlin C, Craft S, et al. Mechanism of awareness of hypoglycemia: Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. Diabetes 1993; 42: 1791-98. ▲
11. Pladziewicz D, Nesto R. Hypoglycemia-induced silent myocardial ischemia. Am J Cardiol 1989; 63: 1531-32. ▲
12. Perros P, Frier B. The long-term sequelae of severe hypoglycemia on the brain in insulin-dependent diabetes mellitus. Horm Metab Res 1997; 29: 197-202. ▲
13. Bolli G, DeFeo P, Perriello G, et al. Role of hepatic autoregulation in defense against hypoglycemia in humans. J Clin Invest 1985; 75: 1623-31. ▲
14. Mitrakou A, Fannelli C, Veneman T, et al. Reversibility of unawareness of hypoglycemia in patients with insulinomas. N Engl J Med 1993; 329: 834-39. ▲
15. Korytkowski M, Mokan M, Veneman T, et al. Reduced □-adrenergic sensitivity in patents with type I diabetes and hypoglycemia unawareness. Diabetes Care 1998; 21: 1939-43. ▲
16. Boyle P, Nagy R, O'Connor A, et al. Adaptation of brain glucose uptake following recurrent hypoglycemia. Proc Natl Acad Sci USA 1994; 91: 9352-56. ▲

17. Boyle P, Schwartz N, Shah S, et al. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med 1988; 318: 1487-92. ▲
18. Marker J, Cryer P, Clutter W. Attenuated glucose recovery from hypoglycemia in the elderly. Diabetes 1992; 41: 671-78. ▲
19. Amiel S, Maran A, Powrie J, et al. Gender differences in counterregulation to hypoglycaemia. Diabetologia 1993; 36: 460-64. ▲
20. Hirsch I, Boyle P, Craft S, et al. Higher glycemic thresholds for symptoms during □-adrenergic blockade in IDDM. Diabetes 1991; 40: 1177-86. ▲
21. Rosenn B, Miodovnik M, Khoury J, et al. Counterregulatory hormonal responses to hypoglycemia during pregnancy. Obstet Gynecol 1996; 87: 568-74. ▲
22. Bottini P, Boschetti E, Pampanelli S, et al. Contribution of autonomic neuropathy to reduced plasma adrenaline responses to hypoglycemia in IDDM. Evidence for a nonselective defect. Diabetes 1997; 46: 814-23. ▲
23. Consoli A, Kennedy F, Miles J, et al. Determination of Krebs Cycle metabolic carbon exchange in vivo and its use to estimate the individual contributions of gluconeogenesis and glycogenolysis to overall hepatic glucose output in man. J Clin Invest 1987; 80: 1303-10. ▲
24. Stumvoll M, Meyer C, Mitrakou A, et al. Renal glucose production and utilization: New aspects in humans. Diabetologia 1997; 40: 749-57. ▲
25. Landau B, Wahren J, Chandramouli V, et al. Contributions of gluconeogenesis to glucose production in the fasted state. J Clin Invest 1996; 98: 378-85. ▲
26. Consoli A, Kennedy F, Miles J, et al. Determination of Krebs Cycle metabolic carbon exchange in vivo and its use to estimate the individual contributions of gluconeogenesis and glycogenolysis to overall hepatic glucose output in man. J Clin Invest 1987; 80: 1303-10. ▲
27. Landau B, Wahren J, Chandramouli V, et al. Contributions of gluconeogenesis to glucose production in the fasted state. J Clin Invest 1996; 98: 378-85. ▲
28. Stumvoll M, Meyer C, Mitrakou A, et al. Renal glucose production and utilization: New aspects in humans. Diabetologia 1997; 40: 749-57. ▲
29. Kennedy F, Bolli G, Go V, et al. The significance of impaired pancreatic polypeptide and epinephrine responses to hypoglycemia in patients with insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1987; 64: 602-08. ▲
30. Gerich J, Campbell P. Overview of counterregulation and its abnormalities in diabetes mellitus and other conditions. Diabetes Metab Rev 1988; 4: 93-111. ▲
31. Lecavalier L, Bolli G, Cryer P, et al. Contributions of gluconeogenesis and glycogenolysis during glucose counterregulation in normal humans. Am J Physiol 1989; 256: E844-E851. ▲
32. White N, Skor D, Cryer P, et al. Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 1983; 308: 485-91. ▲
33. DeFeo P, Perriello G, Torlone E, et al. Contribution of adrenergic mechanisms to glucose counterregulation in humans. Am J Physiol 1991; 261: E725-E736. ▲
34. Fanelli C, DeFeo P, Perriello G, et al. Adrenergic mechanisms contribute to the late phase of glucose counterregulation in humans by stimulating lipolysis. J Clin Invest 1992; 89: 2005-13. ▲
35. Gerich J, Campbell P. Overview of counterregulation and its abnormalities in diabetes

mellitus and other conditions. Diabetes Metab Rev 1988; 4: 93-111. ▲
36. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. Diabet Metab Rev 1988; 4: 17-30. ▲
37. Seltzer H. Drug-induced hypoglycemia. A review of 1418 cases. Endocrinol Metab Clin North Am 1989; 18: 163-183. ▲
38. Arky R. Hypoglycemia associated with liver disease and ethanol. Endocrinol Metab Clin North Am 1989; 18: 75-90. ▲
39. Madison L. Ethanol-induced hypoglycemia. In Levine R, Luft R (eds): Advances in Metabolic Disorders, vol 3. New York, Academic, 1968, pp 85-109. ▲
40. Flanagan D, Wood P, Sherwin R, et al. Gin and tonic and reactive hypoglycemia: What is important—the gin, the tonic, or both? J Clin Endocrinol Metab 1998; 83: 796-800. ▲
41. Siler S, Neese R, Christiansen M, et al. The inhibition of gluconeogenesis following alcohol in humans. Am J Physiol 1998; 275: E897-E907. ▲
42. Krebs H, Freedland R, Stubbs M. Inhibition of hepatic gluconeogenesis by ethanol. Biochem J 1969; 112: 117-24. ▲
43. Lecavalier L, Bolli G, Cryer P, et al. Contributions of gluconeogenesis and glycogenolysis during glucose counterregulation in normal humans. Am J Physiol 1989; 256: E844-E851. ▲
44. Reith D, Dawson A, Epid D, et al. Relative toxicity of beta blockers in overdose. Clin Toxicol 1996; 34: 273-8. ▲
45. Poretsky L, Moses A. Hypoglycemia associated with trimethoprim/sulfamethoxazole therapy. Diabetes Care 1984; 7: 508-9. ▲
46. Seltzer H. Drug-induced hypoglycemia. A review of 1418 cases. Endocrinol Metab Clin North Am 1989; 18: 163-183. ▲
47. Fanelli C, DeFeo P, Perriello G, et al. Adrenergic mechanisms contribute to the late phase of glucose counterregulation in humans by stimulating lipolysis. J Clin Invest 1992; 89: 2005-13. ▲
48. Rizza R, Cryer P, Haymond M, et al. Adrenergic mechanisms for the effect of epinephrine on glucose production and clearance in man. J Clin Invest 1980; 65: 682-9. ▲
49. Baron S. Salicylates as hypoglycemic agents. Diabetes Care 1982; 5: 64-71. ▲
50. Bouchard P, Sai P, Reach G, et al. Diabetes mellitus following pentamidine-induced hypoglycemia in humans. Diabetes 1982; 31: 40-5. ▲
51. Mizock B. Alterations in carbohydrate metabolism during stress: A review of the literature. Am J Med 1995; 98: 75-84. ▲
52. Kinney J. Metabolic responses of the critically ill patient. Crit Care Clin 1995; 11: 569-85. ▲
53. Chiolero R, Revelly J, Tappy L. Energy metabolism in sepsis and injury. Nutrition 1997; 13(suppl): 45-51. ▲
54. Hinshaw L. Concise review: The role of glucose in endotoxin shock. Circ Shock 1976; 3: 1-10. ▲
55. Brady W, Butler K, Fines R, et al. Hypoglycemia in multiple trauma victims. Am J Emerg Med 1999; 17: 4-5. ▲
56. Lang C, Bagby G, Blakesley H, et al. Importance of hyperglucagonemia in eliciting the sepsis-induced increase in glucose production. Circ Shock 1989; 29: 181-91. ▲
57. Wichterman K, Chaudry I, Baue A. Studies of peripheral glucose uptake during sepsis.

Arch Surg 1979; 114: 740-45. ▲
58. Meszaros K, Lang C, Bagby G, et al. In vivo glucose utilization by individual tissues during nonlethal hypermetabolic sepsis. FASEB J 1988; 2: 3083-86. ▲
59. Hedayati H, Beheshti M. Profound spontaneous hypoglycaemia in congestive heart failure. Curr Med Res Opin 1977; 4: 501-4. ▲
60. Marks V, Rose F. Hypoglycemia, ed 2. Oxford, Blackwell, 1981. ▲
61. Mann FC, Magath TB. Studies on the physiology of the liver. II. The effect of the removal of the liver on blood sugar level. Arch Intern Med 1922; 30:73. ▲
62. Zimmerman HG, Thomas LJ, Scherr EH. Fasting blood sugar in hepatic disease with reference to infrequency of hypoglycemia. Arch Intern Med 1953, 091L 577-584. ▲
63. Fisher KF, Lees JA, Newman JH. Hypoglycemia in hospitalized patients: Causes and outcomes. N Eng J Med 1986; 315:1245-1250 ▲
64. Frizzell M, Larsen PR, Field JB: Spontaneous hypoglycemia associated with chronic renal failure. Diabetes 1973; 22:493-498. ▲
65. White N, Skor D, Cryer P, et al. Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 1983; 308: 485-91. ▲
66. Gerich J. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 1988; 37: 1608-1617. ▲
67. Cryer PE. Symptoms of hypoglycemia, thresholds for their occurrence, and hypoglycemia unawareness. Endocrinol & Metab Clin North Am 1999; 28(3): 495-500. ▲
68. Laidlaw GF. Nesidioblastosis: The islet cell tumor of the pancreas. Am J Pathol 1937; 14: 125-139. ▲
69. Jaffe R, Hashida Y, Yunis EJ. Pancreatic pathology in hyperinsulinemic hypoglycemia of infancy. Lab Invest 1980; 42: 356-65. ▲
70. Harness JK, Geelhoed GW, Thompson NW, et al. Nesidioblastosis in adults: a surgical dilemma. Arch Surg 1981; 116: 575-80. ▲
71. Thomas P. Genetic mutations as a cause of hyperinsulinemic hypoglycemia in children. Endocrinol Metab Clin North Am 1999; 28: 647-656. ▲
72. Mozell EJ, Woltering EA, O'Dorisio TM, et al. Adult onset nesidioblastosis: response of glucose, insulin, and secondary peptides to therapy with sandostatin. Am J Gastoenterol 1990; 86: 181-88. ▲
73. Witteles RM, Straus FH, Sugg SL, et al. Adult-Onset Nesidioblastosis Causing Hypoglycemia: An Important Clinical Entity and Continuing Treatment Dilemma. Arch Surg 2001; 136(6): 656-663. ▲
74. Witteles RM, Straus FH, Sugg SL, et al. Adult-Onset Nesidioblastosis Causing Hypoglycemia: An Important Clinical Entity and Continuing Treatment Dilemma. Arch Surg 2001; 136(6): 656-663. ▲
75. Witteles RM, Straus FH, Sugg SL, et al. Adult-Onset Nesidioblastosis Causing Hypoglycemia: An Important Clinical Entity and Continuing Treatment Dilemma. Arch Surg 2001; 136(6): 656-663. ▲
76. Anderson N, Lokich J. Mesenchymal tumors associated with hypoglycemia: Case report and review of the literature. Cancer 1979; 44:787-90. ▲
77. McFadzean A, Yeung R. Further observations on hypoglucaemia in hepatocellular carcinoma. Am J Med 1969; 47: 220-235. ▲
78. Anderson N, Lokich J. Mesenchymal tumors associated with hypoglycemia: Case report

and review of the literature. Cancer 1979; 44:787-90. ▲
79. Seckl M, Mulholland P, Bishop A, et al. Hypoglycemia due to an insulin-secreting small-cell carcinoma of the cervix. N Engl J Med 1999; 341: 733-36. ▲
80. Anderson N, Lokich J. Mesenchymal tumors associated with hypoglycemia: Case report and review of the literature. Cancer 1979; 44:787-90. ▲
81. Chowdhury F, Bleicher S. Studies of tumor hypoglycemia. Metabolism 1973; 22: 663-74. ▲
82. Daughaday W. The pathophysiology of IGF-II hypersecretion in non-islet cell tumor hypoglycemia. Diabetes Rev 1995; 3: 62-72. ▲
83. Moller N, Blum W, Mengel A, et al. Basal and insulin stimulated substrate metabolism in tumour induced hypoglycaemia; evidence for increased muscle glucose uptake. Diabetologia 1991; 34: 17-20. ▲
84. Silbert C, Rossini A, Ghazvinian S, et al. Tumor hypoglycemia: Deficient splanchnic glucose output and deficient glucagon secretion. Diabetes 1976; 25: 202-206. ▲
85. Chung J, Henry R. Mechanisms of tumor-induced hypoglycemia with intraabdominal hemangiopericytoma. J Clin Endocrinol Metab 1996; 81: 919-25. ▲
86. Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc 1991; 66: 711-719. ▲
87. Witteles RM, Straus FH, Sugg SL, et al. Adult-Onset Nesidioblastosis Causing Hypoglycemia: An Important Clinical Entity and Continuing Treatment Dilemma. Arch Surg 2001; 136(6): 656-663. ▲
88. Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc 1991; 66: 711-719. ▲
89. Service FJ. Medical Progress: Hypoglycemic Disorders. N Engl J Med 1995; 332(17): 1144-1152. ▲
90. Morrison H. Contributions to the microscopic anatomy of the pancreas by Paul Langerhans [Berlin, 1869; translated from the German]. Bull Hist Med 1937; 5: 259-267. ▲
91. Nicholls AG. Simple adenoma of the pancreas arising from an islet of Langerhans. J Med Res 1902; 8: 385. ▲
92. Banting FG, Best CH. The internal secretion of the pancreas. J Lab Clin Med 1922; 7: 251-266. ▲
93. Fletcher A, Campbell W. The blood sugar following insulin administration and the symptom complex-hypoglycemia. J Metab Res 1922; 2: 637. ▲
94. Wilder RM, Allan FN, Power MH et al. Carcinoma of the islets of the pancreas: hyperinsulinism and hypoglycemia. JAMA 1927; 89: 348-355. ▲
95. Whipple AO, Frantz VK. Adenoma of islet cell tumors with hyperinsulinism. Am Surg 1935; 101: 1299-1335. ▲
96. Robbins DC, Tager HS, Rubenstein AH. The biologic and clinical importance of proinsulin. N Engl J Med 1984; 310: 165-75. ▲
97. Starr JI, Rubenstein AH. Metabolism of endogenous proinsulin and insulin in man. J Clin Endocrinol Metab 1974; 38: 305-7. ▲
98. Gorden P, Skarulis MC, Roach P, et al. Plasma proinsulin-like component in insulinoma: a 25-year experience. J Clin Endocrinol Metab 1995; 80: 2884-7. ▲

99. Stefanini P, Carboni M, Patrassi N. Beta-islet cell tumors of the pancreas: results of a study on 1,067 cases. Surgery 1974; 75: 597-609. ▲
100. Grama D, Eriksson B, Martensson H et al. Clinical characteristics, treatment and survival in patients with pancreatic tumors causing hormonal syndromes. World J Surg 1992; 16: 632-639. ▲
101. Service FJ, Dale AJD, Elveback LR et al. Insulinoma: clinical and diagnostic features of 60 consecutive cases. Mayo Clin Proc 1976; 51: 417-429. ▲
102. Fajans SS, Vinik AI. Insulin-producing islet cell tumors. Endocrinol Metab Clin North Am 1989; 18: 45-74. ▲
103. Fajans SS, Vinik AI. Insulin-producing islet cell tumors. Endocrinol Metab Clin North Am 1989; 18: 45-74. ▲
104. Service FJ, Natt N. The Prolonged Fast. J Clin Endo and Metab 2000; 85(11): 3973-3974. ▲
105. Service FJ. Medical Progress: Hypoglycemic Disorders. N Engl J Med 1995; 332(17): 1144-1152. ▲
106. Service FJ. Diagnostic approach to adults with hypoglycemic disorders. Endocrinol Metab Clin North Am 1999; 28: 519-32. ▲
107. Hirshberg B, Livi A, Bartlett D, et al. Forty-eight-hour Fast: The Diagnostic Test for Insulinoma. J Clin Endo and Metab 2000; 85(9): 3222-3226. ▲
108. O'Brien T, O'Brien PC, Service FJ. Insulin surrogates in insulinoma. J Clin Endocrinol Metab 1993; 77: 448-51. ▲
109. Hoff AO, Vassilopoulou-Sellin R. The role of glucagon administration in the diagnosis and treatment of patients with tumor hypoglycemia. Cancer 1998; 82(8): 1585-92. ▲
110. Fajans SS, Vinik AI. Insulin-producing islet cell tumors. Endocrinol Metab Clin North Am 1989; 18: 45-74. ▲
111. O'Brien T, O'Brien PC, Service FJ. Insulin surrogates in insulinoma. J Clin Endocrinol Metab 1993; 77: 448-51. ▲
112. Earle K, Rushakofdf RJ, Goldfine I: Case Report: Inadvertent Sulfonylurea over dosage and hypoglycemia in an elderly woman: Failure of serum hypoglycemia screening. Diabetes Technology and Therapeutics 5: 449-451, 2003. ▲
113. Service FJ, O'Brien PC, Kao PC, et al. C-peptide suppression test: effects of gender, age, and body mass index: implications for the diagnosis of insulinoma. J Clin Endocrinol Metab 1992; 74: 204-210. ▲
114. Service FJ, Dale AJD, Elveback LR et al. Insulinoma: clinical and diagnostic features of 60 consecutive cases. Mayo Clin Proc 1976; 51: 417-429. ▲
115. McMahon MM, O'Brien PC, Service FJ. Diagnostic interpretation of the intravenous tolbutamide test for insulinoma. Mayo Clin Proc 1989; 64: 1481-8. ▲
116. Dagget PR, Goodburn EA, Kurtz AB, et al. Is preoperative localization of insulinomas necessary? Lancet 1981; 1: 483-486. ▲
117. Hashimoto LA, Walsh RM. Preoperative localization of insulinomas is not necessary. J Am Col Surg 1999; 189(4): 368-73. ▲
118. Angelini L, Bezzi M, Tucci G, et al. The ultrasonic detection of insulinomas during surgical exploration of the pancreas. World J Surg 1987; 11: 642-647. ▲
119. Gower WR, Fabri PJ. Endocrine neoplasms (non-gastrin) of the pancreas. Semin Surg Oncol 1990; 6: 98-109. ▲
120. Simon D, Starke A, Goretzki PE, et al. Reoperative surgery for organic hyperinsulinism:

indications and operative strategy. World J Surg 1998; 22(7): 666-71. ▲
121. Hirshberg B, Libutti SK, Alexander HR, et al. J Am Coll Surg 2002. Blind distal pancreatectomy for occult insulinoma, an inadvisable procedure; 194(6): 761-4. ▲
122. Brown CK, Bartlett DL, Doppman JL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. Surgery 1997; 122(6): 1189-93. ▲
123. Schumacker B, Lubke HJ, Frieling T, et al. Prospective study on the detection of insulinomas by endoscopic ultrasonography. Endoscopy 1996; 28(3): 273-6. ▲
124. Ardengh HC, Rosenbaum P, Ganc AJ, et al. Role of EUS in the preoperative localization of insulinomas compared with spiral CT. Gastro Endo 2000; 51(5): 552-5. ▲
125. Anderson MA, Carpenter S, Thompson NW, et al. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastro 2000; 95(9): 2271-77. ▲
126. Brown CK, Bartlett DL, Doppman JL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. Surgery 1997; 122(6): 1189-93. ▲
127. Brown CK, Bartlett DL, Doppman JL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. Surgery 1997; 122(6): 1189-93. ▲
128. Hashimoto LA, Walsh RM. Preoperative localization of insulinomas is not necessary. J Am Col Surg 1999; 189(4): 368-73. ▲
129. Hiramoto JS, Feldstein VA, LaBerge JM and Norton JA. Intraoperative ultrasound and preoperative localization detects all occult insulinomas. Arch Surg 2001; 136(9): 1020-26. ▲
130. Norton JA, Cromack DT, Shawker TH, et al. Intraoperative ultrasonographic localization of islet cell tumors. A prospective comparison to palpation. Ann Surg 1988; 207(2): 160-8. ▲
131. Norton JA. Intraoperative methods to stage and localize pancreatic and duodenal tumors. Ann Onc 1999; 10 Suppl 4: 182-4. ▲
132. Kato M, Doi R, Imamura M, et al. Response to human insulinoma cells to extracellular calcium is different from normal B cells. Digest Dis & Sci 1998; 43(11): 2429-38. ▲
133. Chavan A, Kirchhoff TD, Brabant G, et al. Role of the intra-arterial calcium stimulation test in the preoperative localization of insulinomas. Eur Rad 2000; 10(10): 1582-6. ▲
134. Brown CK, Bartlett DL, Doppman JL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. Surgery 1997; 122(6): 1189-93. ▲
135. Boukhman mp, Karam JM, Shaver J, Siperstein AE, et al. Localization of insulinomas. Arch Surg 1999; 134: 818-23. ▲
136. Vinik AI, Delbridge L, Moattari R, et al. Transhepatic portal vein catheterization for localization of insulinomas: a ten-year experience. Surgery 1991; 109(1): 1-11; discussion 111. ▲
137. Dunnick NR, Long JA, Krudy A. Localizing insulinomas with combined radiographic methods. Am J Roentgenol 1980; 135: 747-52. ▲
138. Fulton RE, Sheedy PT, McIlrath DC. Preoperative angiographic localization of insulin-producing tumors of the pancreas. Am J Roentgenol 1975; 123: 367-77. ▲
139. Pasieka JL, McLeod MK, Thompson NW, et al. Surgical approach to insulinomas:

assessing the need for preoperative localization. Arch Surg 1992; 127: 442-447. ▲
140. Brown CK, Bartlett DL, Doppman JL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. Surgery 1997; 122(6): 1189-93. ▲
141. Grant CS, vanHeerden JA, Charboneau JW, et al. Insulinoma: the value of intraoperative ultrasonography. Arch Surg 1988; 123: 843-48. ▲
142. Boukhman mp, Karam JM, Shaver J, Siperstein AE, et al. Localization of insulinomas. Arch Surg 1999; 134: 818-23. ▲
143. Brown CK, Bartlett DL, Doppman JL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. Surgery 1997; 122(6): 1189-93. ▲
144. Moore NR, Rogers CE, and Britton BJ. Magnetic resonance imaging of endocrine tumours of the pancreas. Br J Rad 1995; 68(808): 341-7. ▲
145. Brown CK, Bartlett DL, Doppman JL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. Surgery 1997; 122(6): 1189-93. ▲
146. Ardengh HC, Rosenbaum P, Ganc AJ, et al. Role of EUS in the preoperative localization of insulinomas compared with spiral CT. Gastro Endo 2000; 51(5): 552-5. ▲
147. Boukhman mp, Karam JM, Shaver J, Siperstein AE, et al. Localization of insulinomas. Arch Surg 1999; 134: 818-23. ▲
148. Brown CK, Bartlett DL, Doppman JL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. Surgery 1997; 122(6): 1189-93. ▲
149. Rothmund M, Angelini L, Brunt LM, et al. Surgery for benign insulinoma: an international review. World J Surg 1990; 14: 393-99. ▲
150. Norton JA, Shawker TH, Doppman JL, et al. Localization and surgical treatment of occult insulinomas. Ann Surg 1990; 212(5): 615-20. ▲
151. Grant CS, vanHeerden JA, Charboneau JW, et al. Insulinoma: the value of intraoperative ultrasonography. Arch Surg 1988; 123: 843-48. ▲
152. Schumacker B, Lubke HJ, Frieling T, et al. Prospective study on the detection of insulinomas by endoscopic ultrasonography. Endoscopy 1996; 28(3): 273-6. ▲
153. Angelini L, Bezzi M, Tucci G, et al. The ultrasonic detection of insulinomas during surgical exploration of the pancreas. World J Surg 1987; 11: 642-647. ▲
154. Grant CS. Surgical aspects of hyperinsulinemic hypoglycemia. Endo & Metab Clin N Am 1999; 28(3): 533-54. ▲
155. Phan GQ, Yeo CJ, Cameron JL, et al. Pancreaticoduodenectomy for selected periampullary neuroendocrine tumors: fifty patients. Surgery 1997; 122(6): 989-96. ▲
156. Doherty GM, Doppman JL, Shawker TH, et al. Results of a prospective strategy to diagnose, localize and resect insulinomas. Surgery 1991; 110: 989-997. ▲
157. Menegaux F, Schmitt G, Mercadier M, et al. Pancreatic insulinomas. Am J Surg 1992; 165: 243-48. ▲
158. Boukhman mp, Karam JM, Shaver J, Siperstein AE, et al. Localization of insulinomas. Arch Surg 1999; 134: 818-23. ▲
159. Rothmund M, Angelini L, Brunt LM, et al. Surgery for benign insulinoma: an international review. World J Surg 1990; 14: 393-99. ▲
160. Hirshberg B, Libutti SK, Alexander HR, et al. J Am Coll Surg 2002. Blind distal

pancreatectomy for occult insulinoma, an inadvisable procedure; 194(6): 761-4. ▲
161. Thompson GB, Service FJ, vanHeerden JA, et al. Reoperative insulinomas, 1927-1992: an institutional experience. Surgery 1993; 114: 1196-1206. ▲
162. Thompson GB, Service FJ, vanHeerden JA, et al. Reoperative insulinomas, 1927-1992: an institutional experience. Surgery 1993; 114: 1196-1206. ▲
163. Thompson GB, Service FJ, vanHeerden JA, et al. Reoperative insulinomas, 1927-1992: an institutional experience. Surgery 1993; 114: 1196-1206. ▲
164. Doherty GM, Doppman JL, Shawker TH, et al. Results of a prospective strategy to diagnose, localize and resect insulinomas. Surgery 1991; 110: 989-997. ▲
165. Menegaux F, Schmitt G, Mercadier M, et al. Pancreatic insulinomas. Am J Surg 1992; 165: 243-48. ▲
166. Angelini L, Bezzi M, Tucci G, et al. The ultrasonic detection of insulinomas during surgical exploration of the pancreas. World J Surg 1987; 11: 642-647. ▲
167. Shawker TH, Norton JA, Oldfield EH. The use of intraoperative ultrasound during cancer surgery. In Important Advances in Oncology. VT Devita, S Hellman, SA Rosenberg, editors. Philadelphia, Lippincott, 1992. ▲
168. Hashimoto LA, Walsh RM. Preoperative localization of insulinomas is not necessary. J Am Col Surg 1999; 189(4): 368-73. ▲
169. Demeure MJ, Klonoff DC, Karam JH, et al. Insulinomas associated with multiple endocrine neoplasia type I: the need for a different surgical approach. Surgery 1991; 110(6): 998-1004. ▲
170. Lo CY, Lam KY, Fan ST. Surgical strategy for insulinomas in multiple endocrine neoplasia type I. Am J Surg 1998; 175(4): 305-7. ▲
171. Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc 1991; 66: 711-19. ▲
172. Creutzfeldt W, Arnold R, Creutzfeldt C, et al. Biochemical and morphological investigations of 30 human insulinomas. Diabetologica 1973; 9: 217-31. ▲
173. Danforth DN Jr, Gorden P, Brennan MF. Metastatic insulin-secreting carcinoma of the pancreas: clinical course and the role of surgery. Surgery 1984; 96: 1027-36. ▲
174. Kahn RC, Rosen SW, Weintraub BD, et al. Ectopic production of chorionic gonaditropin and its subunits by islet-cell tumors: a specific marker for malignancy. N Engl J Med 1977; 297: 565-69. ▲
175. Pasieka JL, McLeod MK, Thompson NW, et al. Surgical approach to insulinomas: assessing the need for preoperative localization. Arch Surg 1992; 127: 442-447. ▲
176. Doherty GM, Doppman JL, Shawker TH, et al. Results of a prospective strategy to diagnose, localize and resect insulinomas. Surgery 1991; 110: 989-997. ▲
177. Chung DC, Smith AP, Louis DN, et al. A novel pancreatic endocrine tumor suppressor gene locus on chromosome 3p with clinical prognostic implications. J Clin Invest 1997; 100: 404-10. ▲
178. Kahn RC, Rosen SW, Weintraub BD, et al. Ectopic production of chorionic gonaditropin and its subunits by islet-cell tumors: a specific marker for malignancy. N Engl J Med 1977; 297: 565-69. ▲
179. Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc 1991; 66: 711-19 ▲

180. Lo CY, vanHeerden JA, Thompson GB, et al. Islet cell carcinoma of the pancreas. World J Surg 1996; 20(7): 878-83. ▲
181. McEntee GP, Nagorney DM, Kvols LK, et al. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery 1990; 108: 1091-96. ▲
182. Que FG, Nagorney DM, Batts KP, et al. Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 1995; 169: 36-43. ▲
183. Chen H, Hardacre JM, Uzar A, et al. Isolated liver metastases from neuroendocrine tumors: does resection prolong survival? J Am Col Surg 1998; 187(1): 88-92. ▲
184. Berber E, Flesher N, Siperstein AE. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases. World J Surg 2002; 26(8): 985-90. ▲
185. Moertel CG, Lefkopoulo M, Lipsitz S. Streptozocin-doxorubicin, streptozocin-fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 1992; 326: 519-23. ▲
186. Fajans SS, Floyd JC Jr, Thiffault CA. Further studies on diazoxide suppression of insulin release from abnormal and normal islet tissue in man. Ann NY Acad Sci 1968; 150: 261-80. ▲
187. Goode PN, Farndon JR, Anderson J, et al. Diazoxide in the management of patients with insulinoma. World J Surg 1986; 10: 586-92. ▲
188. Goode PN, Farndon JR, Anderson J, et al. Diazoxide in the management of patients with insulinoma. World J Surg 1986; 10: 586-92. ▲
189. Witteles RM, Straus FH, Sugg SL, et al. Adult-Onset Nesidioblastosis Causing Hypoglycemia: An Important Clinical Entity and Continuing Treatment Dilemma. Arch Surg 2001; 136(6): 656-663. ▲
190. Fajans SS, Vinik AI. Insulin-producing islet cell tumors. Endocrinol Metab Clin North Am 1989; 18: 45-74. ▲
191. Moore TJ, Peterson LM, Harrington DP, et al. Successful arterial embolization of an insulinoma. JAMA 1982; 248: 1353-57. ▲
192. Uflacker R. Arterial embolization as definitive treatment for benign insulinoma of the pancreas. J Vasc Interv Radiol 1992; 3(4): 639-44. ▲