

Review Article

Adult onset nesidioblastosis after gastric bypass surgery, a clinical and pathologic review

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Abstract: Despite the many benefits of bariatric surgery in patients with morbid obesity, concerns have been raised over its association with severe hyperinsulinemic hypoglycemia and nesidioblastosis following Roux-en-Y gastric bypass surgery. Cases have been described with severe post-prandial hypoglycemia with neurological symptoms following surgery. Some of these cases are recalcitrant to medical treatment and may require partial pancreatectomy. Histological examination of the resected pancreas specimens shows features of adult nesidioblastosis characterized by hyperplasia of islets of Langerhans and beta cell hyperplasia and hypertrophy. Although the underlying mechanisms of gastric bypass-associated nesidioblastosis and hypoglycemia are still not fully understood, the exaggerated gut hormone response to altered nutrient flow in Roux-en-Y gastric bypass may be the cause of nesidioblastosis, hyperinsulinemia, hypoglycemia, and relevant neurological symptoms. We summarize the clinical and pathological features of adult nesidioblastosis following the Roux-en-Y gastric bypass procedure. The underlying mechanisms of post gastric bypass-associated hypoglycemia and nesidioblastosis are also discussed in this review.

Keywords: Gastric bypass, hyperinsulinemic hypoglycemia, nesidioblastosis, pancreas

Introduction

The most common cause of persistent hyperinsulinemic hypoglycemia is insulinoma in adults or nesidioblastosis in infants [1-4]. Nesidioblastosis is a pathological term describing the neof ormation of islets of Langerhans and pancreatic beta cell hyperplasia with a clinical presentation of persistent hyperinsulinemic hypoglycemia [4]. Histologically, it is characterized by enlargement of islets of Langerhans, insulin-producing islet cell hyperplasia, and islet cell neogenesis from stem cells adjacent to the pancreatic ducts [4]. It was generally believed that nesidioblastosis affects predominantly infants and children. However this entity has recently been described in adult populations in the literature, specifically in the post Roux-en-Y gastric bypass patients.

In infants, nesidioblastosis presents with recurrent episodes of profound hypoglycemia, which can lead to severe brain damage if not treated adequately. It is a clinically, pathologically, and

genetically heterogeneous entity [1-4]. Most commonly, it is sporadic with no known genetic abnormalities. Familial cases are rare and are most commonly seen in Ashkenazi Jews with an autosomal recessive inheritance pattern [2, 4]. Currently, at least 8 genes have been identified to be associated with congenital nesidioblastosis including ABCC8, KCNJ11, GCK, GLUD1, HADH, SLC16A1, HNF4A, and UCP2 genes [2-4]. In contrast, the adult onset nesidioblastosis with pancreatic beta cell hypertrophy is extremely rare and was first described by Harness *et al.* in 1981 [5, 6]. Subsequently, it has been reported in association with other conditions such as Zollinger-Ellison syndrome, multiple endocrine adenomatosis, cystic fibrosis, and familial adenomatous polyposis as described in a review by Jabri and Bayard [7]. In 2005, Service *et al.* described 6 patients who developed severe hypoglycemia after Roux-en-Y gastric bypass surgery [8]. Since then, more cases of hyperinsulinemic hypoglycemia and nesidioblastosis have been reported in the patients who received Roux-en-Y gastric bypass

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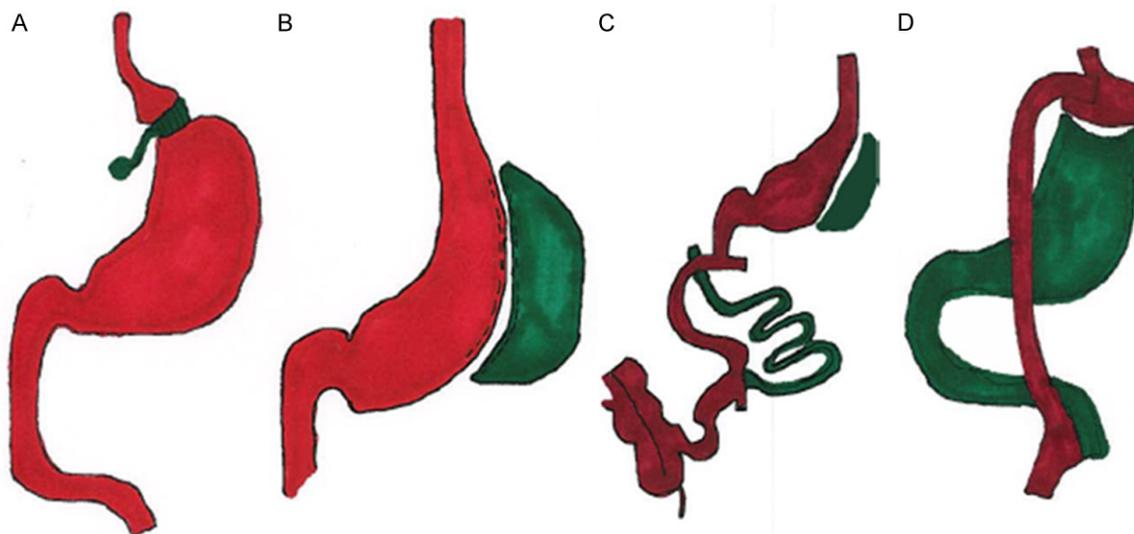


Figure 1. Diagram of different type bariatric surgery. A: Adjustable Gastric Band; B: Vertical Sleeve Gastrectomy; C: Biliopancreatic Diversion with Duodenal Switch; D: Roux-en-Y Gastric Bypass.

procedure for morbid obesity. In this article, we attempt to conduct a comprehensive review on the adult form of nesidioblastosis including its clinical and pathological features, pathophysiological mechanisms, and its clinical and surgical management.

Hyperinsulinemic hypoglycemia following the Roux-en-Y gastric bypass

Obesity is a major health issue in the United States. It is associated with high risks for metabolic syndrome, type II diabetes mellitus, cardiovascular diseases, and malignant tumors such as colorectal cancer. Numerous strategies such as changes in life-style and diet have been introduced to prevent obesity with a goal to decrease obesity-associated morbidity and mortality. Surgery is considered as a treatment option when patients have a very high body mass index (BMI, great than 40 kg/m²) or with obesity-related serious health issues such as hypertension, type II diabetes mellitus, hyperlipidemia, and obstructive sleep apnea. Bariatric surgical procedures result in weight loss by decreasing gastric volume, altering gastrointestinal absorption capacity, or by their combination. The commonly performed bariatric procedures are adjustable gastric band, sleeve gastrectomy, biliopancreatic diversion with duodenal switch, Roux-en-Y, gastric bypass with Roux-en-Y gastric bypass remaining the most popular among them (**Figure 1**).

The adjustable gastric band procedure decreases food intake and subsequently results in weight loss by placing a small bracelet-like band around the top of the stomach to limit the opening from the esophagus to the stomach. Vertical sleeve gastrectomy is a procedure which is performed to decrease food intake by removing a large portion of stomach. Biliopancreatic diversion with duodenal switch is a procedure that works by creating a tubular stomach pouch similar to the sleeve gastrectomy, and then bypassing a large portion of the small intestine. This alters the normal nutrient absorption process. The Roux-en-Y gastric bypass procedure diverts food directly from the gastric pouch to the small intestine. Therefore, the food is processed in a non-physiological way because the majority of the stomach, duodenum, and upper intestine are no longer involved (**Figure 1**). As with any major surgery, bariatric surgery poses several potential long and short term complications. One of these complications is severe hypoglycemia, which may not respond to medication, and lead to a partial or complete removal of the pancreas in order to prevent dangerous insulin-induced declines in blood glucose. This is defined as adult onset hyperinsulinemic hypoglycemia. As discussed in the next section, it is generally believed that the exaggerated gut hormone in response to altered nutrient flow may be the cause of nesidioblastosis, hyperinsulinemia, hypoglycemia, and relevant neurological symp-

toms. This theory is indeed supported by the clinical observation that nesidioblastosis and hypoglycemia is more commonly associated with Roux-en-Y gastric bypass, whereas it had never been described in patients with the adjustable gastric band procedure. It is reasonably speculated that nesidioblastosis and hypoglycemia is also associated with Biliopancreatic Diversion with Duodenal Switch although data is sparse in literature if there is any. The pancreas in these patients often demonstrates nesidioblastosis similar to that seen in the infant onset counterpart. However, unlike the beta cell hyperplasia seen in the infant nesidioblastosis, the adult onset form is not associated with any gene mutation. The exact incidence of hyperinsulinemic hypoglycemia following the Roux-en-Y gastric bypass is still unclear. A Swedish nationwide cohort study based on national registries with 5040 patients who underwent gastric bypass or vertical banded gastroplasty revealed that the prevalence of significant hypoglycemia and syncope after gastric bypass surgery is less than 1% [9]. Another study conducted at University of Washington indicated that the absolute risk for severe hypoglycemia was relatively low, with approximately 0.2% in post-gastric bypass patients [10]. However, these cohort studies may underestimate the problem as a whole, because less severe patients were likely ignored.

Episodes of hypoglycemia after bypass surgery are commonly seen between 2 to 4 years after the procedure. These patients often experience repeated episodes of postprandial hyperinsulinemic hypoglycemia with neuroglycopenic symptoms including cold sweats, chills, hypotension, altered mental status, loss of consciousness, and seizures [10-14]. Laboratory findings include low blood glucose, high insulin level, and high serum C-reactive protein concentration in serum [10-14]. The characteristic pathological finding of resected pancreas specimens is pancreatic islet hyperplasia, consistent of nesidioblastosis [15-18]. It appears that the severity of postprandial hypoglycemia is variable [10]. At one end of the spectrum, there are relatively mild cases with mild hypoglycemia and lack of neurological symptoms. These patients could be managed by dietary modification [10]. In contrast, the severe refractory form is rare, but requires hospitalization due to neuroglycopenic symptoms [10].

Mechanisms of hyperinsulinemic hypoglycemia and nesidioblastosis after Roux-en-Y gastric bypass

The Roux-en-Y gastric bypass surgery is superior to other bariatric surgical procedures to achieve weight loss by rearranging the gastrointestinal tract [10]. The nutrients bypass a large part of the stomach and duodenum and directly enter the jejunum. This procedure alters the gastrointestinal physiology by alternation of bile flow, vagal manipulation, gastrointestinal hormone secretion such as glucagon-like peptide-1 (GLP-1), Ghrelin, and insulin-like growth factors. GLP-1 is a neuropeptide derived from the transcription product of the proglucagon gene. The major source of GLP-1 is the intestinal L cell that secretes GLP-1 as a gut hormone [19]. L cells are primarily found in the ileum and large intestine, but some are also found in the duodenum and jejunum. GLP-1 secretion by ileal L cells is dependent on the presence of nutrients in the lumen of the small intestine [19]. The major nutrients like carbohydrate, protein and lipid are the agents stimulating GLP-1 secretion [19]. Counterintuitively, unlike glucagon which increases blood sugar level by converting glycogen to glucose, GLP-1 can bind to beta cells and function as a potent antihyperglycemic hormone through glucose-dependent stimulation of insulin secretion and glucagon suppression [10, 19-21]. The Roux-en-Y gastric bypass surgery diverts the nutrients directly into the small intestine, which leads to a marked non-physiological increase in GLP-1 release following food intake [10, 19, 20]. The increased GLP-1 hormone level in Roux-en-Y gastric bypass patients stimulates insulin secretion by enhancing glucose sensitivity of pancreatic β -cells and increasing expression of GLUT2 and glucokinase on islet beta cells [10, 19, 20]. GLP-1 is also known to inhibit pancreatic β -cell apoptosis and stimulate the proliferation and differentiation of insulin-secreting β -cells. Furthermore, GLP-1 has been shown to induce expression of the transcription factor pancreatic-duodenum homeobox-1 (PDX-1), which promotes growth of the islets of Langerhans [22]. The pancreas in the patients with nesidioblastosis secondary to the Roux-en-Y gastric bypass shows increased expression of PDX-1 in beta cells [23]. These changes well correlated with the elevated serum GLP-1 level. Another important hormone that might be

Nesidioblastosis after gastric bypass

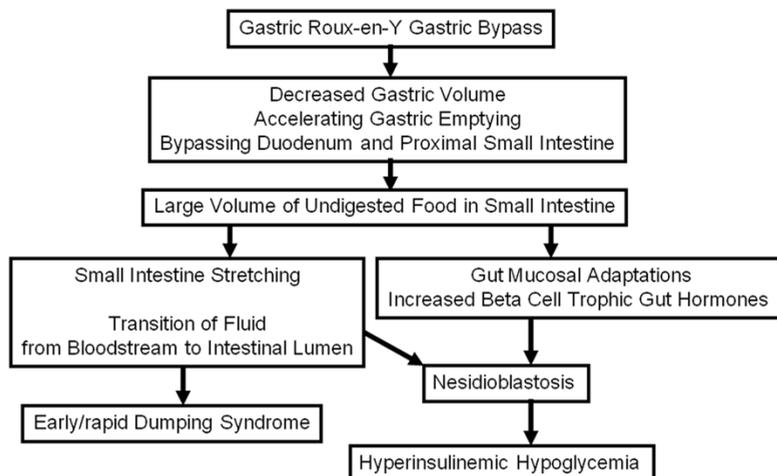


Figure 2. Schematic of mechanisms leading to nesidioblastosis and hypoglycemia in post Roux-en-Y gastric bypass patients.

involved in hyperinsulinemia in post gastric bypass patients is insulin-like growth factor I (IGF-1). IGF-1 is a growth hormone functionally and structurally similar to insulin. The major physiological functions of IGF-1 are to stimulate expression of glucose transporters, and enhance insulin sensitivity of skeletal muscle and adipose tissue, thus regulating insulin-dependent glucose control. Interestingly, it has been shown that IGF-1 receptors are overexpressed in pancreatic islets in nesidioblastosis [15, 24]. A recent study by Itariu *et al.* demonstrated that serum IGF-1 concentration in the gastric-bypass-associated hypoglycemic patients was significantly higher than those patients without hypoglycemia [24]. These findings provide support for the possibility that beta-cell trophic factors might be responsible for the growth of pancreatic beta cells and consequent hyperfunction of islets, ultimately culminating in post-prandial hypoglycemia.

Gastric dumping syndrome is common after gastric bypass surgery. This is a condition due to rapid gastric emptying, where foods pass the stomach too rapidly and enter the small intestine remaining largely undigested. An early dumping phase may happen approximately 30 to 60 minutes after food intake. Symptoms of the early phase dumping syndrome happen because the food is rapidly “dumping” into the small intestine. This results in the small intestines stretching and in circulatory hypovolemia due to transition of fluid from bloodstream into the small intestine. In contrast, the late onset

dumping syndrome happens 1 to 3 hours after eating. Symptoms may include weakness, flushing, sweating, dizziness, fainting, loss of concentration, and mental confusion [10, 11]. The symptoms of this so-called late onset dumping syndrome probably represent a hypoglycemic status due to hormonal alternations as described above [10, 11]. Overall, it is generally agreed that inappropriately released growth factors and altered gut hormones are major mediators of nesidioblastosis and hyperinsulinemic hypoglycemia in the Roux-en-Y gastric bypass patients (Figure 2).

Histological findings of the adult onset nesidioblastosis after Roux-en-Y gastric bypass

The endocrine component of the pancreas is a complex structural-functional unit including the islets of Langerhans and scattered neuroendocrine cells [25]. Pancreatic endocrine cells are derived from stem cells of the foregut endoderm within the terminal pancreatic ductal system. The islets of Langerhans in infants are well formed and predominantly located in the center of pancreatic lobular units surrounded by acinar cells. Normal islets of Langerhans in infants measure 75-95 micrometers in diameter with a non-uniform three dimensional configuration [25]. In adults, most of the islets range from 50 to 250 micrometers with a mean value of approximately 140 micrometers. Islet cell neogenesis from ductal stem cells represents an important mechanism for beta cell growth and regeneration. During early development, islets have been shown to be in close contact with ductal epithelium, which separate with age. Nevertheless, even in adults it is not difficult to identify a close duct-islet arrangement in normal pancreas [25].

Nesidioblastosis was first described by Laidlaw in 1938 [26]. In the absence of gastrointestinal surgery, nesidioblastosis is very rare in adults. As mentioned earlier, the mechanisms that cause acquired adult nesidioblastosis after gastric bypass are likely adaptive responses to

Nesidioblastosis after gastric bypass

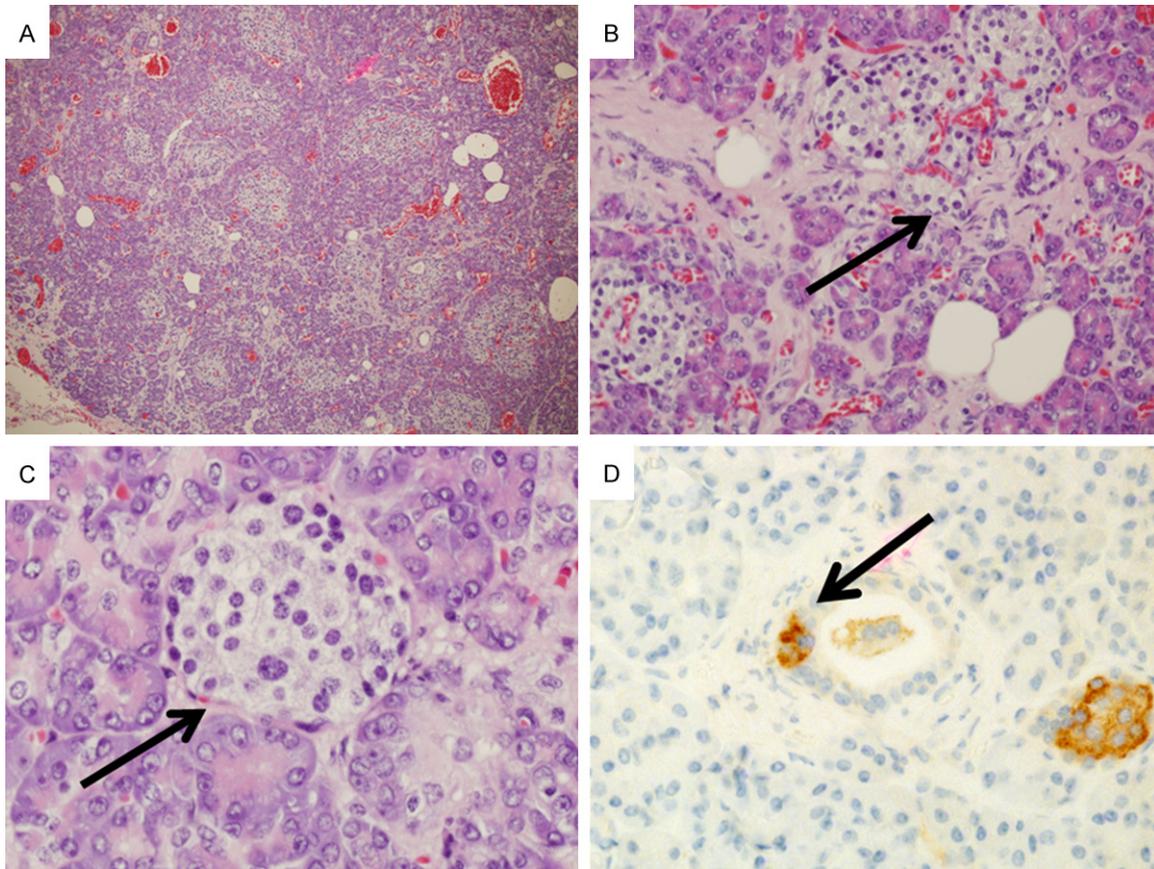


Figure 3. Histological features of nesidioblastosis: A: Increased density of Islets of Langerhans with variation in size and shape. B: The ductuloinsular complexes; C: Islet cell hypertrophy with enlarged and hyperchromatic nuclei and clear cytoplasm; D: Immunohistochemical stain for insulin highlighting a ductuloinsular complex.

altered gut hormonal signaling and late onset dumping syndrome, which lead to beta cell neof ormation, hyperplasia and hypertrophy. The confirmative diagnosis of the adult form nesidioblastosis remains very challenging despite the improvement of morphological and functional imaging techniques. Histologically, nesidioblastosis is mainly characterized by enlarged size of islets of Langerhans [15-18, 27, 28]. The islets often demonstrate a lobulated and irregular contour with variation in size (**Figure 3A**). New islet cells derived from stem cell differentiation can be easily identified by the clusters of neuroendocrine cells along terminal pancreatic ducts, which have been defined as ductuloinsular complexes (**Figure 3B**). Other histological features supporting the diagnosis of nesidioblastosis include focally increased density of islets of Langerhans (**Figure 3A**), and poorly defined endocrine cell clusters scattered in the acinar parenchyma [27, 28]. Adult onset nesidioblastosis also

shows distinct islet cell hypertrophy with enlarged and hyperchromatic nuclei and clear cytoplasm (**Figure 3C**). The above mentioned ductuloinsular complexes can be easily highlighted by immunohistochemistry that shows insulin-positive cell budding off the ductal epithelium [16] (**Figure 3D**). Rumilla *et al.* measured islet growth factor expression in nesidioblastosis in post gastric bypass patients and revealed an increase in expression of insulin-like growth factor 1 receptor, insulin-like growth factor 2, and transforming growth factor-beta receptor [15]. Rumilla and colleagues speculated that these growth factors and their receptors participate in the development of nesidioblastosis because these factors have been implicated in beta cell proliferation in animal and human studies [23, 24]. The published criteria for diagnosis of the adult nesidioblastosis include both major and minor criteria [28]. The major criteria include (1) exclusion of an insulinoma, (2) multiple beta cells with enlarged

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hyperchromatic nuclei and clear cytoplasm, (3) islets showing normal spatial distribution of the various cell types, and (4) endocrine cells without proliferative activity. Minor criteria include (1) enlarged islets, (2) increased numbers of islets, (3) lobulated islet structure, and (4) macronucleoli in β cells. The major criteria are present in each case and are essential for the diagnosis, whereas minor criteria are present in some but not all cases. However, it is worth emphasizing that variable findings in nesidioblastosis are common, and in fact, up to one third of cases may show only minimal changes. Furthermore, none of the histological features described above are specific for nesidioblastosis. These histological features could occasionally be seen in the normal pancreas. For example, it is not uncommon to see ductuloinsular complexes in normal pancreas. The islets of Langerhans with a diameter of larger than 250 micrometers might occasionally present in the normal pancreas based on our observation. We believe that a clinical and pathological correlation is critical to render the diagnosis of adult onset nesidioblastosis. For surgical pathology gross processing of resected pancreatic specimens, it is critical to rule out the possibility of insulinoma since clinical presentation of insulinoma is similar to nesidioblastosis [17]. The resected pancreas should be carefully examined macroscopically with thin slices. Tissue should be submitted entirely for microscopic examination to rule out insulinoma.

Nesidioblastosis is classified into focal and diffuse types characterized by different clinical outcomes [29, 30]. Focal nesidioblastosis exhibits nodular hyperplasia of islet like cell clusters, including ductuloinsular complexes and hypertrophied beta cells with giant nuclei [29]. In contrast, diffuse nesidioblastosis involves the entire pancreas with irregularly sized islets [30]. The variety of islet pathology reported after gastric bypass suggests the presence of a spectrum of changes from initial hyperplasia to subsequent nesidioblastosis to neoplasia, which can be induced in some patients.

Clinical management of hypoglycemia and nesidioblastosis in post gastric bypass patients

Because of the paucity of the experience with these patients, there is no current standard treatment recommendation for adult nesidio-

blastosis. The most common treatment begins with a modified low-carbohydrate diet [31]. When dietary alterations fail, consideration should be given to a trial of the beta-cell inhibitors, the secretory inhibitor (somatostatin analogues), alpha-glucosidase inhibitors (such as acarbose), or calcium-channel blockers [32]. Pancreatic resection has been advocated for the patients with refractory hypoglycemia due to the life-threatening risk of severe neuroglycopenia [8, 33, 34]. The extent of pancreatic resection requires maintaining a delicate balance between the need to adequately debulk the hyperplastic islets and preserving enough β -cell volume to prevent diabetes. These resections often remove 70% to 80% of the total pancreatic volume [27, 35]. In spite of the often large extent of pancreatic resection, many of these patients experience recurrent hypoglycemia, and some require reoperation to remove more tissue [33].

In summary, the adult onset nesidioblastosis is rare and most commonly seen in patients who received the Roux-en-Y gastric bypass procedure. The gut hormone secretion is increased in these patients due to abnormal nutrients bypassing a large portion of stomach and duodenum. Long standing beta cell trophic effects of increased gut hormones result in nesidioblastosis and hypoglycemia.

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