target tissues. The tumors are usually apparent clinically, plasma ratios of IGF-II to IGF-I are high, and free IGF-II levels (and levels of pro-IGF-II [1–21]) are elevated. Curative surgery is seldom possible, but reduction of tumor bulk may ameliorate hypoglycemia. Therapy with a glucocorticoid, a growth hormone, or both has also been reported to alleviate hypoglycemia. Hypoglycemia attributed to ectopic IGF-I production has been reported but is rare.

Endogenous Hyperinsulinism Hypoglycemia due to endogenous hyperinsulinism can be caused by (1) a primary β-cell disorder—typically a β-cell tumor (*insulinoma*), sometimes multiple insulinomas, or a functional β-cell disorder with β-cell hypertrophy or hyperplasia; (2) an antibody to insulin or to the insulin receptor; (3) a β-cell secretagogue such as a sulfonylurea; or perhaps (4) ectopic insulin secretion, among other very rare mechanisms. None of these causes is common.

The fundamental pathophysiologic feature of endogenous hyperinsulinism caused by a primary β-cell disorder or an insulin secretagogue is the failure of insulin secretion to fall to very low levels during hypoglycemia. This feature is assessed by measurement of plasma insulin, C-peptide (the connecting peptide that is cleaved from proinsulin to produce insulin), proinsulin, and glucose concentrations during hypoglycemia. Insulin, C-peptide, and proinsulin levels need not be high relative to normal, euglycemic values; rather, they are inappropriately high in the setting of a low plasma glucose concentration. Critical diagnostic findings are a plasma insulin concentration ≥3 μU/mL (≥18 pmol/L), a plasma C-peptide concentration ≥0.6 ng/mL (≥0.2 nmol/L), and a plasma proinsulin concentration ≥5.0 pmol/L when the plasma glucose concentration is <55 mg/dL (<3.0 mmol/L) with symptoms of hypoglycemia. A low plasma β-hydroxybutyrate concentration (≤2.7 mmol/L) and an increment in plasma glucose level of >25 mg/dL (>1.4 mmol/L) after IV administration of glucagon (1.0 mg) indicate increased insulin (or IGF) actions.

The diagnostic strategy is (1) to measure plasma glucose, insulin, C-peptide, proinsulin, and β-hydroxybutyrate concentrations and to screen for circulating oral hypoglycemic agents during an episode of hypoglycemia and (2) to assess symptoms during the episode and seek their resolution following correction of hypoglycemia by IV injection of glucagon (i.e., to document Whipple's triad). This is straightforward if the patient is hypoglycemic when seen. Since endogenous hyperinsulinemic disorders usually, but not invariably, cause fasting hypoglycemia, a diagnostic episode may develop after a relatively short outpatient fast. Serial sampling during an inpatient diagnostic fast of up to 72 h or after a mixed meal is more problematic. An alternative is to give patients a detailed list of the required measurements and ask them to present to an emergency room, with the list, during a symptomatic episode. Obviously, a normal plasma glucose concentration during a symptomatic episode indicates that the symptoms are not the result of hypoglycemia.

An *insulinoma*—an insulin-secreting pancreatic islet β-cell tumor—is the prototypical cause of endogenous hyperinsulinism and therefore should be sought in patients with a compatible clinical syndrome. However, insulinoma is not the only cause of endogenous hyperinsulinism. Some patients with fasting endogenous hyperinsulinemic hypoglycemia have diffuse islet involvement with β-cell hypertrophy and sometimes hyperplasia. This pattern is commonly referred to as *nesidioblastosis*, although β-cells budding from ducts are not invariably found. Other patients have a similar islet pattern but with postprandial hypoglycemia, a disorder termed *noninsulinoma pancreatogenous hypoglycemia*. Postgastric bypass postprandial hypoglycemia, which most often follows Roux-en-Y gastric bypass, is also characterized by diffuse islet involvement and endogenous hyperinsulinism. Some have suggested that exaggerated GLP-1 responses to meals cause hyperinsulinemia and hypoglycemia, but the relevant pathogenesis has not been clearly established. If medical treatments with agents such as an α-glucosidase inhibitor, diazoxide, or octreotide fail, partial pancreatectomy may be required. Autoimmune hypoglycemias include those caused by an antibody to insulin that binds post-meal insulin and then gradually disassociates, with consequent late postprandial hypoglycemia. Alternatively, an insulin receptor antibody can function as an agonist. The presence of an insulin secretagogue, such as a sulfonylurea or a glinide, results in a clinical and biochemical pattern similar to that of an insulinoma but can be distinguished by the presence of the circulating secretagogue. Finally, there are reports of very rare phenomena such as ectopic insulin secretion, a gain-of-function insulin receptor mutation, and exercise-induced hyperinsulinemia.

Insulinomas are uncommon, with an estimated yearly incidence of 1 in 250, 000. Because more than 90% of insulinomas are benign, they are a treatable cause of potentially fatal hypoglycemia. The median age at presentation is 50 years in sporadic cases, but the tumor usually presents in the third decade when it is a component of multiple endocrine neoplasia type 1 (Chap. 408). More than 99% of insulinomas are within the substance of the pancreas, and the tumors are usually small (<2.0 cm in diameter in 90% of cases). Therefore, they come to clinical attention because of hypoglycemia rather than mass effects. CT or MRI detects ~70–80% of insulinomas. These methods detect metastases in the roughly 10% of patients with a malignant insulinoma. Transabdominal ultrasound often identifies insulinomas, and endoscopic ultrasound has a sensitivity of ~90%. Somatostatin receptor scintigraphy is thought to detect insulinomas in about half of patients. Selective pancreatic arterial calcium injections, with the endpoint of a sharp increase in hepatic venous insulin levels, regionalize insulinomas with high sensitivity, but this invasive procedure is seldom necessary except to confirm endogenous hyperinsulinism in the diffuse islet disorders. Intraoperative pancreatic ultrasonography almost invariably localizes insulinomas that are not readily palpable by the surgeon. Surgical resection of a solitary insulinoma is generally curative. Diazoxide, which inhibits insulin secretion, or the somatostatin analogue octreotide can be used to treat hypoglycemia in patients with unresectable tumors; everolimus, an mTOR (mammalian target of rapamycin) inhibitor, is promising.

ACCIDENTAL, SURREPTITIOUS, OR MALICIOUS HYPOGLYCEMIA

Accidental ingestion of an insulin secretagogue (e.g., as the result of a pharmacy or other medical error) or even accidental administration of insulin can occur. Factitious hypoglycemia, caused by surreptitious or even malicious administration of insulin or an insulin secretagogue, shares many clinical and laboratory features with insulinoma. It is most common among health care workers, patients with diabetes or their relatives, and people with a history of other factitious illnesses. However, it should be considered in all patients being evaluated for hypoglycemia of obscure cause. Ingestion of an insulin secretagogue causes hypoglycemia with increased C-peptide levels, whereas exogenous insulin causes hypoglycemia with low C-peptide levels reflecting suppression of insulin secretion.

Analytical error in the measurement of plasma glucose concentrations is rare. On the other hand, glucose monitors used to guide treatment of diabetes are not quantitative instruments, particularly at low glucose levels, and should not be used for the definitive diagnosis of hypoglycemia. Even with a quantitative method, low measured glucose concentrations can be artifactual—e.g., the result of continued glucose metabolism by the formed elements of the blood ex vivo, particularly in the presence of leukocytosis, erythrocytosis, or thrombocytosis or with delayed separation of the serum from the formed elements (pseudohypoglycemia).

INBORN ERRORS OF METABOLISM CAUSING HYPOGLYCEMIA

Nondiabetic hypoglycemia also results from inborn errors of metabolism. Such hypoglycemia most commonly occurs in infancy but can also occur in adulthood. Cases in adults can be classified into those resulting in fasting hypoglycemia, postprandial hypoglycemia, and exercise-induced hypoglycemia.

Fasting Hypoglycemia Although rare, disorders of glycogenolysis can result in fasting hypoglycemia. These disorders include glycogen storage disease (GSD) of types 0, I, III, and IV and Fanconi-Bickel syndrome (Chap. 433e). Patients with GSD types I and III characteristically have high blood lactate levels before and after meals, respectively. Both groups have hypertriglyceridemia, but ketones are high in GSD type III. Defects in fatty acid oxidation also result in fasting hypoglycemia. These defects can include (1) defects in the carnitine