Chapter 16
Secondary Causes of Diabetes Mellitus

Yana B. Garger, Prajesh M. Joshi, Ashutosh S. Pareek, Carla M. Romero, Amit K. Seth, and Adrienne M. Fleckman

Introduction

The diabetic syndromes include type 1 diabetes with immune destruction of the pancreatic islets, type 2 diabetes with a complex pathophysiology of insulin resistance combined with insulin secretory failure, distinct monogenetic abnormalities (maturity onset diabetes of the young – MODY), and extreme insulin resistance of several different etiologies. In addition, secondary causes of diabetes mellitus refer to a category in which diabetes is associated with other diseases or conditions. Presumably, the diabetes is caused by those conditions and could be reversed if those conditions were cured.

Secondary causes constitute less than 2% of total cases of diabetes mellitus. Mechanistically they can be considered in the broad categories of decreased insulin secretion, insulin resistance, and increased counter-regulation, although classification schemes are typically anatomical and pathophysiological (Table 16.1).

Decreased insulin secretion is generally seen in pancreatic diabetes following destruction of the endocrine pancreas with loss or impairment of insulin secretion and in somatostatinoma. Liver disease causes insulin resistance via unknown mechanisms. Counter-regulatory hormones balance the glucose-lowering action of insulin. Excess levels of the counter-regulatory hormones glucagon, catecholamines, cortisol, and growth hormone seen with exogenous administration or excess secretion by their respective tumors can elevate the blood glucose level. The pathogenesis of secondary diabetes is sometimes defined to include autoimmune mechanisms and antagonism of insulin action (discussed in other chapters). There are also a variety of infections (congenital rubella, cytomegalovirus) and rare genetic syndromes that are associated with insulin resistance or diabetes mellitus through unknown mechanisms.[1]

Diseases of the Exocrine Pancreas

Acute Pancreatitis

Acute inflammation of the pancreas can cause transient glucose elevation.[2] The incidence of abnormal carbohydrate metabolism in acute pancreatitis varies from 8 to 83%.[3] The wide range can be related to the cause of acute inflammation, with alcohol having a more damaging effect on pancreatic tissue and a higher incidence of glucose intolerance.[4] Hyperglycemia has also been correlated with tissue necrosis and a higher mortality.[2,5] The plasma insulin concentration is lower in patients with acute pancreatitis than in healthy control subjects and is associated with impaired insulin secretion in response to glucose or glucagon. Glucagon concentration is usually elevated and tends to remain high for at least 1 week.[6,7] Hyperglycemia usually subsides within weeks of the

A.M. Fleckman (✉)
Department of Medicine, Albert Einstein College of Medicine, Beth Israel Medical Center, New York, NY, USA
e-mail: fleckman@chpnet.org

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Table 16.1 Classification of secondary causes of diabetes mellitus

Diseases of the exocrine pancreas	*Endocrinopathies*
Pancreatectomy	Acromegaly
Acute pancreatitis	Cushing's syndrome
Chronic pancreatitis	Pheochromocytoma
Hemochromatosis	Hyperthyroidism
Carcinoma	Hyperparathyroidism
Cystic fibrosis	Hyperaldosteronism
Abnormalities of the endocrine pancreas and the endocrine gut	*Genetic syndromes*
Glucagonoma	Klinefelter's syndrome
Somatostatinoma	Turner's syndrome
Gastrinoma	Wolfram's syndrome
VIPoma (vasoactive intestinal peptide tumor)	Friedreich's syndrome
Carcinoid syndrome	Huntington's chorea
	Lawrence–Moon–Biedl syndrome
	Myotonic dystrophy
	Porphyria
	Prader–Willi syndrome
Liver disease	
Chronic liver disease and cirrhosis	
Hepatitis C	
Acute hepatitis	

acute attack. However, 24–35% of patients have glucose intolerance and 12% have diabetes mellitus following a single bout of acute pancreatitis.[8]

Chronic Pancreatitis

Chronic pancreatitis is an inflammatory condition that influences both digestive and endocrine function of the pancreas.[9] Although glucose intolerance is frequent in patients with chronic pancreatitis, overt diabetes mellitus usually occurs late in the course of the disease. Patients with chronic calcifying pancreatitis are at higher risk (60–70%) of developing diabetes and glucose intolerance than are patients with non-calcifying disease (15–30%),[10] with both insulin and glucagon secretion disturbed more strongly in calcific than in noncalcific pancreatitis.[11] Diabetes caused by chronic pancreatitis requires insulin therapy because of β-cell destruction, although lack of immunologic destruction may contribute to a slower destruction of the β-cells in chronic pancreatitis than in type 1 diabetes with greater preservation of β-cell function. Concomitant damage to the glucagon-secreting alpha cells results in a high incidence of hypoglycemia, with residual counter-regulation attributable to catecholamine secretion.[12] Despite the requirement for insulin in diabetes mellitus secondary to chronic pancreatitis, glucagon-like peptide 1(7–36) amide (GLP-1), an intestinally derived insulinotropic hormone, may be considered in select patients with preservation of α- and β-cell secretory capacity.[13] Neuropathy and retinopathy occur in increased frequency in these patients, while nephropathy and diabetic ketoacidosis are rare.[14]

Pancreatic Cancer

Impaired glucose tolerance, an early manifestation of pancreatic cancer in over 40%, may occur before the tumor becomes apparent.[15] Pancreatic cancer may be associated with abnormal islet cell function by primary alteration of islet cells by carcinogen, secondary damage by cancer cells,[16] or stimulation of the secretion of islet amyloid polypeptide (IAPP) through an unknown mechanism. IAPP causes cytotoxicity and apoptosis.[17,18] It was found

that pancreatectomy in pancreatic cancer with diabetes mellitus and high level of IAPP is associated with the cure of diabetes and the disappearance of IAPP.[19]

Pancreatectomy

Total pancreatectomy, primarily used for the treatment of pancreatic cancer with large lesions in the head of the pancreas, is associated with a high incidence of glucose intolerance. Pancreatic resections that spare the duodenum, such as distal pancreatectomy, are associated with a lower incidence of new or worsened diabetes than is the standard or pylorus-preserving pancreaticoduodenectomy (Whipple procedure) or total pancreatectomy.

In addition to insulin deficiency, the endocrine abnormalities that accompany pancreatic resection can include pancreatic polypeptide (PP) deficiency with preservation of glucagon production if the resection is proximal or glucagon deficiency if the resection is distal. Glucagon deficiency increases susceptibility to hypoglycemia through loss of counter-regulation, and PP deficiency is considered to impair hepatic insulin action, thereby contributing to hyperglycemia. The resulting hepatic insulin resistance with persistent endogenous glucose production and enhanced peripheral insulin sensitivity results in a brittle form of diabetes, which can be difficult to manage.[20]

Cystic Fibrosis-Related Diabetes (CFRD)

Cystic fibrosis (CF) comprises a clinical triad of abnormalities involving the sweat glands, the exocrine pancreas, and the respiratory epithelium. CFRD, the principal extra-pulmonary complication of cystic fibrosis, occurs in 15–30% of adults with mean age of onset of 18–21 years[21,22] and up to 1% of children with the disease.[23] CFRD is primarily an insulinopenic condition. Early in the course of the disease, the β-cells appear normal. As the disease progresses, insulin secretion is impaired and delayed as a result of β-cell failure secondary to fibrosis, fatty infiltration, and amyloid deposition. Insulin resistance plays only a minor role. CFRD is associated with worsening of nutritional status, increased morbidity, decreased survival, and decrease in pulmonary function in patients with CF.[24] Early treatment with insulin may decrease morbidity.[25]

Pancreatic Infiltrative Diseases

Primary/Secondary Hemochromatosis

Hemochromatosis (bronze diabetes) is a state of iron overload due to either hereditary or secondary (acquired) causes. The acquired causes include transfusional iron overload anemias (thalassemia major, sideroblastic anemia, and chronic hemolytic anemia), chronic liver diseases (hepatitis C, alcoholic liver disease, nonalcoholic fatty liver),[26] and dietary or parenteral iron overload. Deposition of iron in the pancreas causes fibrosis and secondary diabetes in 30–60% of patients with advanced disease. Contributing factors include an inherited predisposition for diabetes mellitus, cirrhosis, and direct damage to the pancreas by deposition of iron.[27]

Although the exact mechanism of iron-induced diabetes is uncertain, iron excess seems to contribute initially to insulin resistance and subsequently to decreased insulin secretion as well as hepatic dysfunction.[28] Pancreatic islets have an extreme susceptibility to oxidative damage from iron-derived free radicals, perhaps because of the reliance on mitochondrial metabolism of glucose for glucose-induced insulin secretion, and low expression of the antioxidant defense system (Table 16.2).[29]

Abnormalities of the Endocrine Pancreas and the Endocrine Gut

β-Cells of the pancreas are responsible for insulin secretion and glucose homeostasis. Abnormalities in the non-β-cells of the pancreas can also be associated with abnormalities in glucose metabolism and cause glucose

Table 16.2 Frequency of diabetes mellitus in pancreatic diseases

Disease	Frequency (%)	Disease	Frequency (%)
Acute pancreatitis	8–83	Partial pancreatectomy	20
Chronic pancreatitis	15	Total pancreatectomy	100
Chronic calcific pancreatitis	60–70	Cystic fibrosis	13
Pancreatic cancer	40	Hemochromatosis	30–60

intolerance or secondary diabetes. Endocrine tumors of the non-β-cells of the pancreas and/or the gut that cause glucose intolerance include the following:

1. Hypersecretion of glucagon (glucagonoma)
2. Hypersecretion of somatostatin (somatostatinoma)
3. VIPoma (vasoactive intestinal peptide tumor)
4. Hypersecretion of gastrin (gastrinoma)
5. Carcinoid syndrome

Glucagonoma

The glucagonoma syndrome is a rare disorder of a glucagon-secreting tumor, with an annual incidence of 0.1 cases per million.[30,31] Presentation is usually in the fifth decade of life, with an even distribution between females and males. The tumors arise almost exclusively in the pancreas and are malignant in behavior, with 50% having metastasized to liver or lymph nodes at the time of diagnosis. Patients develop the "4D syndrome" of *d*iabetes, *d*ermatitis (necrolytic migratory erythema), *d*eep-vein thrombosis, and *d*epression. Hypersecretion of glucagon also produces glucose intolerance in 80% of patients, with or without frank diabetes mellitus.[32] Glucagon is one of the "counter-regulatory" hormones that balance the glucose-lowering action of insulin with actions to raise the circulating glucose levels. Glucagon increases hepatic glucose output via glycogenolysis and gluconeogenesis[33] causing hyperglycemia in the glucagonoma syndrome.

Somatostatinoma

Somatostatinomas are neuroendocrine tumors that usually originate in the pancreas or the intestine. The release of large amounts of somatostatin causes a distinct clinical syndrome characterized by diabetes mellitus, gallbladder disease, diarrhea, and weight loss. The development of diabetes mellitus is likely secondary to the inhibitory action of somatostatin on insulin release as well as replacement of functional pancreatic tissue.[34,35]

VIPoma Syndrome

The VIPoma syndrome is due to a rare pancreatic endocrine tumor that secretes excessive amounts of vasoactive intestinal peptide (VIP). This causes a distinct syndrome of fasting large volume diarrhea, hypokalemia, and hypochlorhydria (due to gastric acid suppression). Hyperglycemia is noted in 25–50% of patients with VIPomas. It has been attributed to the glycogenolytic effects of VIP on the liver.[36]

Gastrinoma (Zollinger–Ellison) Syndrome

Zollinger–Ellison (ZE) syndrome is characterized by gastrin-producing tumors (gastrinoma), hypersecretion of gastric acid, and recurrent peptic ulcers. The tumors usually originate from the pancreas and less frequently from the duodenum. Glucose intolerance and diabetes have been reported in patients with ZE syndrome.[37] It is

unclear if gastrin overproduction is the cause of glucose intolerance. Twenty to sixty percent of patients with ZE syndrome have gastrinoma as part of the genetic multiple endocrine neoplasia (MEN) syndrome.

Carcinoid Syndrome

One report focuses on the link between diabetes mellitus and carcinoid tumors, relating a 50–80% incidence of diabetes or glucose intolerance to active secretion of serotonin.[38] It is more probable that diabetes seen with carcinoid syndrome is related to tumor secretory products such as somatostatin, glucagon, or ACTH causing Cushing's syndrome.[39]

Liver Disease as a Cause of Secondary Diabetes Mellitus

The liver plays a major role in glucose homeostasis.[40] It produces glucose by both glycogenolysis (breakdown of glycogen) and gluconeogenesis (newly synthesized glucose). It is a major organ in glucose storage in the form of glycogen.

Insulin increases hepatic glucose uptake and suppresses hepatic glucose production. This results in increase in glycogen synthesis and deposition in the liver. Opposing this action, glucagon decreases hepatic glucose uptake from the portal system.

Nonalcoholic Fatty Liver Disease (NAFLD), Chronic Hepatitis, and Cirrhosis

The incidence of impaired glucose tolerance and diabetes is increased in chronic liver disease.[41,42] Insulin resistance is a characteristic feature of patients with liver cirrhosis.[43] Even in the absence of cirrhosis, portal hypertension is associated with insulin resistance,[44] manifested as insulin resistance in 80% of cirrhotic patients, with 20–60% developing overt diabetes mellitus.[45] In total, an astounding 95% of patients with cirrhosis have diabetes or glucose intolerance.[46] Both insulin resistance and inadequate insulin secretion by the β-cells contribute to glucose intolerance in patients with cirrhosis.[43] Inflammatory pathways are invoked as a link between liver disease and glucose intolerance, especially in NAFLD.[47,48] Hyperglycemia in chronic liver disease may also occur as a result of the therapeutic administration of various medications including interferons and corticosteroids. Cirrhotic patients with overt diabetes have a high mortality rate, with an increased risk of liver cell failure. Thus, the presence of diabetes in cirrhotic patients is a risk factor for long-term survival.[46,49,50]

Hepatitis C

Overt diabetes mellitus is more prevalent in patients with chronic hepatitis C than in patients with other liver diseases.[51–57] Risk factors for the development of glucose intolerance in patients with hepatitis C include hepatitis C viremia, male gender, hypertension, BMI, and age.[58] The mechanism by which hepatitis C virus (HCV) infection induces glucose intolerance and diabetes is unknown. Many theories, including cytopathic and immunological mechanisms, have been proposed for the effect of HCV on extrahepatic tissues.[59,60] One possible mechanism is the upregulation of TNF-α by HCV. TNF-α has been shown to block tyrosine phosphorylation of insulin receptor substrate (IRS)-1, disrupting an important step in the insulin signaling cascade, with restoration of insulin sensitivity following administration of antibodies against TNF-α.[61] The HCV core protein upregulates the suppressor of cytokine signaling (SOCS)3 and downregulates, via ubiquitination, insulin receptor substrates (IRS) 1 and 2.[61–64] Thus, via these two mechanisms, the HCV core protein is thought to lead to insulin resistance. Insulin resistance impairs sustained response to antiviral therapy and is associated with increased severity of fibrosis in patients with chronic HCV.[65–68]

Acute Hepatitis

Acute hepatitis is associated with transient glucose intolerance or hypoglycemia,[69,70] with rare persistence of diabetes.[71,72]

For more detailed discussion of the relationship between liver disease and diabetes, please see Chapter 35.

Drug-Induced or Chemical-Induced Diabetes

Many drugs are known to cause glucose intolerance or diabetes mellitus (Table 16.3).[73]

Table 16.3 Some drugs causing impaired glucose tolerance and diabetes

Alcohol	Atypical antipsychotics
Nicotinic acid (Niacin)	Steroids, particularly glucocorticoids
Thiazides	Thyroid hormone
β-Blockers	β-Interferon
Calcium channel blockers	Cyclosporin
Clonidine	Diazoxide
Dilantin	Pentamidine
HIV* protease inhibitors	Megestrol acetate
Oral contraceptive pills	Vacor

*Human immunodeficiency virus.

Alcohol, when ingested acutely, has been associated with hypoglycemia due to its inhibitory effect on gluconeogenesis. This effect is mostly seen in fasted individuals with depleted glycogen stores who are dependent on gluconeogenesis to maintain hepatic glucose production. Acute large alcohol intake can cause insulin resistance in peripheral tissues, particularly in the muscles. When ingested on chronic basis, excessive alcohol intake has been associated with moderate to severe insulin resistance and glucose intolerance.

β-Adrenergic blockers are widely used in clinical practice. They are considered, along with diuretics, the first line of therapy for hypertension. They are known to promote hypoglycemia both by inhibiting hepatic glucose production directly and by blocking the counter-regulatory hormonal response to hypoglycemia. Studies have shown that non-diabetic patients on β-blockers (particularly the non-selective) may exhibit disturbance in their glucose homeostasis in the form of worsening glucose tolerance. This might be due to worsening insulin secretion or insulin action.

Pentamidine has multiphasic effect on the β-cell of the pancreas. Initially, pentamidine causes β-cell degranulation with the release of insulin, which results in hypoglycemia. Later, it causes β-cell destruction and impaired insulin secretion, resulting in hyperglycemia and even diabetic ketoacidosis.[74] Intravenous pentamidine can permanently destroy pancreatic β-cells and has been incriminated in the development of secondary diabetes in multiple cases.[75,76] These reactions, however, are considered rare. Impairment of insulin action can result from the administration of multiple drugs and hormones, such as nicotinic acid and steroids.[77,78]

Patients on α-interferon treatment for chronic hepatitis C are reported to develop diabetes with islet cell antibodies and, in some cases, insulin deficiency.[79] Vacor (pyriminil, synthetic organic rodenticide) can cause hyperglycemia, ketoacidosis, and irreversible diabetes, in addition to its toxic effect on the central and peripheral nervous system.[80]

Protease Inhibitors, Human Immunodeficiency Virus (HIV), and Glucose Intolerance

Undesirable physical and metabolic changes associated with HIV infection and therapy assume greater importance as life expectancy improves.[81] An acquired lipodystrophy syndrome occurs in a high proportion of chronically HIV-infected individuals and variably includes central obesity, dorsal fat pad, facial wasting, and

wasting of the extremities. Insulin resistance, frank diabetes, and hyperlipidemia are associated with this lipodystrophy and presumably carry an increased risk of premature cardiovascular mortality.[82] The metabolic syndrome can occur in HIV-infected individuals in the absence of HIV-specific medications, increases in incidence with the use of some classes of drugs including reverse transcriptase inhibitors, and is greatest in those patients on protease inhibitors.[83] Investigation into mechanisms has included the role of mitochondrial toxicity in producing the syndrome, protection of lipid particles from degradation,[84] increased fatty acid and cholesterol biosynthesis,[85] inhibition of fat cell differentiation,[86] and inhibition of glucose transport into fat and muscle.[87] There is no accepted or proven safe therapy.

For detailed discussion of the relationship between HIV infection and diabetes, see Chapter 38.

Endocrinopathies

Acromegaly, a State of Growth Hormone Excess, Is Associated with Hyperglycemia and Insulin Resistance

The major players in the growth hormone (GH) system are GH and IGF-1 (insulin-like growth factor-1). GH and IGF-1 affect glucose and fat metabolism, as well as growth. They have opposing effects on carbohydrate metabolism (Fig. 16.1). A family of IGF-binding proteins (IGF-BPs) affects tissue delivery, availability of IGF-1, and gene transcription, thereby altering the balance between growth hormone and IGF-1. In some tissues, the IGF effects cooperate with the GH effects (for example, growth of long bones) and in other tissues, they are antagonistic (the metabolic effects).

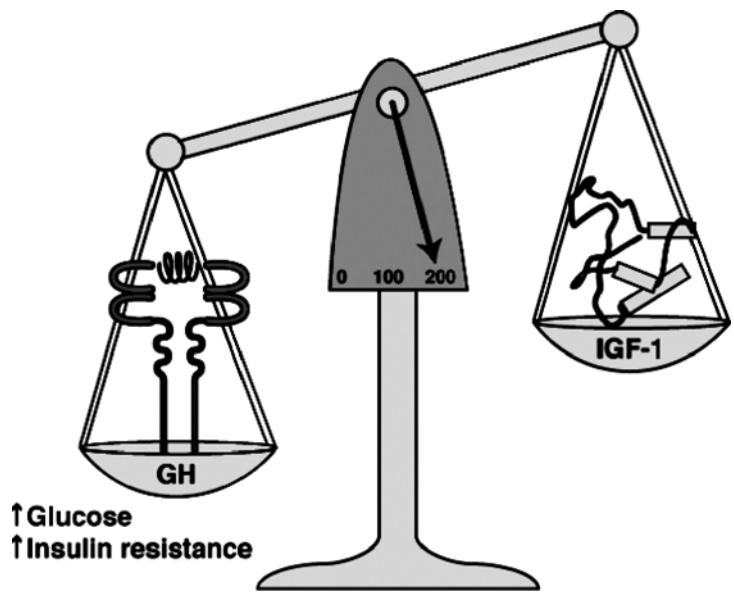

Fig. 16.1 Growth hormone (GH) and IGF-1 have opposite effects on glucose metabolism. Hepatic IGF-1 appears to be an insulin sensitizer and can lower blood glucose levels, while elevated GH raises blood glucose and is associated with insulin resistance[93]

Growth, mediated by IGF-1, is an anabolic process that requires cellular uptake of building components, such as amino acids and glucose. Administered separately from growth hormone, IGF-1 lowers elevated blood glucose levels and can cause hypoglycemia. In fact, IGF-1 has been used to treat diabetic ketoacidosis in insulin-resistant individuals.[88]

Growth hormone can be regarded as the metabolic partner of IGF-1 because growth hormone provides substrate for the effects of IGF-1. GH-stimulated fat mobilization and new glucose formation (gluconeogenesis)

are required to make building components (substrate) available. Growth hormone acts on the fat cell to stimulate the hormone-sensitive lipase, causing lipolysis (breakdown of fat) with the release of glycerol and free fatty acids (FFAs). Glycerol is a precursor of hepatic gluconeogenesis. FFAs stimulate gluconeogenesis and are the precursors of ketogenesis.[89] FFA elevation also increases output of the lipoprotein VLDL, thereby elevating triglyceride levels.[90] FFAs become the preferred substrate for muscle uptake and oxidation. GH also causes inhibition of muscle uptake and oxidation of glucose, even though insulin concentrations are increased because of insulin resistance secondary to GH action.[91] GH excess in children and adolescents prior to closure of the growth plate of the long bones results in continued growth (gigantism). In adults, GH excess causes acromegaly (acral overgrowth). Acromegaly occurs with GH-secreting pituitary tumors and rarely with ectopic production of growth hormone-releasing hormone, usually by bronchial carcinoids or pancreatic neuroendocrine tumors. Even though GH stimulates IGF-1 secretion and IGF-1 levels are elevated in acromegaly, GH excess is potentially diabetogenic. The actions of GH to mobilize FFAs, stimulate gluconeogenesis, and inhibit insulin action may lead to impaired fasting glucose (30%) and frank diabetes mellitus (16%) in acromegaly.[92]

Cushing's Syndrome, Glucocorticoids, and 11-β-Hydroxysteroid Dehydrogenase

Glucocorticoids were named for their ability to raise blood glucose.[94] Excess glucocorticoid secretion or administration can lead to diabetes mellitus. Cushing's syndrome results from excess endogenous glucocorticoid (cortisol) secretion from adrenal gland tumors; from pituitary or other tumors secreting excessive amounts of ACTH, which stimulates adrenal cortisol production; or from exogenously administered glucocorticoids used in the treatment of asthma or autoimmune disorders. Glucose intolerance and diabetes mellitus are common in Cushing's syndrome, with frank diabetes or impaired glucose tolerance occurring in 50–90% of affected individuals. Cortisol is one of the counter-regulatory hormones and acts at many steps. One action is to increase the appetite, thereby increasing energy intake with an initial rise in blood glucose level. The lipogenic action of cortisol, to store nutrients in visceral fat tissue, contributes to insulin resistance. The major actions of cortisol, like those of growth hormone, lead to extrahepatic substrate mobilization. The lipolytic action of cortisol mobilizes energy from adipose tissue, providing precursors for increased hepatic glucose production.[95] Cortisol antagonizes the effects of insulin in muscle, preventing protein synthesis and inhibiting glucose utilization; further, its catabolic actions include muscle breakdown,[96] with the effect of delivering gluconeogenic precursors to the liver. In the liver, cortisol stimulates both gluconeogenesis and glycogen breakdown.

The pivotal role that cortisol may play in insulin resistance and type 2 diabetes mellitus is highlighted by observations that increased cortisol production in visceral fat can be shown in a transgenic mouse model to recreate the metabolic syndrome of insulin resistance, diabetes, and hypertension (Fig. 16.2).[97,98]

Pheochromocytoma

Pheochromocytomas, a general term applied to tumors of the adrenal medulla and the extra-adrenal chromaffin tissue, secrete catecholamines, especially norepinephrine. Headache related to extreme elevations of blood pressure (α_1-adrenergic stimulation), palpitations (β_1-adrenergic stimulation), anxiety, and diaphoresis dominates the clinical presentation. Diabetes occurs in up to 65% of pheochromocytomas, may mirror the paroxysmal rises in blood pressure, and has been demonstrated to resolve following tumor resection.[100] Pheochromocytomas whose major secretory product is epinephrine are much more likely than norepinephrine-secreting tumors to present with arrhythmias, non-cardiac pulmonary edema, hypotension, and hyperglycemia. This distinct presentation reflects the combined α- and β-adrenergic stimulation of epinephrine (Fig. 16.3). The more common norepinephrine-secreting tumors may also cause hyperglycemia since norepinephrine is also a mixed agonist, although with less β activity than does epinephrine.[101]

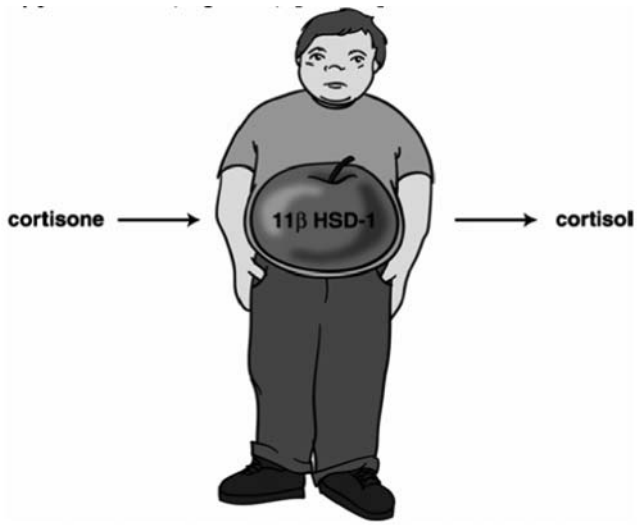

Fig. 16.2 Increased activity of 11-β-hydroxysteroid dehydrogenase type 1 in transgenic mice increases cortisol production in visceral fat and causes abdominal obesity and the metabolic syndrome resembling that seen in "apple-shaped" people[99]

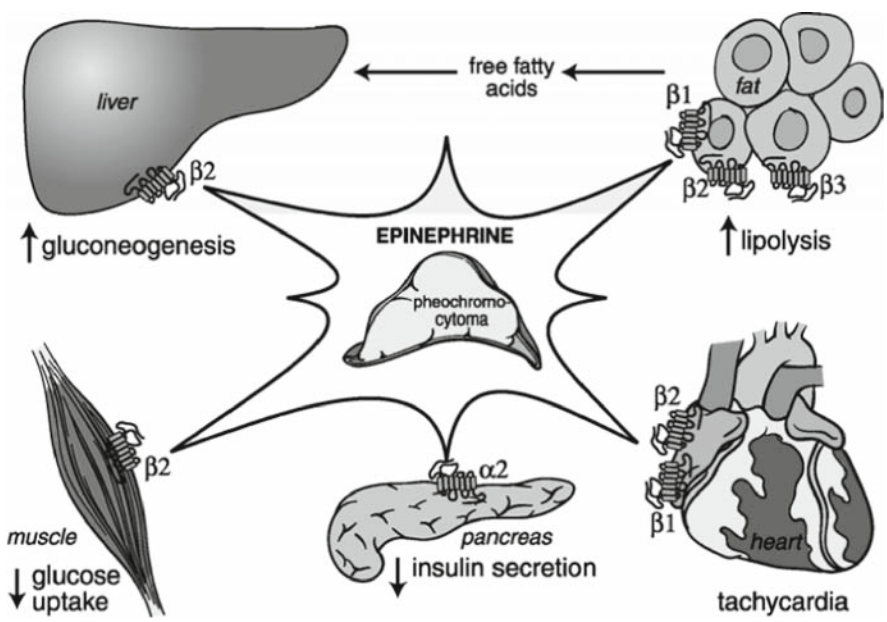

Fig. 16.3 The coordinated actions of elevated epinephrine in pheochromocytoma raise blood glucose[102]

Hyperthyroidism

Thyroid hormone increases glucose transporters 4 (GLUT-4) in fat tissue and muscle, thereby enhancing the stimulatory effect of insulin.[103] Given the increase in metabolic rate caused by thyroid hormones, it is logical that increased fuel would be made available to tissues. It is paradoxical then that hyperthyroidism is sometimes associated with deterioration of glucose control or with onset of frank diabetes mellitus. Partial explanations

implicate increased growth hormone secretion[104]; a hepatic gene expression profile that promotes gluconeogenesis and glycogenolysis, and decreases insulin action[105]; and increased hepatic GLUT-2 transporters, through which glucose effluxes out of the liver.[106]

Hyperaldosteronism

Primary hyperaldosteronism, the elevated secretion of the mineralocorticoid aldosterone resulting from adrenal cortical tumors, genetic mutations, or idiopathic hyperaldosteronism, is classified with the endocrinopathies that cause "other specific types" of diabetes mellitus.[1] Yet, little is known about the occurrence, the mechanism, or the resolution of the glucose intolerance seen with hypersecretion of aldosterone. One retrospective study found a prevalence of diabetes of 5–24% in hyperaldosteronism.[107] Physiologic potassium levels play a fundamental role in insulin secretion. Potassium stimulates glucose-induced insulin secretion, and insulin lowers serum potassium by driving the cation intracellularly.[108] The hypokalemia that occurs with renal potassium wasting in primary aldosteronism presumably has a restraining or inhibiting effect on insulin secretion and leads to glucose intolerance and diabetes in susceptible individuals. In addition, insulin resistance may occur.[109] The diabetes that occurs with hyperaldosteronism may (personal observation) or may not[110] resolve with cure of hyperaldosteronism.

Conclusion

Diverse organs and drugs are implicated in secondary diabetes mellitus. Pancreatic destruction is treatable only with insulin replacement. The link between liver disease and diabetes is poorly understood. The lipodystrophy and metabolic consequences of HIV infection and its therapies are under active investigation. Sometimes medications that cause diabetes may be discontinued, but others are life saving and lack appropriate substitutions. Cure of the endocrinopathies that cause diabetes may ameliorate or cure the associated diabetes. Ultimately, the explanation for the mechanisms that cause secondary diabetes mellitus can be sought in the basic physiology and pathophysiology of the secretion of insulin and its action on target tissues.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2008;31(Suppl 1):S55–S60.
2. Pitchumoni CS, Patel NM, Shah P. Factors influencing mortality in acute pancreatitis. *J Clin Gastroenterol*. 2005;39:798–814.
3. Thow J, Semad A, Alberti KGMM. Epidemiology and general aspects of diabetes secondary to pancreatopathy. In: Tiengo A, Alberti KGMM, Del Prato S, Vranic M, eds. *Diabetes Secondary to Pancreatopathy*. Amsterdam: Excerpta Medica; 1988: 7–20.
4. Del Prato S, Tiengo A. Diabetes secondary to acquired disease of the pancreas. In: Alberti KGMM, DeFronzo RA, Keen H, Zimmet P, eds. *International Textbook of Diabetes Mellitus*. New York: John Wiley & Sons, Inc.; 1992:199.
5. Ueda T, Takeyama Y, Yasuda T, et al. Simple scoring system for the prediction of the prognosis of severe acute pancreatitis. *Surgery*. 2007;141:51–58.
6. Drew SI, Joffe B, Vinik AI, et al. The first 24 hours of acute pancreatitis. Changes in biochemical and endocrine homeostasis inpatients with pancreatitis compared to those in control subjects undergoing stress for reasons other than pancreatitis. *Am J Med*. 1978;64:795–803.
7. Donowitz M, Hendeler R, Spiro HM, et al. Glucagon secretion in acute and chronic pancreatitis. *J Intern Med*. 1975;83: 778–781.
8. Kaya E, Dervisoglu A, Polat C. Evaluation of diagnostic findings and scoring systems in outcome prediction in acute pancreatitis. *World J Gastroenterol*. 2007;13(22):3090–3094.
9. Andersen DK. Mechanisms and emerging treatments of the metabolic complications of chronic pancreatitis. *Pancreas*. 2007;35(1):1–15.
10. Mlka D, Hammel P, Sauvanet A, et al. Risk factors for diabetes mellitus in chronic pancreatitis. *Gastroenterology*. 2000;119:1324–1332.
11. Angelopoulos N, Dervenis C, Goula A, et al. Endocrine pancreatic insufficiency in chronic pancreatitis. *Pancreatology*. 2005;5:122–131.

12. Larsen S. Diabetes mellitus secondary to chronic pancreatitis. *Dan Med Bull*. 1993;40(2):153–162.
13. Hedetoft C, Sheikh SP, Larsen S, Holst JJ. Effect of glucagons-like peptide 1(7-36)amide in insulin-treated patients with diabetes mellitus secondary to chronic pancreatitis. *Pancreas*. 2000;20(1):25–31.
14. Mergener K, Baillie J. Chronic pancreatitis. *Lancet*. 1997;350:1379–1385.
15. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology*. 2008;134:95–101.
16. Murat S, Parviz PM. Diabetes and its relationship to pancreatic carcinoma. *Pancreas*. 2003;26(4):381–387.
17. Hull RL, Westermark GT, Westermark P, Kahn SE. Islet amyloid: a critical entity in the pathogenesis of type 2 diabetes. *J Clin Endocrinol Metab*. 2004;89:3629–3643.
18. Casas S, Gomis R, Gribble FM, et al. Impairment of the ubiquitin–proteasome pathway is a downstream endoplasmic reticulum stress response induced by extracellular human islet amyloid polypeptide and contributes to pancreatic β-cell apoptosis. *Diabetes*. 2007;56:2284–2294.
19. Permert J, Larsson J, Fruin AB, et al. Islet hormone secretion in pancreatic cancer patients with diabetes. *Pancreas*. 1997;15:60–68.
20. Slezak LA, Andersen DK. Pancreatic resection: effects on glucose metabolism. *World J Surg*. 2001;25:452–460.
21. Brennan AL, Geddes DM, Gyi KM, Baker EH. Clinical importance of cystic fibrosis-related diabetes. *J Cyst Fibros*. 2004;3(4):209–222.
22. Dobson L, Stride A, Bingham C, et al. Microalbuminuria as a screening tool in cystic fibrosis-related diabetes. *Pediatr Pulmonol*. 2005;39(2):103–107.
23. Shwachman H, Kowalski M, Khaw KT. Cystic fibrosis: a new outlook, 70 patients above 25 years of age. *Medicine*. 1977;56:24–49.
24. Alves Cde A, Aguiar RA, Alves AC, Santana MA. Diabetes mellitus in patients with cystic fibrosis. *J Bras Pneumol*. 2007;33(2):213–221.
25. Bizzarri C, Lucidi V, Ciampalini P, et al. Clinical effects of early treatment with insulin glargine in patients with cystic fibrosis and impaired glucose tolerance. *J Endocrinol Invest*. 2006;29(3):RC1–RC4.
26. Williams R, Williams HS, Scheuer PJ, et al. Iron absorption and siderosis in chronic liver disease. *Quart J Med*. 1967;35: 151–166.
27. Powell LW, Yapp TR. Hemochromatosis. *Clin Liver Dis*. 2000;4(1):211–228.
28. Wilson J, Lindquist J, Grambow S, et al. Potential role of increased iron stores in diabetes. *Am J Med Sci*. 2003;325(6): 332–339.
29. Swaminathan S, Fonseca V, Alam M, Shah S. The role of iron in diabetes and its complications. *Diabetes Care*. 2007;30(7):1926–1933.
30. Wermers RA, Fatourechi V, Wynne AG, et al. The glucagonoma syndrome. *Medicine*. 1996;75:53.
31. Warner R. Enteroendocrine tumors other than carcinoid: a review of clinically significant advances. *Gastroenterol*. 2005;128:1668–1684.
32. Beek AP, de Haas ERM, van Vloten WA, et al. The glucagonoma syndrome and necrolytic migratory erythema: a clinical review. *Eur J Endocrinol*. 2004;151:531–537.
33. Lefgbvre PJ. Glucagon and its family revisited. *Diabetes Care*. 1995;18:715–730.
34. Vinik AI, Strodel WE, Eckhauser FE, et al. Somatostatinomas, PPomas, neurotensinomas. *Semin Oncol*. 1987;14:263–281.
35. Sassolas G, Chayvialle JA. GRFomas, somatostatinomas: clinical presentation, diagnosis, and advances in management. In: Mignon M, Jensen RT, eds. *Endocrine Tumors of the Pancreas: Recent Advances in Research and Management*. Frontiers of Gastrointestinal Research, Vol. 23. Basel, Switzerland: S. Karger; 1995:194.
36. Matuchansky C, Rambuaud JC. VIPomas and endocrine cholera: clinical presentation, diagnosis, and advances in management. In: Mignon M, Jensen RT, eds. *Endocrine Tumors of the Pancreas: Recent Advances in Research and Management*. Frontiers of Gastrointestinal Research, Vol. 23. Basel, Switzerland: S. Karger; 1995;166.
37. McCallum RW, Parameswaran V, Burgess JR. Multiple endocrine neoplasia type 1 (MEN 1) is associated with an increased prevalence of diabetes mellitus and impaired fasting glucose. *Clin Endocrinol*. 2006;65:163–168.
38. Feldman JM, Plonk JW, Bivens CH, Levobitz HE. Glucose intolerance in the carcinoid syndrome. *Diabetes*. 1975;24:664–671.
39. Mitzner LD, Nohria A, Chacho M, Inzucchi SE. Sequential hypoglycemia, hyperglycemia, and the carcinoid syndrome arising from a plurihormonal neuroendocrine neoplasm. *Endocr Pract*. 2000;6:370–374.
40. DeFronzo RA, Ferrannini E. Regulation of hepatic glucose metabolism in humans. *Diabetes Metab Rev*. 1987;3:415–459.
41. Zein NN. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol*. 2000;32:209–217.
42. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes Care*. 2007;30(3):734–743.
43. Albright ES, Bell DSH. The liver, liver disease, and diabetes mellitus. *Endocrinol*. 2003;13(1):58–66.
44. Cavallo-Perin P, Cassader M, Bozzo C, et al. Mechanism of insulin resistance in human liver cirrhosis: evidence of combined receptor and postreceptor defect. *J Clin Invest*. 1985;75:1659–1665.
45. Harrison SA. Liver disease in patients with diabetes mellitus. *J Clin Gastroenterol*. 2006;40:68–76.
46. Holstein A, Hinze S, Thiessen E, et al. Clinical implications of hepatogenous diabetes in liver cirrhosis. *J Gastroenterol Hepatol*. 2002;17(6):677–681.

47. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest*. 2006;116:1793–1801.
48. Samuel VT, Liu ZX, Wang A, et al. Inhibition of protein kinase Cϵ prevents hepatic insulin resistance in nonalcoholic fatty liver disease. *J Clin Invest*. 2007;117:739–745.
49. Fartoux L, Poujol-Robert A, Guéchot J, et al. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut*. 2005;54(7):1003–1008.
50. Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. *Am J Med*. 2007;120(10):829–834.
51. Fraser GM, Harman I, Meller N, et al. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B infection. *Isr J Med Sci*. 1996;32:526–530.
52. Knobler H, Schihmanter R, Zifroni A, et al. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. *Mayo Clin Proc*. 2000;75:355–359.
53. Huang JF, Dai CY, Hwang SJ, et al. Hepatitis C viremia increases the association with type 2 diabetes mellitus in a hepatitis B and C endemic area: an epidemiological link with virological implication. *Am J Gastroenterol*. 2007;102(6):1237–1243.
54. Mehta SH, Brancati FL, Strathdee SA, et al. Hepatitis C virus infection and incident type 2 diabetes. *Hepatology*. 2003;38(1):50–56.
55. Zein CO, Levy C, Basu A, Zein NN. Chronic hepatitis C and type II diabetes mellitus: a prospective cross-sectional study. *Am J Gastroenterol*. 2005;100(1):48–55.
56. Lecube A, Hernández C, Genescà J, Simó R. Glucose abnormalities in patients with hepatitis C virus infection: epidemiology and pathogenesis. *Diabetes Care*. 2006;29(5):1140–1149.
57. Mehta SH, Brancati FL, Sulkowski MS, et al. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Hepatology*. 2001;33(6):1554.
58. Huang JF, Dai CY, Hwang SJ, et al. Hepatitis C viremia increases the association with type 2 diabetes mellitus in a hepatitis B and C endemic area: an epidemiological link with virological implication. *Am J Gastroenterol*. 2007;102(6):1237–1243.
59. Hadziyannis SJ. The spectrum of extrahepatic manifestations in hepatitis C virus infection. *J Vir Hepat*. 1997;4:9–28.
60. Oben JA, Paulon E. Fatty liver in chronic hepatitis C infection: unraveling the mechanisms. *Gut*. 2007;56:1186–1188.
61. Knobler H, Schattner A. TNF-alpha, chronic hepatitis C and diabetes: a novel triad. *QJM*. 2005;98(1):1–6.
62. Chen LK, Chou YC, Tsai ST, et al. Hepatitis C virus infection-related type 1 diabetes mellitus. *Diabetes Med*. 2005;22(3): 340–343.
63. Kawaguchi T, Yoshida T, Harada M, et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol*. 2004;165(5):1499–1508.
64. Aytug S, Reich D, Sapiro LE, et al. Impaired IRS-1/PI3-kinase signaling in patients with HCV: a mechanism for increased prevalence of type 2 diabetes. *Hepatology*. 2003;38(6):1384–1392.
65. Romero-Gómez M, Del Mar Viloria M, Andrade RJ, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology*. 2005;128(3):636–641.
66. Hickman IJ, Powell EE, Prins JB, et al. In overweight patients with chronic hepatitis C, circulating insulin is associated with hepatic fibrosis: implications for therapy. *J Hepatol*. 2003;39(6):1042–1048.
67. Taura N, Ichikawa T, Hamasaki K, et al. Association between liver fibrosis and insulin sensitivity in chronic hepatitis C patients. *Am J Gastroenterol*. 2006;101(12):2752–2759.
68. Trombetta M, Spiazzi G, Zoppini G, Muggeo M. Review article: type 2 diabetes and chronic liver disease in the Verona diabetes study. *Aliment Pharmacol Ther*. 2005;22(Suppl 2):24–27.
69. Record CO, Alberti KG, Williamson DH, Wright R. Glucose tolerance and metabolic changes in human viral hepatitis. *Clin Sci Mol Med*. 1973;45:677–690.
70. Bianchi G, Marchesini G, Zoli M, et al. Prognostic significance of diabetes in patients with cirrhosis. *Hepatology*. 1994;20:119–125.
71. Vesely DL, Dilley RW, Duckworth WC, Paustian FF. Hepatitis A-induced diabetes mellitus, acute renal failure, and liver failure. *Am J Med Sci*. 1999;317(6):419–425.
72. Masuda H, Atsumi T, Fujisaku A, et al. Acute onset of type 1 diabetes accompanied by acute hepatitis C: the potential role of proinflammatory cytokine in the pathogenesis of autoimmune diabetes. *Diabetes Res Clin Pract*. 2007;75(3):357–361.
73. Luna B, Feinglos MN. Drug-induced hyperglycemia. *JAMA*. 2001;286(16):1945–1948.
74. Lambertus MW, Murthy AR, Nagami P, et al. Diabetic ketoacidosis following pentamidine therapy in a patient with the acquired immunodeficiency syndrome. *West J Med*. 1988;149:602–604.
75. Bouchard P, Sai P, Reach G, et al. Diabetes mellitus following pentamidine-induced hypoglycemia in humans. *Diabetes*. 1982;31:40–45.
76. Assan R, Perronne C, Assan D, et al. Pentamidine-induced derangements of glucose homeostasis. *Diabetes Care*. 1995;18: 47–55.
77. Pandit MK, Burke J, Gustafson AB, et al. Drug-induced disorders of glucose tolerance. *Ann Intern Med*. 1993;118:529–540.
78. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetes (parts I and II). *Drugs*. 1990;40:203–219.
79. Shiba T, Morino Y, Tagawa K, et al. Onset of diabetes with high titer anti-GAD antibody after IFN therapy for chronic hepatitis. *Diabetes Res Clin Pract*. 1996;30:237–241.
80. Gallanosa AG, Spyker DA, Curnow RT. Diabetes mellitus associated with autonomic and peripheral neuropathy after Vacor poisoning: a review. *Clin Toxicol*. 1981;18:441–449.

81. Florescu D, Kotler DP. Insulin resistance, glucose intolerance and diabetes mellitus in HIV-infected patients. *Antivir Ther*. 2007;12:149–162.
82. Moyle G. Metabolic issues associated with protease inhibitors. *J Acquir Immune Defic Syndr*. 2007;45:S19–S26.
83. Martinez E, Mocroft A, Garcia-Viejo MA, et al. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. *Lancet*. 2001;357:592–598.
84. Liang J, Distler O, Cooper DA, et al. HIV protease inhibitors protect apolipoprotein B from degradation by the proteasome: a potential mechanism for protease inhibitor-induced hyperlipidemia. *Nat Med*. 2001;7:1327–1331.
85. Riddle TM, Kuhel DG, Woollett LA, et al. HIV protease inhibitor induces fatty acid and sterol biosynthesis in liver and adipose tissues due to the accumulation of activated sterol regulatory element-binding proteins in the nucleus. *J Biol Chem*. 2001;276:37514–37519.
86. Martine C, Auclair M, Vigouroux C, et al. The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. *Diabetes*. 2001;50:1378–1388.
87. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem*. 2000;275:20251–20254.
88. Usala AL, Madigan T, Burguera B, et al. Treatment of insulin-resistant diabetic ketoacidosis with insulin-like growth factor I in an adolescent with insulin-dependent diabetes [Brief report]. *N Engl J Med*. 1992;327:853–857.
89. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. *Diabetes*. 1997;46:3–10.
90. Leung KC, Ho KKY. Stimulation of mitochondrial fatty acid oxidation by growth hormone in human fibroblasts. *J Clin Endocrinol Metab*. 1997;82:4208–4213.
91. Goodman HN. The metabolic actions of growth hormone. In: Jefferson LS, Cherrington AD, Goodman HM, eds. *Handbook of Physiology*, Section, 7; The Endocrine System, Vol. 2. The Endocrine Pancreas and Regulation of Metabolism. New York: Oxford University Press, Inc.; 2001:849–906.
92. Vilar L, Naves LA, Costa SS, et al. Increase of classic and nonclassic cardiovascular risk factors in patients with acromegaly. *Endocr Pract*. 2007;13:363–372.
93. Butler AA, LeRoith D. Minireview: tissue-specific versus generalized gene targeting of the igf1 and igf1r genes and their roles in insulin-like growth factor physiology. *Endocrinol*. 2001;142:1685–1688.
94. Munck A, Naray-Fejes-Toth A. Glucocorticoid physiology. In: DeGroot LJ, Jameson LJ, eds. *Endocrinology*. 5th ed. Philadelphia, PA: Elsevier Saunders; 2006:2287–2309.
95. Salati LM. Regulation of fatty acid biosynthesis and lipolysis. In: Jefferson LS, Cherrington AD, Goodman HM, eds. *Handbook of Physiology*, Section, 7; The Endocrine System, Vol. 2. The Endocrine Pancreas and Regulation of Metabolism. New York: Oxford University Press, Inc.; 2001:495–527.
96. Jefferson LS, Vary TC, Kimball SR. Regulation of protein metabolism in muscle. In: Jefferson LS, Cherrington AD, Goodman HM, eds. *Handbook of Physiology*, Section, 7; The Endocrine System, Vol. 2. The Endocrine Pancreas and Regulation of Metabolism. New York: Oxford University Press, Inc.; 2001:536.
97. Masuzaki H, Paterson J, Shinyama H, et al. A transgenic model of visceral obesity and the metabolic syndrome. *Science*. 2001;294:2166–2170.
98. Qatanani M, Lazar MA. Mechanisms of obesity-associated insulin resistance: many choices on the menu. *Genes Dev*. 2007;21:1443–1455.
99. Gura T. Pot-bellied mice point to obesity enzyme [News of the Week]. *Science*. 2001;294:2071–2072.
100. Manger WM, Gifford RW. *Clinical and Experimental Pheochromocytoma*. 2nd ed. Cambridge: Blackwell Science, Inc.; 1996:209.
101. Pacak K. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab*. 2007;92(11):4069–4079.
102. Cryer PE. Catecholamines, pheochromocytoma and diabetes. *Diabetes Rev*. 1993;1:309–317.
103. Romero R, Casanova B, Pulido N, et al. Stimulation of glucose transport by thyroid hormone in 3T3-L1 adipocytes: increased abundance of GLUT1 and GLUT4 glucose transporter proteins. *J Endocrinol*. 2000;164:187–195.
104. Tosi F, Moghetti P, Castello R, et al. Early changes in plasma glucagon and growth hormone response to oral glucose in experimental hyperthyroidism. *Metab Clin Exp*. 1996;45:1029–1033.
105. Feng X, Jiang Y, Meltzer P, Yen PM. Thyroid hormone regulation of hepatic genes in vivo detected by complementary DNA microarray. *Mol Endocrinol*. 2000 July;14(7):947–955.
106. Mokuno T, Uchimura K, Hayashi R, et al. Glucose transporter 2 concentrations in hyper- and hypothyroid rat livers. *J Endocrinol*. 1999;160:285–289.
107. Kreze A Sr., Kreze-Spirova E, Mikulecky M. Diabetes mellitus in primary aldosteronism. *Bratisl Lek Listy*. 2000;101:187–190.
108. Ferrannini E, Galvan AQ, Santoro D, Natali A. Potassium as a link between insulin and the rennin–angiotensin–aldosterone system. *J Hypertension*. 1992;10(Suppl 1):S5–S10.
109. Hitomi H, Kiyomoto H, Nishiyama A, et al. Aldosterone suppresses insulin signaling via the downregulation of insulin receptor substrate-1 in vascular smooth muscle cells. *Hypertension*. 2007;50:750–755.
110. Strauch B, Widimsky J, Sindelka G, Skrha J. Does the treatment of primary hyperaldosteronism influence glucose tolerance? *Physiol Res*. 2003;52(4):503–506.

Useful Websites

Endotext.org http://www.endotext.org/index.htm – This is a complete textbook of endocrinology on the web that is available free.
http://www.endocrineweb.com/index.html – This is a site designed for patients and their families.
http://digestive.niddk.nih.gov/ddiseases/a-z.asp – Diseases of the pancreas can be found at this site.
http://digestive.niddk.nih.gov/ddiseases/pubs/hemochromatosis/index.htm
http://www.cancer.gov/ – This is a wonderful site to look up all of the endocrine tumors by system, body location, or type.
Mayo Clinic Staff. "Primary Aldosteronism." http://www.mayoclinic.com/health/primary-aldosteronism/DS00563. January 5, 2007. Accessed February 16, 2008.