Chapter 5

Prevalence and Incidence of Secondary and Other Types of Diabetes

Om P. Ganda, MD

SUMMARY

Other types or secondary forms of diabetes include diabetes or glucose intolerance that develops in association with disorders (or factors) other than insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM), or gestational diabetes mellitus (GDM). The prevalence is about 1%-2% of all diabetes. The extent of glucose intolerance in patients with secondary forms of diabetes can vary widely, presenting as overt diabetes that is insulin-requiring or non-insulin-requiring, simulating IDDM or NIDDM, or as milder forms such as impaired glucose tolerance (IGT) or minimally abnormal glucose tolerance. Another complexity in the evolution of secondary diabetes is that an underlying co-existing predisposition to primary diabetes might be unmasked, a not uncommon occurrence considering the relatively high prevalence of diabetes in various populations. Since diabetes, particularly NIDDM, is a heterogenous disorder, the revelation of a specific genetic basis for diabetes in many families continues to delineate many subclasses of NIDDM. Numerous mutations thus far identified include those involving the insulin gene, the insulin-receptor gene and other candidate genes such as glucokinase, insulin-receptor substrate-1 (IRS-1), and mitochondrial DNA. Although all mutations identified thus far account for a small fraction of the diabetic population, the identification of other candidate genes in the future will surely explain the basis underlying the heterogeneity of diabetes and its long-term complications.

• • • • • • •

INTRODUCTION

According to the classification system developed by the National Diabetes Data Group[1], the subclass secondary diabetes contains "a variety of types of diabetes, in some of which the etiologic relationship is known (e.g., diabetes secondary to pancreatic disease, endocrine disease, or administration of certain drugs); whereas in others, an etiologic relationship is suspected because of higher frequency of association of diabetes with a syndrome or a condition (e.g., a number of genetic syndromes)."

Table 5.1 presents a classification of various forms of secondary diabetes. When diabetes is secondary to pancreatic disorders, particularly when β-cell mass is greatly reduced as in malignancy or pancreatectomy, or when diabetes is due to chemical agents toxic to the β-cell, such as pentamidine or vacor, overt diabetes with or without ketoacidosis will often result depending on the extent of β-cell loss. In contrast, when diabetes is secondary to endocrinopathies leading to counterregulatory hormone production (e.g., acromegaly, Cushing's syndrome, hyperthyroidism), overt diabetes or ketoacidosis is unusual, mainly owing to the compensatory responsiveness of the normal β-cell mass. The net metabolic outcome in patients with secondary diabetes thus depends on the direct or indirect impact of the underlying disorders on insulin secretion (i.e., inhibition or compensatory hyperinsulinemia), insulin-sensitivity (i.e., glucose utilization), and/or unmasking of genetic diabetes.

Table 5. 1
A Classification of Secondary Forms of Diabetes or Impaired Glucose Tolerance

A. Pancreatic disorders
  a. Pancreatectomy
  b. Pancreatitis, pancreatic malignancy
  c. Malnutrition-related diabetes
  d. Hemochromatosis

B. Endocrinopathies
  a. Growth hormone excess (acromegaly) and deficiency states
  b. Glucocorticoid excess (Cushing's syndrome)
  c. Catecholamine excess (pheochromocytoma)
  d. Primary hyperaldosteronism
  e. Hyperthyroidism
  f. Tumors of endocrine pancreas or gut
     Glucagonoma, somatostatinoma, pancreatic cholera syndrome, carcinoid syndrome, multiple endocrine neoplasia syndromes
  g. Polyendocrine autoimmunity syndromes
  h. Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome

C. Drugs, chemical agents, and toxins
  a. Diuretics and antihypertensive agents
     Thiazides, chlorthalidone, loop-diuretics (furosemide, ethacrynic acid, metolazone), diazoxide, clonidine, β-adrenergic antagonists
  b. Hormones
     Glucocorticoids, ACTH, α-adrenergic agonists, growth hormone, glucagon, oral contraceptives, progestational agents
  c. Psychoactive agents
     Lithium, opiates, ethanol, phenothiazines
  d. Anticonvulsants
     Diphenylhydantoins (Dilantin)
  e. Antineoplastic agents
     Streptozotocin, L-asparaginase, mithramycin
  f. Antiprotozoal
     Pentamidine
  g. Rodenticides
     Pyriminil (Vacor)
  h. Miscellaneous
     Nicotinic acid, cyclosporine, N-nitrosamines, theophylline

D. Genetic syndromes
  a. Pancreatic deficiencies
    1. Congenital absence of pancreatic islets
    2. Cystic fibrosis
    3. Hereditary relapsing pancreatitis
  b. Mutant insulin syndromes
  c. Severe to extreme insulin resistance syndromes
    1. Type A syndrome—classic and variants
    2. Type B syndrome—associated with autoantibodies to insulin-receptor
    3. Leprechaunism
    4. Lipodystrophic syndromes
    5. Rabson-Mendenhall syndrome (precocious puberty, dental dysplasia, dystrophic nails)
    6. Ataxia-telangiectasia
    7. Alström syndrome (obesity, retinitis pigmentosa, deafness)
    8. Dystrophia myotonica
  d. Glucokinase gene mutations
  e. Mitochondrial tRNA gene mutation
  f. Obesity-associated insulin resistance
    1. Laurence-Moon-Biedl syndrome
    2. Bardet-Biedl syndrome
    3. Prader-Willi syndrome
    4. Achondroplasia
  g. Progeroid syndromes
    1. Werner's syndrome
    2. Cockayne's syndrome (microcephaly, dwarfism, deafness, nephropathy)
  h. Chromosomal defects
    1. Down's syndrome (Trisomy 21)
    2. Klinefelter's syndrome (47, XXY)
    3. Turner's syndrome (45, XO)
  i. Hereditary neuromuscular disorders
    1. Muscular dystrophy
    2. Huntington's chorea
    3. Friedreich's ataxia (spinocerebellar ataxia)
    4. Machado disease (ataxia, dysarthria, nystagmus)
    5. Herrmann's syndrome (photomyoclonus, dementia, deafness, nephropathy)
    6. Stiff-man syndrome
    7. DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, deafness) and variants
    8. Kearns-Sayre syndrome (ophthalmoplegia, retinitis pigmentosa, mitochondrial myopathy, heart block)

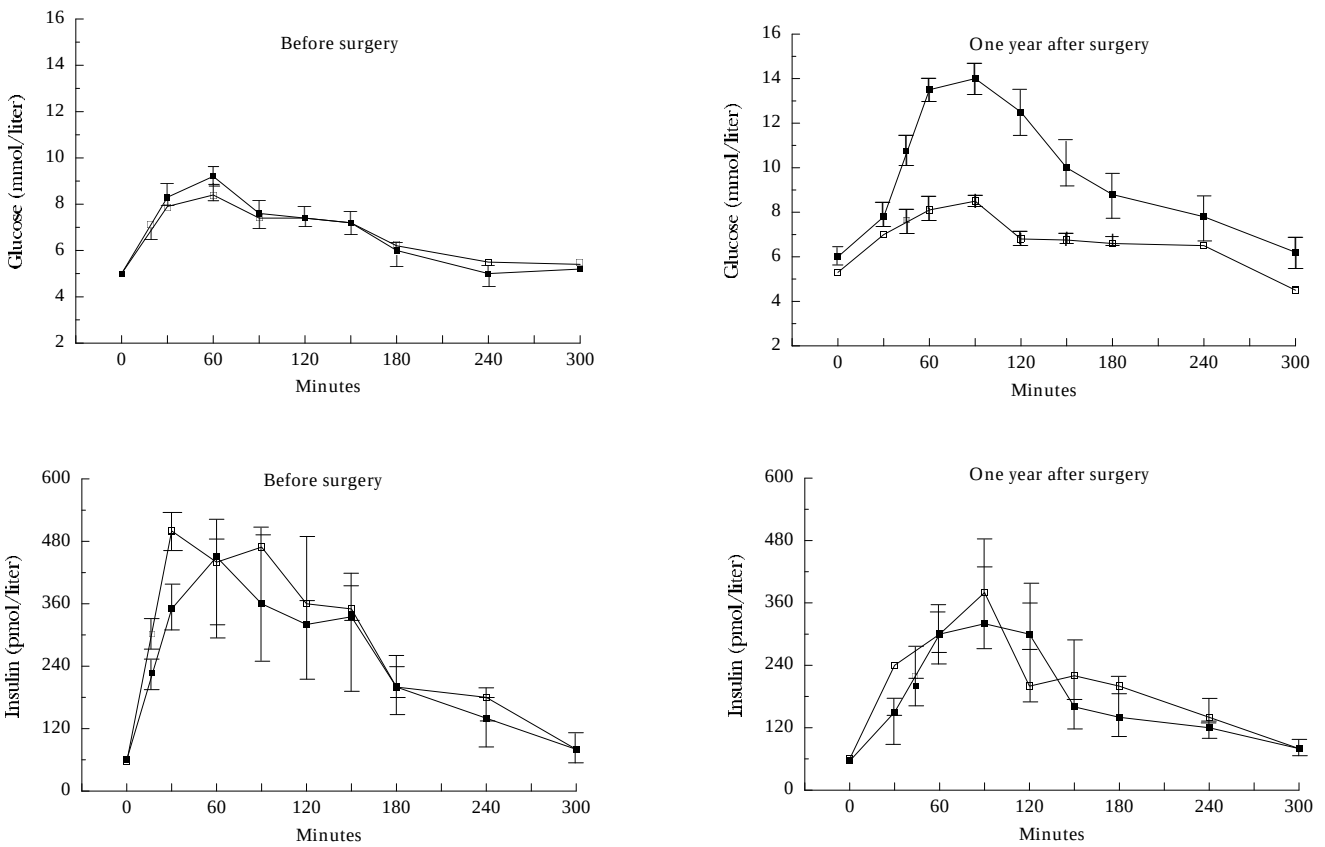
PANCREATIC DIABETES

PANCREATECTOMY

The pancreatectomized state provides a unique model of insulin-deficient secondary diabetes. Elegant studies in baboons with streptozotocin-induced β-cell destruction revealed that *in vivo* β-cell secretion became undetectable and fasting hyperglycemia developed when 40%-50% of β-cell mass was still detectable by islet morphometric assessment[2]. However, of 28 healthy human donors who underwent ~50% pancreatectomy, only seven (25%) developed glucose intolerance and deterioration in insulin and glucagon secretion after 8-15 months[3,4] (Figure 5.1), and none of these individuals developed overt diabetes. Therefore, the extent of β-cell loss required for the development of fasting hyperglycemia is debatable. It has been suggested that development of diabetes in partially pancreatectomized humans depends on several additional factors, such as the rate of regeneration of β-cells, the nutritional status due to weight loss and concomitant exocrine insufficiency, and glucagon deficiency due to loss of α-cells[5].

Subtotal or total pancreatectomy provides a model for diabetes without pancreatic glucagon[6], but there are many reports of normal or elevated immunoreactive glucagon originating from extrapancreatic sources (gastrointestinal) in such patients[7,8]. The biological significance of extrapancreatic glucagon is not clear.

Figure 5.1
Glucose and Insulin Levels Before and After Hemipancreatectomy in Healthy Human Donors



The figure shows mean (±SEM) serum glucose and serum insulin levels measured before and one year after hemipancreatectomy during 5-hour oral glucose tolerance tests. Patients are divided into 21 transplant donors who had normal glucose tolerance at 1 year (open squares) and 7 donors who had abnormal glucose tolerance at 1 year (closed squares).

Source: Reference 3

Insulin withdrawal in such patients, compared with patients with IDDM, leads to slower and less severe ketoacidosis, despite comparable rates of lipolysis, supporting the role of pancreatic glucagon in the induction of ketoacidosis[6].

PANCREATITIS

Diabetes secondary to pancreatitis accounts for <1% of all diabetes in the United States and other Western countries[9,10]. However, in many parts of the world (especially tropical countries such as Nigeria, Indonesia, and South India), pancreatitis associated with pancreatic calculi may account for 10%-15% of all diabetes and up to 50% of young patients (<30 years) with diabetes[11].

Transient hyperglycemia may be seen in up to 50% of patients with acute pancreatitis, but persistent diabetes develops in <5% of these individuals on long-term followup in the absence of further attacks, presumably due to ongoing chronic, painless pancreatitis[10]. On the other hand, in patients with chronic pancreatitis, the incidence of diabetes increases over time, with prevalence rates of 40%-50% after 20 years and an additional 25%-30% having impaired glucose tolerance[9,10]. Up to 80%-90% of patients with fibrocalcific pancreatitis have overt diabetes or impaired glucose tolerance[9,10]. In Western societies, the etiology of pancreatitis is largely alcohol-related, with or without biliary disease (Chapter 21). Diabetes secondary to pancreatic calculi in the tropics is unrelated to alcohol[10,11]. About 10%-15% of patients with cystic fibrosis may manifest overt diabetes as increasing numbers survive into adulthood. The prevalence of impaired glucose tolerance in cystic fibrosis varies between 27% and 57% in patients age >12 years[12].

The precise mechanisms whereby chronic pancreatic inflammation leads to glucose intolerance are not established, but compromised blood flow to islets from

fibrotic scarring of exocrine pancreas appears to play a major role. Insulin and c-peptide secretory responses to various secretagogues, including oral and IV glucose, sulfonylureas, glucagon, and amino acids, are impaired, and these abnormalities are correlated with the magnitude of exocrine pancreatic dysfunction[13,14]. Glucagon levels are markedly increased in acute pancreatitis, both in the basal state and following stimulation with alanine, accounting in part for the transient hyperglycemia frequently seen in this situation[15]. In chronic pancreatitis, basal glucagon levels are normal or elevated, but responses to amino acids[15,16] or to insulin-induced hypoglycemia[17,18] are blunted. In some studies, increased levels of glucagon-like immunoreactivity were found after stimulation[9,19], perhaps due to glucagon derived from extrapancreatic sources, but the significance of this observation is uncertain.

Patients with diabetes secondary to chronic pancreatitis may have delayed recovery from hypoglycemia, similar to the situation in pancreatectomized subjects. However, the incidence and severity of hypoglycemia in these patients is influenced by a number of factors, including alcohol intake, nutritional status, and state of malabsorption.

MALNUTRITION-RELATED DIABETES

In many tropical countries, extending from the West Indies and Latin America to Africa to the Indian subcontinent and Southeast Asia, diabetes presents with many atypical clinical features[11,20,21]. Initially characterized by Hugh-Jones in Jamaica and termed J-type diabetes[22], some of the features include onset at young age, resistance to ketosis, relatively large insulin requirement, and lean body habitus. A number of variants have been described from many of the tropical countries. Malnutrition and protein deficiency are the common features in most of the variants, and the prevalence estimates, although not adequately studied in all areas, range from <10% to >75% of all diabetic persons age <40 years[11].

The World Health Organization has identified two main subgroups: protein-deficient pancreatic diabetes (or J-type diabetes) and fibrocalculous pancreatic diabetes[23]. In fibrocalculous pancreatic diabetes, no history of alcohol, biliary disease, or other known causes of pancreatitis exist. However, β-cell functional loss appears to be correlated with exocrine functional loss[24], similar to the situation with chronic pancreatitis in general[10,13,14]. The etiology of both forms of malnutrition-related diabetes and their relationship, if any, to conventional IDDM or NIDDM remain enigmatic[11,21,25-27]. Theories relating malnutrition to diabetes abound[28], although none has been proven. One possibility is that protein deficiency might render β-cells susceptible to damage by toxic, viral, or autoimmune factors. It has been observed that tropical diabetes is endemic where cassava (tapioca) is the staple food[28,29]. Cassava (95% starch) contains a cyanogenic glycoside that is normally inactivated by thiocyanate derived from sulfhydryl radicals of amino acids. Oral or intraperitoneal administration of cyanide in rats results in transient hyperglycemia. However, the causal relationship is far from proven and there are exceptions to the association between cassava consumption and diabetes in Africa and Brazil[21,30,31].

HEMOCHROMATOSIS

Hemochromatosis, one of the most commonly inherited metabolic abnormalities in white populations, is an autosomal-recessive disorder. Its gene frequency is 7%-10% and disease prevalence is 2-4 per 1,000 in Caucasians[32,33]. The disease is three to five times more frequent in men than women, since ~80% of homozygous women do not accumulate iron significantly. About 70% of patients have antigen HLA-A3, whereas the frequency of HLA-A3 is only ~22%-28% in general Caucasian populations[33].

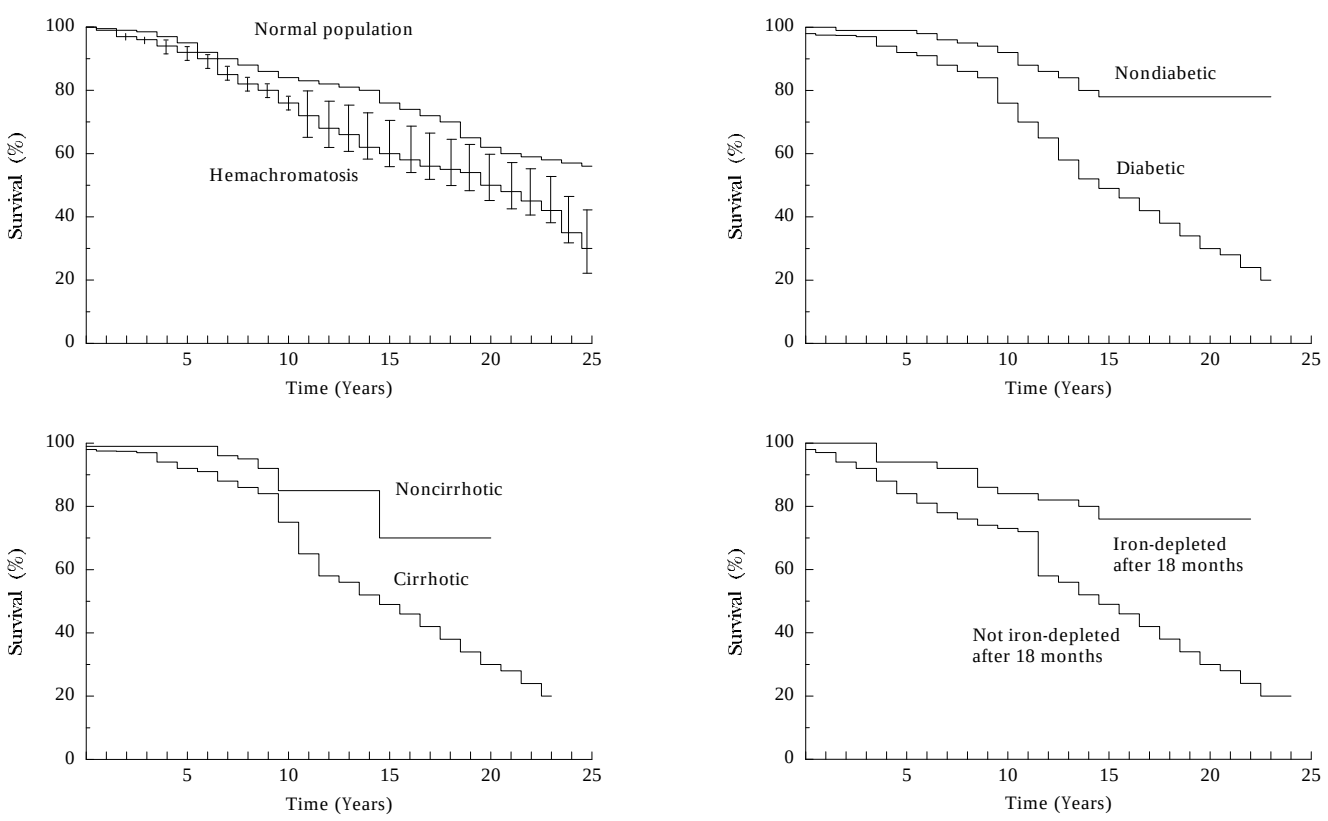
Iron deposition primarily occurs in parenchymal cells of liver, pancreas, adrenal, anterior pituitary, myocardium, and skeletal muscle. The classic triad of hepatomegaly, diabetes, and skin pigmentation ("bronze diabetes") once considered common is, in fact, not a frequent association considering the changing clinical presentation due to early diagnosis and treatment[32,34]. Common presenting symptoms include hepatomegaly with or without abdominal pain, arthralgias, fatigue, and impotence. Presence of symptoms usually correlates with the severity of iron accumulation documented on liver biopsy and with the presence of cirrhosis, which is already present in ~70% of patients at the time of diagnosis[35]. Hepatocellular carcinoma develops in ~15%-30% of patients, despite successful iron removal, depending on patient longevity.

Hemochromatosis may result from a number of secondary causes, including sideroblastic anemias (chiefly, thalassemia major), chronic hemolytic anemias, multiple blood transfusions, porphyria cutanea tarda, and dietary or medical iron overload, e.g., iron-rich beer consumption in the Bantus[32]. In these states, the severity of iron load is variable but usually less than the 30 g or more seen in primary (idiopathic) hemochromatosis. Alcohol promotes iron absorption but does not, by itself, result in hemochromatosis.

Abnormal glucose tolerance occurs in 75%-80% of patients with hemochromatosis, of whom ~50%-60% have overt diabetes[35-37]. Similarly, glucose intolerance is present in ~50% of patients with thalassemia major following chronic transfusion therapy[38,39]. In a large series of patients, 25% had a history of diabetes in first-degree relatives[36]. The pathogenesis of glucose intolerance in iron-overload states remains controversial since multiple factors, including cirrhosis, pancreatic iron deposition, and underlying primary diabetes, are involved. However, the severity of cirrhosis and iron load are correlated with the severity of glucose intolerance, and the control of diabetes improves in 35%-45% of patients following iron depletion[32,35].

Studies of β-cell and α-cell function in hemochromatosis have revealed several interesting observations. β-cell function is usually impaired in patients developing overt diabetes[36-38] and ~40%-50% of these require insulin therapy. However, patients in the pre-cirrhotic stage and in those prior to development of overt diabetes have significant hyperinsulinemia following oral glucose[40,41] or hyperglycemic clamp[41]. Furthermore, insulin-mediated glucose disposal rates are impaired in patients with transfusion-induced iron overload[41]. These observations suggest that insulin resistance, secondary to hepatic or extra-hepatic iron deposition at insulin-sensitive sites (e.g., muscle), precedes the eventual β-cell dysfunction before overt diabetes develops. However, the mechanism of insulin resistance due to iron overload remains unknown. Glucagon secretion in patients with hemochromatosis is augmented by arginine and is nonsuppressible after oral glucose[42,43], similar to responses seen in primary diabetes. In this respect, the α-cell responses seem to differ from those seen in patients with chronic pancreatitis[13,14] and are consistent with the observation that iron deposition in islets, albeit variable, is restricted only to β-cells[44].

Figure 5.2
Survival of Patients with Hemochromatosis



The figure shows cumulative survival in 163 patients with hemochromatosis compared with the normal population; in the same patients with (n=112) or without (n=51) cirrhosis; with (n=89) or without (n=74) diabetes; and in those depleted (n=77) or not depleted (n=75) of iron during the first 18 months of venesection. All differences were statistically significant ($p<0.05$ to <0.002 by log-rank test).

Source: Reference 35

Successful iron depletion, initiated early in the course of disease, clearly reduces the incidence and progression of cirrhosis, improves diabetes control, and frequently reduces other target organ damage and overall morbidity and mortality. In a prospective study of 163 patients with mean followup of 10.5±5.6 years, major determinants of reduced survival included presence of cirrhosis, diabetes, and lack of iron depletion[45] (Figure 5.2). Mortality ratios (observed/expected) for liver cancer, cardiomyopathy, cirrhosis, and diabetes were 219, 306, 13, and 7, respectively, compared with the general population. Successful iron depletion, however, did not protect from developing liver cancer. In patients unable to undergo phlebotomy, such as patients with thalassemia or other anemic states, chelation therapy with deferoxamine is a useful alternative[45,46], although the effects of this regimen on long-term outcomes are not available.

ENDOCRINOPATHIES

Table 5.2 shows the major sites of action of various counterregulatory hormones on target organs and their principal mechanisms of diabetogenic effects.

ACROMEGALY

Acromegaly represents a prototype of diabetes and glucose intolerance secondary to an endocrinopathy. Growth hormone (GH)-hypersecreting anterior pituitary adenomas account for >90% of cases of acromegaly[47,48]. Other causes include ectopic (nonpituitary) sources of GH or GH-releasing hormone, e.g., pancreatic islet cell tumors, carcinoid tumors, and hypothalamic hamartomas. The prevalence of diagnosed acromegaly is estimated to be ~40 per million population.

Glucose intolerance is prevalent in acromegaly in ~60%-70% of patients; however, overt diabetes requiring treatment occurs in only 10%-15% of patients[47-50]. Diabetes may be the presenting sign in only ~5% of patients with acromegaly[48,50]. Even more frequent than glucose intolerance is GH-induced insulin resistance, manifested by striking hyperinsulinemia in response to oral or intravenous glucose and other secretagogues, as well as markedly attenuated responses to exogenous insulin[51-54]. Furthermore, acromegalic patients with normal glucose tolerance but with hyperinsulinemia have impaired muscle glucose uptake due to diminished nonoxidative glucose metabolism[55]. Overall, GH levels in individual patients correlate poorly with both hyperinsulinemia and the severity of glucose intolerance; a better correlation of disease activity, including glucose intolerance, is found with the serum levels of insulin-like growth factor 1 (IGF-1)[47,56]. In contrast to patients with normal or impaired glucose tolerance, insulin reserve is quite blunted by the time overt diabetes develops, with or without ketosis[52], reminiscent of findings in animal models of metasomatotrophic diabetes[57]. However, the coexistence of primary diabetes (IDDM or NIDDM) cannot be ruled out in the absence of a genetic marker, particularly if diabetes persists after successful treatment of acromegaly. Considerable evidence exists, based on studies with somatostatin infusions, that lipolytic and ketogenic effects of GH supervene only after significant insulinopenia occurs[54,58,59].

Successful treatment of acromegaly, with normalization of GH and IGF-1, is usually accompanied by striking improvements in glucose tolerance, reversal of hyperinsulinemia, and normalization of insulin sensitivity[47,52,56]. However, the results are unpredictable in those with overt, symptomatic diabetes[52,60]. Acromegaly is associated with two- to threefold increased mortality rate[50,61]. Increased incidence of malignancy contributes to the increased mortality. Post-therapy GH levels <5 mU/L (versus >10 mU/L) were associated with normalization of mortality rate, regardless of the presence of diabetes or hypertension,

Table 5.2
Sites of Action of Major Diabetogenic Hormones in Humans

		Liver		Muscle		Adipose tissue	
	β-cell secretion	Glycogen*	Gluconeogenesis	Glucose uptake	Amino acid release	Glucose uptake	Lipolysis
Growth hormone	+	+	+	-	?	-	+
Glucocorticoids	+	+	+	-	+		+
Catecholamines	-	-	+	-	-	?	+
Glucagon	+	-	+	0	?	0	?
Thyroid hormones	+	-	+	0	0	?	+

+, stimulation; -, inhibition; 0, no effect; ?, uncertain. *Net effect on glycogen content via glycogen synthesis or glycogenolysis.

in one survey[61].

ISOLATED GROWTH HORMONE DEFICIENCY

It has long been appreciated that GH has cytotrophic effects on β-cells *in vitro*[62,63] . Exogenous GH administration to both normal and hypopituitary subjects augments their insulin responses to a variety of secretagogues before a significant change in blood glucose ensues[64]. In light of these observations, it is of interest that patients with monotropic GH deficiency (sexual ateliotic dwarfs) have mild to moderately severe glucose intolerance and insulin deficiency[65]. In the majority of these patients, insulin responses to glucose or arginine are impaired, and treatment with GH results in augmented insulin release[66]. This model of diabetes supports the role of GH in sustaining β-cell growth and maturation.

CUSHING'S SYNDROME

Glucocorticoids such as GH are the principal insulin-antagonistic hormones. They have diverse metabolic effects on liver, adipose tissue, and muscle[67,68]. In normal humans, short-term increments in plasma cortisol levels within the range seen in moderate stress situations result in only a slight increase in glucose levels, mediated by hepatic and extrahepatic effects, but cause a significant increase in ketone and branched-chain amino acid levels. Insulin resistance induced by the chronic administration of moderate doses of glucocorticoids in normal humans is usually compensated by augmented insulin release, resulting in minimal changes in glucose levels. Thus, the spectrum of glucose intolerance in patients with Cushing's syndrome or exogenous steroid use largely depends on endogenous β-cell reserve, similar to the situation in acromegaly. Glucose intolerance occurs in 75%-80% of patients with Cushing's syndrome, but only 10%-15% of patients develop overt diabetes[69,70]. Nearly all patients, however, manifest basal and stimulated hyperinsulinemia and insulin resistance.

PHEOCHROMOCYTOMA

Catecholamines, acting via adrenergic receptors, affect insulin secretion and produce anti-insulin effects at several loci in the intermediary metabolism[71,72] . Glucose intolerance occurs in ~30% of patients with pheochromocytoma[72,73]. It results from multiple mechanisms including the α_2-adrenergic inhibition of insulin secretion, β-adrenergic stimulation of hepatic glycogenolysis and gluconeogenesis, and enhanced lipolysis. Overt diabetes and ketoacidosis are distinctly unusual. Administration of α-adrenergic blocking agents, such as phentolamine or phenoxybenzamine, characteristically improves insulin secretion and glucose tolerance[74,75]. Surgical removal of the tumor restores or improves glucose tolerance within several weeks post-operatively[73,76]; however, in some cases, it may take up to several months.

PRIMARY HYPERALDOSTERONISM

The triad of hypertension, hypokalemia, and glucose intolerance (Conn's syndrome) was described in 1955[77]. It occurs in <2% of patients with hypertension. Glucose intolerance, previously thought to be present in ~50% of these patients, is considerably less common and is usually mild. It probably results, to a variable degree, from potassium depletion, which may be responsible for blunted insulin secretion[77,78] and perhaps increased glycogenolysis. However, it is not certain if the glucose intolerance seen in Conn's syndrome is entirely explained by potassium depletion[79].

HYPERTHYROIDISM

Hyperthyroidism or thyrotoxic states are associated with significant aberrations of carbohydrate, lipid, and protein metabolism[80]. These states are characterized by increased oxygen consumption, rapid gastric emptying, enhanced gluconeogenesis and glycogenolysis, increased lipolysis and ketogenesis, and increased proteolysis. Many of these effects are reproducible in experimental hyperthyroidism induced in nondiabetic[81] or diabetic[82] individuals. The metabolic clearance rate of insulin is increased by ~40%[83]. The data on peripheral glucose disposal and insulin sensitivity are controversial, perhaps due to differences in methodology employed.

An increased incidence of glucose intolerance, usually of mild to moderate severity, has been documented in 30%-50% of patients with hyperthyroidism[84-86] . An increased sympathetic sensitivity, mediated via β-adrenergic mechanism[87], probably contributes to the increased propensity to lipolysis and ketogenesis in such patients. In patients with preexisting diabetes, the metabolic consequences of untreated hyperthyroidism on hepatic glucose production, lipolysis, and increased insulin clearance lead to deterioration of glycemic control and recurrent ketoacidosis[88]. In previously nondiabetic individuals, glucose intolerance persisted in 32% (7 of 22) of patients with hyperthyroidism after 12 years of followup after treatment[86]. This may be explained partly by common autoim-

mune mechanisms underlying Graves' disease and IDDM.

TUMORS OF ENDOCRINE PANCREAS OR GUT

Glucose intolerance or overt diabetes is a frequent component of non-β-cell tumors of the endocrine pancreas that secrete glucagon (glucagonoma) or somatostatin (somatostatinoma)[89]. Approximately 100 patients with glucagonoma and >20 patients with pancreatic somatostatinoma have been described. These tumors are often malignant and quite large when diagnosed. The prognosis is usually poor, with rare exceptions. Other clinical features of glucagonoma include a characteristic skin rash (necrolytic migratory erythema) and anemia. Patients with somatostatinoma frequently have gallbladder disease and diarrhea with or without steatorrhea. Mild glucose intolerance has occasionally also been described in patients with non-islet cell tumors secreting vasoactive-intestinal polypeptide (VIPOMA, pancreatic cholera syndrome) and with carcinoid tumors of the pancreas or gut. Finally, in patients with multiple endocrine neoplasia type 1, transmitted as an autosomal dominant disorder and resulting in endocrine, pancreas, parathyroid, and pituitary tumors, glucose intolerance may result from the production of diabetogenic hormones such as glucagon, VIP, corticotropin, and somatostatin.

Table 5.3
Characteristics of Polyendocrine Autoimmunity Syndromes

	Type I	Type II
HLA association	None	DR3/DR4
Age at onset	Childhood	Adult
Gender ratio (F/M)	1/4	1/8
Clinical components		
Frequent	Hypoparathyroidsm (80%) Mucocutaneous candidiasis (75%) Addison's disease (65%)	Addison's disease (100%) Hypothyrodism (70%) Diabetes mellitus (50%)
Infrequent	Alopecia (30%) Malabsorption (25%) Gonadal failure (15%) Pernicious anemia (15%) Chronic active hepatitis (10%) Thyroiditis (10%) Vitiligo (10%) Diabetes (2%-4%)	Gonadal failure (5%) Vitiligo (5%) Celiac disease (5%) Alopecia Myasthenia gravis Pernicious anemia

Source: References 90 and 91

POLYENDOCRINE AUTOIMMUNITY SYNDROMES

Insulin-requiring diabetes has been observed in ~50% of patients with polyendocrine autoimmunity syndrome type II, in contrast to <5% prevalence in type I syndrome[90,91]. The other salient clinical features of these syndromes are outlined in Table 5.3. Type II syndrome has strong association (>95%) with HLA DR3/DR4 and characteristically multiple generations are affected, whereas in type I syndrome the affected relatives are siblings in a single generation and there is no increase in HLA DR3/DR4. The early detection of diabetes in type II syndrome (Schmidt's syndrome) may be possible by prospective evaluation with cytoplasmic anti-islet antibodies and assessment of first-phase insulin response to intravenous glucose. These patients may have insidious onset of diabetes years after onset of initial endocrinopathy such as Addison's disease or thyroid disease.

POEMS SYNDROME

POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes) is a rare form of plasma cell disorder associated with osteosclerotic type of myeloma and systemic features including hepatosplenomegaly, lymphadenopathy, severe sensorimotor neuropathy, hyperpigmentation, and hypertrichosis. About 100 cases have been reported[92-94]. In most cases (>90%), the M-component is of the lambda-light chain type. Other eponyms of this entity include Takatsuki syndrome and Crow-Fukase syndrome. A relationship of this syndrome to multicentric angiofollicular lymph node hyperplasia (Castleman's disease) has also been suggested[95]. The etiology of these entities is obscure but they appear to be secondary to circulating immunoglobulins. Glucose intolerance, sometimes insulin-requiring, has been reported in 30%-50% of cases[92,93]. Other endocrine features include hypogonadism, hypothyroidism, hyperprolactinemia, and adrenal insufficiency.

DRUGS, CHEMICAL AGENTS, AND TOXINS

A variety of drugs or chemical agents (Table 5.1) can result in glucose intolerance or diabetes in previously nondiabetic subjects or in worsening of hyperglycemia in known diabetic patients[96,97]. The diabetogenic effects may be brought about by effects on islet cell secretion or on insulin action at hepatic or extrahepatic sites, or by variable combinations of these factors.

Table 5.4 presents the principal mechanisms of the diabetogenic effects of certain therapeutic agents that are more commonly associated with glucose intolerance or diabetes.

DIURETICS AND β-ADRENERGIC ANTAGONISTS

The diabetogenic effects of diuretics, particularly thiazides and chlorthalidone, and β-adrenergic antagonists have been well recognized in clinical practice. These effects appear to be dose-dependent. A 12-year follow-up epidemiologic study revealed, regardless of a family history of diabetes, a three- to fourfold greater risk of developing diabetes with thiazides, five- to sixfold greater risk with β-blockers, and 11-fold greater risk in subjects on both drugs[98]. For thiazides, most studies have indicated the mechanism to be an insulin secretory defect due to hypokalemia, with at least partial correction of this defect by potassium replacement[99]. However, the potassium depletion may not, by itself, entirely explain this phenomenon, since loop diuretics such as furosemide and ethacrynic acid are less likely to cause this defect. There is also evidence for extrapancreatic effects[100,101]. Furthermore, diazoxide, a non-diuretic thiazide, has pronounced β-cell inhibitory as well as peripheral effects[102]. For β-blockers, an inhibitory effect on β-cell secretion has been shown[103] and, in some cases, drugs such as propranolol precipitated hyperglycemic, hyperosmolar, non-ketotic coma[104]. However, evidence for peripheral effects resulting in insulin resistance with propranolol has also been reported[100,101].

Table 5.4
Sites of Action of Drugs or Agents More Commonly Associated with Diabetes or Glucose Intolerance

	Impaired insulin secretion	Impaired insulin action	Comments
Diuretics			
Thiazide	+	±	Effects primarily mediated
Loop diuretics	+	0	by potassium depletion
Diazoxide	+	+	A non-diuretic thiazide
β-adrenergic antagonists	+	+	Effects more common with non-selective agents
Diphenyl-hydantoin	+	0	Direct β-cell effects
Glucocorticoids	0	+	Also cause hyperglucagonemia
Oral contra-ceptives	0	+	Effects less prominent than glucocorticoids
Pentamidine	+	0	Structurally similar to
Pyriminil (Vacor)	+	±	streptozotocin and alloxan
Nicotinic acid	0	+	Minimal effects in normal subject
Cyclosporine	+	+	Often used in combination with glucocorticoids
Opiates	+	±	Also stimulate glucagon secretion

DIPHENYLHYDANTOINS

Phenytoin (Dilantin) has direct inhibitory effects on β-cell secretion[105]. This appears to be dose-related and there are occasional case reports of hyperglycemic, nonketotic coma precipitated by Dilantin[106].

GLUCOCORTICOIDS, ORAL CONTRACEPTIVES, AND PROGESTINS

Glucocorticoid-induced glucose intolerance is characterized by insulin resistance and hyperinsulinemia. Similar to patients with Cushing's syndrome, chronic administration of glucocorticoids induces distinct effects on hepatic and extra-hepatic sites. In a recent community-based case-control study, the adjusted odds ratios for initiation of hypoglycemic therapy (oral agents or insulin) were 1.77, 3.02, 5.82, and 10.34, according to prednisone-equivalent average daily dosage of <10 mg, 10-20 mg, 20-30 mg, and >30 mg, respectively[107]. The effects of sex steroid hormones on carbohydrate metabolism are somewhat controversial[96]. The bulk of evidence from better-designed recent studies suggests that postmenopausal estrogen use in current formulations, with or without low-dose progestins, has no appreciable deleterious effects on glucose or insulin levels, as shown in a recent multicommunity study[108]. However, the effects of oral contraceptives on carbohydrate metabolism in young women are much more dependent on the formulations, particularly on the dose and relative potency of the progestin component of the pill. In a large cross-sectional study, employing oral glucose tolerance tests in 1,060 women on oral contraceptives, incremental glucose and insulin responses were 43%-61% and 12%-40% higher, respectively, than in nonusers[109]. However, incidence of overt diabetes is distinctly rare in individuals without a family history of diabetes[110].

PENTAMIDINE AND VACOR

Pentamidine (an anti-protozoal agent) and Vacor (a nitrosourea-derived pesticide) chemically resemble streptozotocin and alloxan. Pentamidine is used increasingly in the prophylaxis and treatment of pneumocystis carinii infection in patients with acquired

immune deficiency syndrome (AIDS), and increasing incidence of insulin-dependent diabetes following its use has been reported[111,112]. Similarly, after accidental or intentional ingestion of Vacor, IDDM with or without ketoacidosis due to β-cell destruction may result[113,114]. The sequence of events leading to diabetes with these agents is similar to that seen with streptozotocin and involves: a) initially, release of insulin due to β-cell lysis lasting for hours and frequently associated with hypoglycemia; and b) a delayed, persistent hyperglycemia following β-cell loss after days to weeks[113,115].

NICOTINIC ACID

Nicotinic acid causes glucose intolerance by inducing peripheral insulin insensitivity[116]. In normal individuals this is accompanied by minimal changes in glucose tolerance due to adaptive hyperinsulinemia. However, significant hyperglycemia or deterioration in glucose tolerance may result in patients with limited β-cell reserve or preexisting diabetes[117].

CYCLOSPORIN

An increased incidence of diabetes has been reported in renal transplant patients treated with cyclosporin[118,119], particularly in the black population, in whom a 20% incidence posttransplant was reported[118]. This increase is probably independent of the concomitant diabetogenic effects of corticosteroids in these patients. Direct inhibitory effects of cyclosporin on β-cells are the likely explanation[120], although a peripheral effect on muscle glucose transport is also probable[121].

OPIATES

A hyperglycemic effect of morphine and other opiates has been recognized. β-endorphin and enkephalin are produced in human islets. In normal and diabetic subjects, infusions of β-endorphin result in hyperglycemia, accompanied by hyperglucagonemia[122]. These results are in keeping with the observation of impaired β-cell responsiveness to glucose in narcotic addiction[123].

GENETIC SYNDROMES

The availability of newer molecular biologic techniques and their clinical application is unraveling distinct genetic subtypes of diabetes, although all genetic syndromes identified thus far account for only a small percentage of the diabetic population as a whole. This confirms the heterogeneity of diabetes[124].

Table 5.5 summarizes the genetic defects identified in relation to various candidate genes. Of these, molecular defects in families with mutant insulins have been best characterized[125]. In 10 families, single point mutations in the proinsulin gene, transmitted in an autosomal dominant pattern, resulted in either an abnormal insulin molecule (Table 5.6) or an abnormal

Table 5.5
Diabetes Secondary to Identified Defects in Genetic Loci

Ref.	Gene affected	Number of mutations identified	Prevalence in diabetic persons	Comments
125, 126	Insulin	6	<1%	Abnormal insulin or proinsulin synthesis
127, 128	Insulin receptor	>40	~1%-2%	Numerous defects in receptor synthesis, transport, function or degradation
129-131	Glucokinase	16	~1%-2% (~55% of MODY families in France)	Impaired glucose sensing of β-cells
132	Adenosine deaminase-linked	1	One large kindred (RW)	
134, 135	Mitochondrial tRNA	1*	~1%-2%	Impaired insulin secretion; maternally transmitted diabetes and deafness
137	IRS-1	2	?	Site of defect unclear
138	Glycogen synthase	Polymorphism of non-coding region	Unknown	Functional significance uncertain. No change in protein content.
139	Rad (Ras-associated with diabetes)		Unknown (expression of gene in muscle 3- to 18-fold greater in NIDDM than in IDDM or controls)	AGTP-binding protein

MODY, maturity-onset diabetes of the young. *The same mutation (tRNA-leu (UUR)) is also observed in MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.

Source: References are listed within the table

Table 5.6
Characteristics of Probands from Six Families with Abnormal Insulin

	Chicago	Los Angeles 1	Los Angeles 2	Wakayama 1	Wakayama 2	Wakayama 3
Age (years), sex	51, male	28, female	60, female	56, female	57, male	44, female
Location	Los Angeles, CA	Los Angeles, CA	Montreal, Canada	Osaka, Japan	Wakayama, Japan	Saitama, Japan
OGTT results	DM	DM	IGT	DM	Normal	DM
Therapy	Diet → insulin	Diet → oral hypoglycemic	None	Insulin → oral hypoglycemic	Diet	Oral hypoglycemic
Plasma glucose (mg/dl)	143-182	143-175	93-140	113-340	70- 102	154-244
Immunoreactive insulin (μu/ml)	67-113	86-130	310-440	33-130	58-130	111-314
Insulin-C-peptide ratio (mol)	0.4-0.5	0.7-2.1	1.2	0.5-3.5	0.6-1.6	1.0-1.6
Structure	Leu-B25	Ser-B24	Ser-B24	Leu-A3	Leu-A3	Leu-A3
Receptor binding (%)	4.0-5.0	0.7-2.0	0.7-2.0	0.2-0.4	0.2- 0.4	0.2-0.4
Biological activity (%)	4.0-5.0	0.7-2.0	0.7-2.0	0.2-0.4	0.2- 0.4	0.2-0.4

OGTT, oral glucose tolerance test; DM, diabetes mellitus; IGT, impaired glucose tolerance.

Source: Reference 125

proinsulin molecule (Table 5.7). Of the six families with abnormal insulin, three different single point mutations causing amino acid substitutions resulted in insulin with normal immunoreactivity but greatly reduced (<1%-5%) receptor binding and bioactivity. The hyperinsulinemia mainly results from defective clearance of the mutant insulin. The affected subjects presented with only glucose intolerance or mild diabetes since they were heterozygous and a varying proportion of circulating insulin was normal. In four other families, single point mutations causing defects in processing the proinsulin molecule resulted in hyperproinsulinemia (Table 5.7). In each family, the phenotypic expression consisted of either normal or mildly abnormal glucose tolerance. Further search may disclose other forms of insulin gene mutations. However, in a restriction-fragment-length polymorphism analysis of the insulin gene in 213 individuals with NIDDM, only one possible defect (frequency ~5/1,000) was detected in one survey[126]. Glucose intolerance or diabetes may also result from severe to extreme insulin resistance due to abnormalities of insulin receptor structure or function. A wide variety of mutations at numerous sites of the insulin receptor gene have been delineated, but the overall prevalence of these anomalies in NIDDM is probably very low[127,128].

Perhaps more common than the insulin gene and the insulin receptor gene defects are the mutations in the glucokinase (GK) gene on chromosome 7, responsible for mild hyperglycemia in many families with maturity-onset diabetes of the young (MODY). Although the prevalence of this defect in NIDDM in various populations is unknown, there have been 16 different mutations of the GK gene described in 18 of 32 French families with MODY[129]. Mutations of the GK gene have also been reported in a few kindreds from other parts of the world, including Great Britain and Japan[130,131] . Only ~50% of patients with GK gene mutations developed diabetes, i.e., there is incomplete penetrance. A different mutation, on a gene linked to the adenosine deaminase gene on chromosome 20, was described in a large kindred of MODY in the United States[132]. However, in many other MODY pedigrees the molecular nature of the genetic defect remains unknown, despite extensive search for candidate genes[133]. Since MODY represents a significant fraction of NIDDM in many parts of the world, further search for the prevalence of defects in GK and other

Table 5.7
Characteristics of Probands from Four Families with Abnormal Proinsulin

	Boston, MA	Providence, RI	Tokyo, Japan, 1	Tokyo, Japan, 2
Age (years), sex	15, male	12, male	65, male	69, male
OGTT results	Normal	DM/IGT	DM	DM
Therapy	Not required	Insulin → diet	Diet	Diet → insulin
Plasma glucose (mg/dl)	74-92	77-96	120	60-170
Immunoreative insulin (μu/ml)	24-287	45-71	77	37-70
Structure	Xaa-65	Asp-B10	His-65	His-65
HPLC analysis (plasma)	AC proinsulin	Normal proinsulin	AC proinsulin	AC proinsulin
Hypoglycemia	-	?	+	+ ? in family

OGTT, oral glucose tolerance test; DM, diabetes mellitus; IGT, impaired glucose tolerance; HPLC, high-performance liquid chromatography; AC, A chain-C-peptide; +, documented; -, not documented; ?, uncertain.

Source: Reference 125

genetic loci might be rewarding. Another interesting genetic subtype of diabetes is associated with a point mutation in mitochondrial DNA at position 3243 of leucine tRNA[134,135]. Diabetes in these families is maternally transmitted, often insulin-requiring, and associated with deafness in ~60% of patients. This mutation was originally identified in patients with another mitochondrial disorder, the MELAS syndrome (Mitochondrial myopathy, Encephalopathy, Lactic acidosis, and Stroke-like episodes)[136]. Other candidate gene mutations in NIDDM include a recently described polymorphism of the insulin-receptor substrate-1 (IRS-1) gene[137], a polymorphism of the glycogen synthase gene[138], and an overexpressed gene, Rad, a member of the Ras-guanosine triphosphatase superfamily, that was expressed 3- to 18-fold greater in skeletal muscle of patients with NIDDM, compared with nondiabetic and IDDM patients[139].

There are many other distinct but quite rare genetic syndromes associated with glucose intolerance or diabetes (Table 5.1). The precise genetic defect(s) leading to diabetes in these disorders are not known. Some are characterized by obesity-associated insulin resistance, including Prader-Willi syndrome[140], Laurence-Moon-Biedl syndrome, and its variant, Bardet-Biedl syndrome[141]. In the latter, ~45% of patients have glucose intolerance. In a few of the other syndromes, the appearance of insulin-dependent diabetes simulating IDDM is an integral feature. These conditions include Stiff-man syndrome, an autoimmune disorder[142], and two hereditary neurological disorders, Friedreich's ataxia[143] and DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, sensorineural deafness) or Wolfram's syndrome and its variants[144,145]. In the former, up to 20% of patients have diabetes, although some may not be insulin-dependent[146]. In contrast, in Wolfram's syndrome, autopsy studies revealed a selective loss of islet β-cells[147], explaining the onset of diabetes in early childhood and absolute insulin requirement in these patients.

Dr. Om P. Ganda is Diabetologist, the Joslin Diabetes Center, Boston, MA.

REFERENCES

1. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039-57, 1979
2. McCulloch DK, Koerker DJ, Kahn SE: Correlations of in vivo β-cell function tests with β-cell mass and pancreatic insulin content in streptozotocin-administered baboons. *Diabetes* 40:673-91, 1991
3. Kendall DM, Sutherland DER, Najarian JS: Effects of hemipancreatectomy on insulin secretion and glucose tolerance in healthy humans. *N Engl J Med* 322:898-903, 1990
4. Seaquist ER, Robertson RP: Effects of hemipancreatectomy on pancreatic alpha and beta cell function in healthy human donors. *J Clin Invest* 89:1761-66, 1992
5. Weir GC, Bonner-Weir S, Leahy JL: Islet mass and function in diabetes and transplantation. *Diabetes* 39:401-05, 1990
6. Barnes AJ, Bloom SR: Pancreatectomized man: A model for diabetes without glucagon. *Lancet* 1:219-21, 1976
7. Boden G: Extrapancreatic glucagon in human subjects. In *Glucagon, Physiology, Pathophysiology and Morphology of the Pancreatic A β-cells*, Unger RH, Orci L, eds. New York, Elsevier, 1981, p. 349-57
8. Holst JJ, Pedersen JH, Baldessera F, Stadil F: Circulating glucagon after total pancreatectomy in man. *Diabetologia* 25:396-99, 1983
9. Vinik AI, Jackson WPU: Endocrine secretions in chronic pancreatitis. In *Secondary Diabetes: The Spectrum of the Diabetic Syndromes*, Podolsky S, Viswanathan M, eds. New York, Raven Press, 1980, p. 165-89
10. Banks S: Chronic pancreatitis: Clinical features and medical management. *Am J Gastroenterol* 81:153-67, 1986
11. Abu-Bakare A, Taylor R, Grill GV, Alberti KGMM: Tropical or malnutrition diabetes. *Lancet* 1:1135-38, 1986
12. Boat TF, Welsh MJ, Beaudet AL: Cystic fibrosis. In *The Metabolic Basis of Inherited Disease, 6th Edition*, Scriver CR, Beaudet AL, Sly WS, Valle D, eds. New York, McGraw-Hill, 1989, p. 2649-80
13. Kalk WJ, Vinik AI, Jackson WPU, Bank S: Insulin secretion and pancreatic exocrine function in patients with chronic pancreatitis. *Diabetologia* 16:355-58, 1979
14. Anderson BN, Krarup T, Pedersen NT: β-cell function in patients with chronic pancreatitis and its relation to exocrine pancreatic function. *Diabetologia* 23:86-89, 1982
15. Donowitz M, Hendler R, Spiro HM: Glucagon secretion in acute and chronic pancreatitis. *Ann Intern Med* 83:778-81, 1975
16. Tiengo A, Bessioud M, Valverde I: Absence of islet α-cell function in pancreatectomized patients. Diabetologia 22:25-32, 1982
17. Persson I, Gyntelberg F, Heding LG, Boss-Nielsen J: Pancreatic glucagon-like immunoreativity after intravenous insulin in normals and chronic-pancreatitis patients. *Acta Endocrinologica* 67:401-04, 1971
18. Larsen S, Hilsted J, Philipsen EK: Glucose counter-regulation in diabetes secondary to chronic pancreatitis. *Metabolism* 39:138-43, 1990
19. Kalk WJ, Vinik AI, Paul M: Immunoreactive glucagon responses to intravenous tolbutamide in chronic pancreatitis. *Diabetes* 24:851-55, 1975
20. Ekoe JM: Recent trends in the prevalence and incidence of diabetes mellitus syndrome in the world. *Diab Res Clin Pract* 1:249-64, 1986
21. Johnson TO: Malnutrition-related diabetes mellitus: A syndrome seeking clarity. *IDF Bulletin* 37 (no. 3):5-6, 1992
22. Hugh-Jones P: Diabetes in Jamaica. *Lancet* 2:891-97, 1955
23. World Health Organization Study Group: Diabetes Mellitus. Technical Report Series No. 727. WHO, Geneva, 1985
24. Yajnik ES, Shelgikar KM, Sahasrabudhe RA: The spectrum of pancreatic exocrine and endocrine (β-cell) function in tropical calcific pancreatitis. *Diabetologia* 33:417-21, 1990
25. Ahuja MMS: Profile of young Indian diabetics. *Acta Diab Lat* 10:439-53, 1973
26. Bajaj JS: Malnutrition-related, ketosis-resistant dibetes mellitus: Classification, causes and mechanisms. In *World Book of Diabetes in Practice*, Krall LP, ed. Amsterdam: Elsevier Science Publishers, 1986, p.276-80
27. Ramachandran A, Mohan V, Snehlatha C: Clinical features of diabetes in the young as seen at a diabetes center in South India. *Diab Res Clin Prac* 4:117-25, 1988
28. Rao RH: Diabetes in the undernourished: Coincidence or consequence? *Endocrine Rev* 9:67-87, 1988
29. McMillan DE, Geevarghese PJ: Dietary cyanide and tropical malnutrition diabetes. *Diabetes Care* 2:202-08, 1979
30. Teuscher T, Baillod P, Rosman JB, Teuscher A: Absence of diabetes in a rural West African population with a high carbohydrate/cassava diet. *Lancet* 1:765-68, 1987
31. Swai ABM, Mlingi N, Mclarty DG: Diabetes is not caused by cassava toxicity. A study in a Tanzanian community. *Diabetes Care* 13:1378-85, 1992
32. Crosby WH: Hemochromatosis: Current concepts and management. *Hosp Practice* 22:173-92, 1987
33. Edwards CQ, Kushner JP: Screening for hemochromatosis. *N Engl J Med* 328:1616-20, 1993
34. Adams PC, Kertesz AE, Valberg LS: Clinical presentation of hemochromatosis: A changing scene. *Am J Med* 90:445-49, 1991
35. Niederau C, Fischer R, Sonnenberg A: Survival and causes of death in cirrhotic and in non-cirrhotic patients with primary hemochromatosis. *N Engl J Med* 313:1256-62, 1985
36. Dymock JW, Cassar J, Pyke DA: Observations on the pathogenesis complications and treatment of 115 cases of hemochromatosis. *Am J Med* 52:203-10, 1972
37. Rowe JW, Wands JR, Mezey E: Familial hemochromatosis: Characteristics in the pre-cirrhotic stage in a large kindred. *Medicine* 56:197-211, 1977
38. Lassman MN, Genel M, Wise JK: Carbohydrate homeostasis and pancreatic islet cell function in thalassemia. *Ann Intern Med* 80:65-69, 1974
39. Saudek CD, Hemm RM, Peterson CM: Abnormal glucose tolerance in β-thalassemia major. *Metabolism* 26:43-52, 1977
40. Niederau C, Berger M, Stremmel W: Hyperinsulinemia in non-cirrhotic hemochromatosis: Impaired hepatic insulin degradation? *Diabetologia* 26:441-44, 1984
41. Merkel PA, Simonson DC, Amiel SA: Insulin resistance and hyperinsulinemia in patients with thalassemia major treated by hypertransfusion. *N Engl J Med* 318:809-14, 1988

42. Passa P, Luyckx AS, Carpentier JL: Glucagon secretion in diabetic patients with idiopathic hemochromatosis. *Diabetologia* 13:509-13, 1977

43. Nelson RL, Baldus WD, Rubenstein AH: Pancreatic α-cell function in diabetic hemochromatotic subjects. *J Clin Endocrinol Metab* 49:412-16, 1979

44. Rahier JR, Loozen S, Goebbels DM, Abraham M: The hemochromatotic human pancreas: A quantitative immunohistochemical and ultrastructural study. *Diabetologia* 30:5-12, 1987

45. Schafer AI, Rabinowe S, LeBoff MS: Long-term efficacy of deferoxamine iron chelation therapy in adults with acquired transfusional iron overload. *Arch Intern Med* 145:1217-21, 1985

46. Bronspiegel-Weintrob N, Olivieri NF, Tyler B: Effect of age at the start of iron chelation therapy on gonadal function in β-thalassemia major. *N Engl J Med* 323:713-19, 1990

47. Melmed S, Braunstein GD, Chang J, Becker DP: Pituitary tumors secreting growth hormone and prolactin. *Ann Intern Med* 105:238-53, 1986

48. Molitch M: Clinical manifestations of acromegaly. *Endocrinolol Metab Clin N Am* 21:597-614,1992

49. Jadresic A, Banks LM, Child DF: The acromegaly syndrome. Relations between clinical features, growth hormone values, and radiologic characteristics of the pituitary tumors. *Quart J Med* 202:189-204, 1982

50. Nabarrro JDN: Acromegaly. *Clin Endocrinol* 26:481-512, 1987

51. Beck P, Schalch DS, Parker ML: Correlative studies of growth hormone and insulin plasma concentration with metabolic abnormalities in acromegaly. *J Lab Clin Med* 66:366-79, 1965

52. Sonksen PH, Greenwood FC, Ellis JP: Changes of carbohydrate tolerance in acromegaly with progress of the disease and in response to treatment. *J Clin Endocrinol Metab* 27:1418-30, 1967

53. Hansen I, Taslikian E, Beaufrere B: Insulin resistance in acromegaly: Defects in both hepatic and extrahepatic insulin action. *Am J Physiol* 250:E269-73, 1986

54. Ganda OP, Simonson, DC: Growth-hormone, acromegaly, and diabetes. *Diabetes Reviews* 1:286-300, 1993.

55. Foss MC, Saad MJA, Paccola GMGF: Peripheral glucose metabolism in acromegaly. *J Clin Endocrinol Metab* 72:1048-53, 1991

56. Rieu M, Girard F, Bricaire H, Binoux M: The importance of insulin-like growth factor (somatomedin) measurements in the diagnosis and surveillance of acromegaly. *J Clin Endocrinol Metab* 55:147-53, 1982

57. Pierluissi J, Campbell J: Metasomatostrophic diabetes and its induction: Basal insulin secretion and insulin release responses to glucose, glucagon, arginine and meals. *Diabetologia* 18:223-28, 1980

58. Metcalfe P, Johnston DG, Nosadini R: Metabolic effects of acute and prolonged growth hormone excess in normal and insulin-deficient man. *Diabetologia* 20:123-28, 1981

59. Gerich JR, Lroenzi M, Bier DM: Effects of physiologic levels of glucagon and growth hormone on human carbohydrate and lipid metabolism: Studies involving administration of exogenous hormone during suppression of endogenous hormone secretion with somatostatin. *J Clin Invest* 57:875-84, 1976

60. Boden G, Soeldner JS, Steinke J, Thorn GW: Serum human growth-hormone (HGH) response to IV glucose: Diagnosis of acromegaly in females and males. *Metabolism* 17:1-9, 1968

61. Bates AS, Hoff V, Jones JM, Clayton RN: An audit of outcome of treatment in acromegaly. *Q J Med* 86:293-99, 1993

62. Rabinovitch A, Quigley C, Rechler MW: Growth hormone stimulates islet β-cell replication in neonatal rat pancreatic monolayer cultures. *Diabetes* 32:307-12, 1983

63. Martin JM, Gagiardino JJ: Effect of growth hormone on the isolated pancreatic islets of the rat in vitro. *Nature* 213:630-31, 1967

64. Daughaday WH, Kipnis DH: The growth promoting and anti-insulin action of somatotropin. *Rec Prog Horm Res* 22:49-93, 1966

65. Merimee TJ, Fineberg SE, McKusick VA, Hall JD: Diabetes mellitus and sexual ateliotic dwarfism: A comparative study. *J Clin Invest* 49:1096-1102, 1970

66. Merimee TJ, Rabinowitz D, Rimoin DL, McKusick VA: Isolated human growth hormone deficiency. III. Insulin secretion in sexual ateliotic dwarfism. *Metabolism* 17:1005-11, 1968

67. Cahill GF, Jr: Actions of adrenal cortical steroids on carbohydrate metabolism. In *The Human Adrenal Cortex*, Christy NP, ed. New York, Harper and Row, 1971, p. 205-38

68. Exton JH, Miller TB, Jr., Harper SC, Park CR: Carbohydrate metabolism in perfused livers of adrenalectomized and steroid replaced rats. *Am J Physiol* 230:163-70, 1976

69. Pupo AA, Wajchenberg BL, Schnaider J: Carbohydrate metabolism in hyperadrenocorticism. *Diabetes* 15:24-29, 1966

70. Kahn CR, Catanese VM: Secondary forms of diabetes mellitus. In *Principles and Practice of Endocrinology and Metabolism*, Becker KL, ed. Philadelphia, J.P. Lippincott, Co., 1990, p. 1087-93

71. Cryer P: Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. *N Engl J Med* 303:436-44, 1980

72. Landsberg L, Young JB: Catecholamines and the adrenal medulla. In *Williams Textbook of Endocrinology, 7th Edition*, WIlson JD, Foster DW, eds. Philadelphia, W.B. Saunders Co., 1985, p. 891-965

73. Stenström G, Sjöström L, Smith U: Diabetes mellitus in phaeochromocytoma: Fasting blood glucose levels before and after surgery in 60 patients with phaeochromocytoma. *Acta Endocrinol* 106:511-15, 1984

74. Vance JE, Buchanan KD, O'Hara D: Insulin and glucagon responses in subjects with pheochromocytoma. Effect of alpha adrenergic blockade. *J Clin Endocrinol Metab* 29:911-16, 1969

75. Turnbull DM, Johnston DG, Alberti KGMM, Hall R: Hormonal and metabolic studies in a patient with a pheochromocytoma. *J Clin Endocrinol Metab* 51:930-33, 1980

76. Hamaji M: Pancreatic α-and β-cell function in pheochromocytoma. *J Clin Endocrinol Metab* 49:322-25, 1979

77. Conn JW: Hypertension, the potassium ion and impaired carbohydrate tolerance. *N Engl J Med* 273:1135-43, 1965

78. Sagild U, Anderson V, Andreasen PB: Glucose tolerance and insulin responsiveness in experimental potassium depletion. *Acta Med Scand* 169:243-51, 1961

79. Gorden P: Glucose intolerance with hypokalemia. Failure of short-term potassium depletion in normal subjects to reproduce the glucose and insulin abnormalities of clinical hypokalemia. *Diabetes* 22:544-51, 1973

80. Loeb JN: Metabolic changes in thyrotoxicosis. In *Werner and Ingbar's The Thyroid, 6th Edition*. Braverman LE, Utiger RD, eds. Philadelphia, JB Lippincott, 1991, p. 845-53

81. Sandler MP, Robinson RP, Rabin D, Abumrad NN: The effect of thyroid hormones on gluconeogenesis and forearm metabolism in man. *J Clin Endocrinol Metab* 56:479-85, 1983

82. Bratusch-Marrain PR, Komjati M, Waldhäusl WK: Glucose metabolism in non-insulin-dependent diabetic patients with hyperthyroidism. *J Clin Endocrinol Metab* 60:1063-68, 1985

83. Randin JP, Tappy L, Scazziga B: Insulin sensitivity and exogenous insulin clearance in Graves' disease. Measurement by the glucose clamp technique and continuous indirect calorimetry: *Diabetes* 35:178-81, 1986

84. Kreines K, Jett M, Knowles HC, Jr: Observation in hyperthyroidism of abnormal glucose tolerance and other traits related to diabetes mellitus. *Diabetes* 14:740-44, 1965

85. Doar JWH, Stamp TCB, Wyun V, Auydhya TK: Effect of oral and intravenous glucose loading in thyrotoxicosis. Studies of plasma glucose, free fatty acid, plasma insulin and blood pyruvate levels. *Diabetes* 18:633-39, 1969

86. Maxon HR, Kreines KW, Goldsmith RE, Knowles HC, Jr: Long-term observations of glucose tolerance in thyrotoxic patients. *Arch Intern Med* 135:1477-80, 1975

87. Beylot M, Riou JP, Bienvenu F, Mornex R: Increased ketonemia in hyperthyroidism evidence for a β-adrenergic mechanism. *Diabetologia* 19:505-10, 1980

88. Cooppan R, Kozak GP: Hyperthyroidism and diabetes mellitus. Analysis of 70 patients. *Arch Intern Med* 140:370-73, 1980

89. Ganda OP: Diabetes secondary to endocrinopathies. In *Ellenberg and Rifkin's Diabetes Mellitus, Theory and Practice, 4th Edition*, Rifkin H, Porte D, eds. New York, Elsevier, 1990, p. 911-21

90. Neufeld M, Maclaren NK, Blizzard RM: Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. *Medicine* 60:355-62, 1981

91. Eisenbarth GS, Jackson RA: The immunoendocrinopathy syndromes. In *Williams Textbook of Endocrinology, 8th Edition*, Wilson JD, Foster DW, eds. WB Saunders, 1992, p. 1555-65

92. Bardwick PA, Zvaifler NJ, Gill GN: Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes: The POEMS syndrome. *Medicine* 59:311-22, 1980

93. Viard J-P, Lesavre P, Boitard C: POEMS syndrome presenting as systemic sclerosis. Clinical and pathologic study of a case with microangiopathic glomerular lesions. *Amer J Med* 84:524-28, 1988

94. Miralles GD, O'Fallon JR, Talley NJ: Plasma cell dyscrasia with polyneuropathy. The spectrum of POEMS syndrome. *N Engl J Med* 327:1919-23, 1992

95. Feigert JM, Sweet DL, Coleman M: Multicentric angiofollicular lymph node hyperplasia with peripheral neuropathy, pseudotumor cerebri, IgA dysproteinemia, and thrombocytosis in women. A distinct syndrome. *Ann Intern Med* 113:362-67, 1990

96. Pandit MK, Burke J, Gustafson AB: Drug-induced disorders of glucose tolerance. *Ann Intern Med* 118:529-39, 1993

97. Ganda OP: Secondary forms of diabetes. In *Joslin's Diabetes Mellitus, 13th Edition*, Kahn CR, Weir GC, eds. Lea and Febiger, 1994

98. Bengtsson C, Blohmé G, Lapidus L: Do antihypertensive drugs precipitate diabetes? *Brit Med J* 289:1495-97, 1984

99. Grunfeld C, Chappell DA: Hypokalemia and diabetes mellitus. *Amer J Med* 75:553-54, 1983

100. Dornhorst A, Powell SH, Pensky J: Aggravation by propranolol of hyperglycemic effect of hydrochlorthiazide in Type II diabetes without alteration of insulin secretion. *Lancet* 2:123-26, 1985

101. Swisloski ALM, Hoffman BB, Reaven GM: Insulin resistane, glucose intolerance and hyperinsulinemia in patients with hypertension. *Am J Hypertension* 2:419-23, 1985

102. Fajans SS, Floyd JC, Jr., Thiffault CA: Further studies on diazoxide suppression of insulin release from abnormal and normal islet tissue. *Ann NY Acad Sci* 150:261-80, 1968

103. Micossi P, Pollavini G, Raggi U: Effects of metoprolol and propranolol on glucose tolerance and insulin secretion in diabetes mellitus. *Horm Metab Res* 16:59-63, 1984

104. Podolsky S, Pattavina CG: Hyperosmolar non-ketotic diabetic coma: A complication of propranolol therapy. *Metabolism* 22:685-93, 1973

105. Pace CS, Livingston E: Ionic basis of phenytoin sodium inhibition of insulin secretion in pancreatic islets. *Diabetes* 28:1077-82, 1979

106. Goldberg EM, Sanbar SS: Hyperglycemic, nonketotic coma following administration of dilantin (diphenylhydantoin). *Diabetes* 18:101-06, 1969

107. Gurwitz JH, Bohn RL, Glynn RJ: Glucocorticoids and the risk for initiation of hypoglycemic therapy. *Arch Intern Med* 154:97-101, 1994

108. Nabulsi AA, Folsom AR, White A: Association of hormone replacement therapy with various cardiovascular risk factors in postmenopausal women. *N Engl J Med* 328:1069-75, 1993

109. Goodsland IF, Crook D, Simpson R: The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. *N Engl J Med* 323:1375-81, 1990

110. Henry K, Rathgaber S, Sullivan C, McCabe K: Diabetes mellitus induced by megestrol acetate in a patient with AIDS and cachexia. *Ann Intern Med* 116:53-54, 1992

111. Bouchard P, Sai P, Caubarrère I: Diabetes mellitus following pentamidine-induced hypoglycemia in humans. *Diabetes* 31:40-45, 1982

112. Assan R, Perronne R, Assan D, Chotard L, Mayaud C, Matheron S, Zucman D: Pentamidine-induced derangements of glucose homeostasis. Determinant roles of renal failure and drug accumulation. A study of 128 patients. *Diabetes Care* 18: 47-55, 1995

113. Lewitt PA: The neurotoxicity of the rat poison vacor. A clinical study of 12 cases. *N Engl J Med* 302:73-77, 1980

114. Karam JH, Lewitt PA, Young CW: Insulinopenic diabetes after rodenticide (vacor) ingestion. A unique model of acquired diabetes in man. *Diabetes* 29:971-78, 1980

115. Osei K, Falko JM, Nelson KP, Stephens R: Diabetogenic effect of pentamidine. In vitro and in vivo studies in a patient with malignant insulinoma. *Amer J Med* 77:41-46, 1984

116. Kahn SE, Beard JC, Schwartz MW: Increased β-cell secretory capacity as mechanism for islet adaptation to nicotinic acid-induced insulin resistance. *Diabetes* 38:562-68, 1989

117. Garg A, Grundy SM: Nicotinic acid as therapy for dyslipidemia in non-insulin dependent diabetes. *JAMA* 264:723-26, 1990

118. Sumarini NB, Delaney V, Daskalaxis P: Retrospective analysis

of post-transplantation diabetes mellitus in black renal allograft recipients. *Diabetes Care* 14:760-62, 1991

119. Yamamoto H, Akazawa S, Yamaguchi Y: Effects of cyclosporin A and low dosage of steroid on posttransplantation diabetes in kidney transplant recipients. *Diabetes Care* 14:867-70,1991

120. Yoshimura N, Nakai I, Ohmori Y: Effect of cyclosporin on the endocrine and exocrine pancreas in kidney transplant recipients. *Am J Kidney Dis* 12:11-17, 1988

121. Kida K, Ikeuchi M, Goto Y: The effect of cyclosporin A on glucose transport by muscles in vivo and in vitro. *Diabetes* 40 (Suppl. 1):91A, 1991

122. Feldman M, Kiser RS, Unger RH, Li CH: Beta-endorphin and the endocrine pancreas. Studies in healthy and diabetic human beings. *N Engl J Med* 308:349-53, 1983

123. Giugliano D: Morphine, opioid peptides, and pancreatic islet function. *Diabetes Care* 7:92-98, 1984

124. Rotter JI, Vadheim CM, Rimoin DL: Genetics of diabetes mellitus. In *Diabetes Mellitus: Theory and Practice*, Rifkin H, Porte H, eds. New York, Elsevier, 1990, p. 378-413

125. Steiner DF, Tager HS, Chan SJ: Lessons learned from molecular biology of insulin gene mutations. *Diabetes Care* 13:600-09, 1990

126. Sauz N, Kasam JH, Hosita S, Bell GI: Prevalence of insulin gene mutations in non-insulin dependent diabetes. *N Engl J Med* 314:1322, 1986

127. Flier JS: Syndromes of insulin resistance from patient to gene and back again. *Diabetes* 41:1207-19, 1992

128. Taylor SI: Molecular mechanisms of insulin resistance. Lessons from patients with mutations in the insulin-receptor gene. *Diabetes* 41:1473-90, 1992

129. Froguel P, Zouali H, Vionnet H: Familial hyperglycemia due to mutations in glucokinase-definition of a subtype of diabetes mellitus. *N Engl J Med* 328:697-702, 1993

130. Hattersley AT, Turner RC, Permutt MA: Linkage of type 2 diabetes to the glucokinase gene. *Lancet* 339:1307-10, 1992

131. Shimada F, Makino H, Hashimoto N: Type 2 (non-insulin-dependent) diabetes mellitus associated with a mutation of the glucokinase gene in a Japanese family. *Diabetologia* 36:433-37, 1993

132. Bell GI, Xiang KS, Newman MV: Gene for non-insulin-dependent diabetes mellitus (maturity-onset diabetes of the young subtype) is linked to DNA polymorphism on human chromosome 20q. *Proc Nat Acad Sci USA* 88:1484-88, 1991

133. Vaxillaire M, Vionnet N, Vigoroux C: Search for a third susceptibility gene for maturity-onset diabetes of the young. Studies with eleven candidate genes. *Diabetes* 43:389-95, 1994

134. Kadowaki T, Kadowaki H, Mori Y: A subtype of diabetes mellitus associated with a mutation of mitochondrial DNA. *N Engl J Med* 330:962-66, 1994

135. van den Ouwenland JMW, Lemkes H, Trembath RC: Maternally inherited diabetes and deafness in a distinct subtype of diabetes and associates with a single point mutation in the mitochondrial tRNA Leu (UUR) gene. *Diabetes* 43:746-51, 1994

136. Ciafaloni E, Ricci E, Shanske S: MELAS: Clinical features, biochemistry, and molecular genetics. *Ann Neurol* 31:391-98, 1992

137. Almind K, Bjørback C, Vestergaard T, Echwald S, Pedersen O: Amino acid polymorphisms of insulin receptor substrate-1 in non-insulin-dependent diabetes mellitus. *Lancet* 342:828-32, 1993

138. Groop LC, Kankuri M, Schalin-Jantti C: Association between polymorphism of the glycogen synthase gene and non-insulin-dependent diabetes mellitus. *N Engl J Med* 328:10-14, 1993

139. Reynet C, Kahn CR: Rad: A member of the RAS family overexpressed in muscle of type II diabetic humans. *Science* 262:1441-44, 1993

140. Bray GA, Dahms WT, Swerdloff, RS: The Prader-Willi syndrome: A study of 40 patients and review of the literature. *Medicine* 63:59-80, 1983

141. Green JS, Parfrey PS, Harnett JD: The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. *N Engl J Med* 321:1002-09, 1989

142. McEvoy KM: Stiff-man syndrome. *Mayo Clin Proc* 66:300-04, 1991

143. Schoenle EJ, Boltshauser EJ, Balkkeskov S: Preclinical and manifest diabetes mellitus in young patients with Friedrich's ataxia: No evidence of immune process behind the islet cell destruction. *Diabetologia* 32:378-81, 1989

144. Blasi C, Pierelli F, Rispoli F: Wolfram's syndrome: A clinical, diagnostic and interpretative contribution. *Diabetes Care* 9:521-28, 1986

145. Bu X, Rotter JI: Wolfram syndrome: A mitochondrial-mediated disorder. *Lancet* 342:598-600, 1993

146. Fantus IG, Seni M-H, Andermarin E: Evidence for abnormal regulation of insulin receptors in Friedreich's ataxia. *J Clin Endocronol Metab* 76:60-63, 1993

147. Karasik A, O'Hara C, Srikanta S: Genetically programmed selective islet β-cell loss in diabetic subjects with Wolfram's syndrome. *Diabetes Care* 12:135-38, 1989