Jay S. Skyler
Editor

Atlas of Diabetes

Springer

Jay S. Skyler and Jay S. Skyler (eds.), *Atlas of Diabetes*, 4th ed. 2012, Fourth Edition,
DOI: 10.1007/978-1-4614-1028-7, © Springer Science+Business Media, LLC 2012

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Atlas of Diabetes
Fourth Edition

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ISBN 978-1-4614-1027-0 e-ISBN 978-1-4614-1028-7

Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011941604

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Diabetes mellitus is increasing in incidence, prevalence, and importance as a chronic disease throughout the world. The International Diabetes Federation projects that by 2030 there will be 552 million people with diabetes on a global scale. In the USA, the Centers for Disease Control calculates that 25.8 million people (or 8.3% of the population) have diabetes and nearly 2 million Americans develop diabetes each year. Thus, the burden of diabetes is enormous in terms of the magnitude of the population affected.

Among those under 20 years of age, the disease pattern is changing rapidly. One out of every 300–400 children and adolescents has type 1 diabetes. The incidence of type 1 diabetes is sky-rocketing, particularly in children less than 5 years of age. In addition, th incidence of type 2 diabetes among adolescents has increased 15- to 20-fold since 1982. Indeed, the average age of onset of type 2 diabetes is dropping. With more people developing the disease in their teens, 20s, and 30s, their lifetime potential for complications is dramatically increased.

Strikingly, although type 2 diabetes is increasing among the young, its burden on older patients is growing as well. The prevalence among people 60 years of age or older now is nearly 27%, with diabetes afflicting 10.9 million Americans in this age group. A recent United Health report estimated that health spending associated with diabetes is about $194 billion this year, and that cost is projected to rise to $500 billion by 2020. Al told, the report projects that over the next decade the nation may spend almost $3.4 trillion on diabetes-related care.

There are a number of paradoxes in terms of complications. Diabetes is the leading cause of new blindness in working-age adults (20–74 years old), yet the National Eye Institute estimates that 90% of vision loss caused by diabetic retinopathy is preventable. Diabetic nephropathy is far and away the leading cause of renal failure, accounting for 44% of all new cases, yet the National Institute of Diabetes, Digestive, and Kidney Diseases estimates that most future end-stage renal disease from diabetes is probably preventable. Diabetes accounts for more than 60% of all nontraumatic lower extremity amputations, with diabetes imposing a 15- to 40-fold increased risk of amputation compared to the nondiabetic population; however, the American Diabetes Association and the Centers for Disease Control estimate that more than 85% of limb loss is preventable. The presence of type 2 diabetes imposes a risk of coronary events equal to that of a previous myocardial infarction in the nondiabetic population, yet people with diabetes are not as likely to be prescribed cardioprotective medication. Although in the USA the incidence and mortality rates from heart disease and stroke are decreasing in th nondiabetic population, patients with diabetes are two- to six-fold more likely to develop heart disease and two- to four-fold more likely to suffer a stroke.

Optimal glycemic control is critical for reducing the risk of long-term complications associated with diabetes, particularly those effecting the eyes and kidneys. The Diabetes Control and Complications Trial provided strong evidence of the importance of achievin near-normal blood glucose levels in type 1 diabetic patients by means of intensive insuli therapy programs. The United Kingdom Prospective Diabetes Study suggested similar beneficial effects of improved glycemic control in type 2 diabetes. Yet, diabetes patients still are not achieving the recommended target blood glucose values. Data from the Thir National Health and Nutrition Examination Survey of 1988–1994 showed that approximately 60% of patients with type 2 diabetes had A_{1c} values greater than 7% and that 25% had A_{1c} values greater than 9%. In the 1999–2000 update, over 37% had A_{1} values greater than 8%.

The bottom line is that neither physicians nor patients are paying enough attention to diabetes. Diabetes is underrepresented in medical school curricula compared to the burden of the disease. This is particularly the case when it is appreciated that this disease impacts virtually all medical specialties. Our health care system fails to adequately meet the needs of patients with chronic diseases in general, diabetes in particular. Referrals of patients with diabetes to diabetes specialist teams (which include medical nutrition therapists and certified diabetes educators, as well as diabetologists/endocrinologists) are infrequent, and there are not enough of these teams or the specialists who constitute them.

Meanwhile, treatment options are expanding dramatically. As recently as 1995, the only classes of medications available in the USA to lower glycemia were sulfonylureas and insulins. Now, we have added biguanides, α-glucosidase inhibitors, glitazones, glinides, rapid-acting insulin analogues, long-acting basal insulin analogues, incretin mimetics, incretin enhancers, amylin mimetics, bile acid sequestrants, and dopamine agonists. Several additional classes of agents are in development. The use of insulin pumps has increased dramatically. Continuous glucose monitoring has made its appearance. Attempts to develop an artificial pancreas are underway. Pancreatic transplantation has become a routine procedure in the company of kidney transplantatio

There has been an exciting explosion of knowledge about fundamental mechanisms related to diabetes. We have gained insights into the pathogenesis both of type 1 and typ 2 diabetes, and with that, the prospect of implementing prevention strategies to delay or interdict the disease processes. Great progress has been made in islet transplantation, which offers the potential of reversing diabetes, while approaches to islet replacement by regeneration or stem cell therapy are in their infancy. Whether diabetes prevention will come from advances in understanding the processes of islet neogenesis and proliferation from genetic engineering, or from protecting xenoislets or stem cells from immunologic attack remains unclear. All are potential avenues of pursuit.

It is with this background that we have asked leading authorities to contribute their

thoughts and images concerning various aspects of diabetes. Their input makes this *Atla*
possible.

Jay S. Skyl

Contents

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Jay Skyler (ed.), *Atlas of Diabetes*, 4th ed. 2012, Fourth Edition, DOI: 10.1007/978-1-4614-1028-7_1

1. Regulation of Insulin Secretion and Islet Cell Function

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Abstract
The β cells of the islets of Langerhans are the only cells in the body that produce a meaningful quantity of insulin, a hormone that has evolved to be essential for life, exerting critical control over carbohydrate, fat, and protein metabolism. Islets are scattered throughout the pancreas; although they vary in size, they typically contain abou 1,000 cells, of which approximately 70% are β cells. A human pancreas contains about one million islets, which comprise only about 2% of the mass of the pancreas. Insulin is released into the portal vein, which means the liver is exposed to particularly high concentrations of insulin.
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Insulin secretion from β cells responds very precisely to small changes in glucose concentration within the physiologic range, thereby keeping glucose levels within the range of 70–150 mg/dL in normal individuals. β cells have a unique differentiation that permits linkage of physiologic levels of glucose to the metabolic signals that control the release of insulin. Thus, there is a close correlation between the rate of glucose metabolism and insulin secretion. This is dependent on the oxidation of glucose-derived acetyl-coenzyme A (CoA) and also nicotinamide adenine dinucleotide plus hydrogen generated by glycolysis, which is shuttled to mitochondria to contribute to adenosine triphosphate production. Insulin secretion is also regulated by various other physiologic

signals. During eating, insulin secretion is enhanced not only by glucose, but also by amino acids and the gut hormones glucagon-like peptide-1 (GLP-1) and gastrointestinal insulinotropic peptide. Free fatty acids can also modulate insulin secretion, particularly t help maintain insulin secretion during prolonged fasting. The parasympathetic nervous system has a stimulatory effect exerted by acetylcholine (Ach) and probably the peptidergic mediators, such as vasoactive intestinal polypeptide, these contribute to enhanced insulin secretion during the early period of a meal. Through epinephrine from the adrenal medulla and norepinephrine from nerve terminals, the sympathetic nervous system acts on α-adrenergic receptors to inhibit insulin secretion. This suppression of insulin is particularly useful during exercise. Important drugs include sulfonylureas and exendin-4, which have stimulatory effects useful for the treatment of diabetes, and diazoxide, which has an inhibitory effect useful for treating hypoglycemia caused by insulin-producing tumors.

Type 1 diabetes is caused by reduced β-cell mass resulting from autoimmune destruction of β cells, which leads to profound insulin deficiency that can progress to fatal hyperglycemia and ketoacidosis. The non-β cells of the islet are spared, and glucagon secretion is actually excessive, which accounts for some of the hyperglycemia of the diabetic state. The situation is more complicated in type 2 diabetes, which has a strong genetic basis that predisposes individuals to obesity and insulin resistance, a problem greatly magnified by our Western lifestyle with its plentiful food and lack of physical activity. Diabetes, however, only develops when β cells are no longer able to compensate for this insulin resistance. Indeed, most people with insulin resistance never develop diabetes, but as our population ages, more β-cell decompensation occurs and th prevalence of diabetes increases. Pathology studies indicate that β-cell mass in type 2 diabetes is about 50% of normal and that islets often are infiltrated with amyloid that ma have a toxic effect on β cells.

In all forms of diabetes, whether type 2 diabetes, early type 1 diabetes, or failing pancreas or islet transplants, insulin secretory abnormalities are found that seem largely secondary to exposure of β cells to the diabetic milieu and that are reversible if normoglycemia can be restored. This appears to be due to adverse effects of chronic hyperglycemia, hence the term glucotoxicity. The most prominent abnormality is an impairment of glucose-induced insulin secretion, which is more severe for early release (first phase) than the longer second phase of secretion. In contrast, β-cell responses to such nonglucose secretagogues as arginine, GLP-1, isoproterenol, or sulfonylureas are more intact. The cause of these β-cell secretory abnormalities is not fully understood, bu β cells exposed to abnormally high glucose concentrations lose the differentiation that normally equips them with the unique metabolic machinery needed for glucose-induced insulin secretion. Marked abnormalities are found at the level of gene expression that appears to have a crippling effect on the metabolic integrity of the β cell.

Abnormalities of glucagon secretion are also found in both forms of diabetes, with

secretion not being appropriately suppressed by hyperglycemia or stimulated by hypoglycemia, which is problematic because glucagon is an important counterregulatory hormone for protection against hypoglycemia. This failure of glucagon to respond make people with type 1 diabetes more vulnerable to the dangers of insulin-induced hypoglycemia.

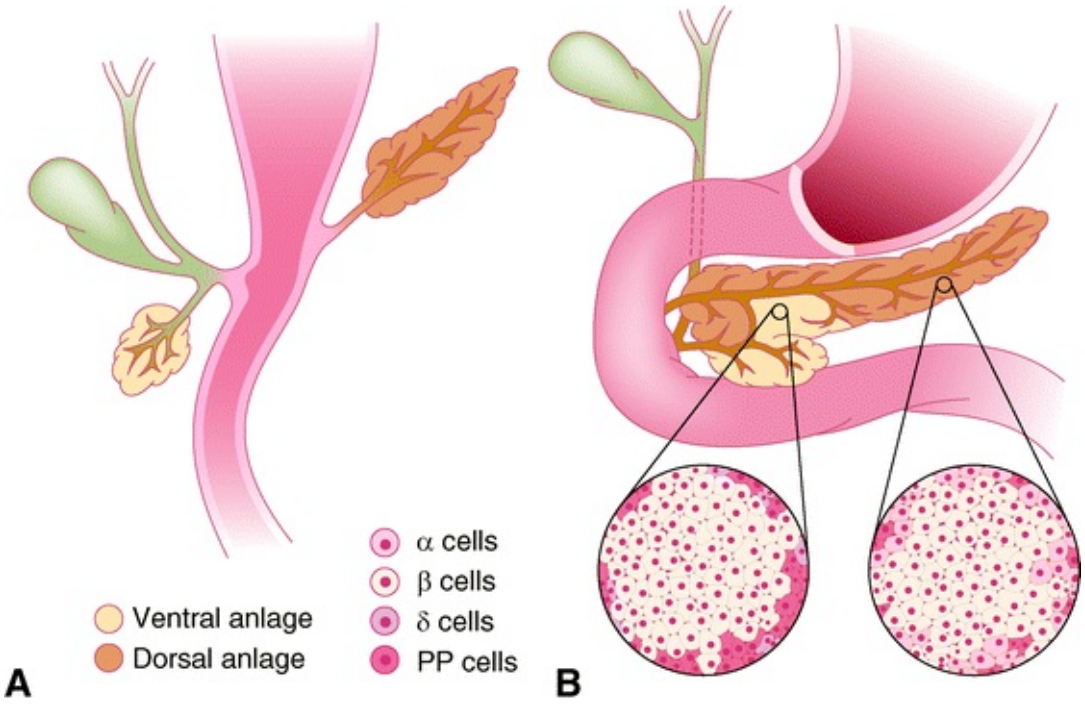

Figure 1-1. Embryologic origin of the pancreas and islet cells. A dorsal anlage and one or two ventr anlagen form from the primitive gut (**a**) and later fuse (**b**). The ventral anlage forms part of the head of the pancreas and has pancreatic polypeptide-rich islet cells with few, if any, α cells. The dorsal anlage forms the major portion of the pancreas, that being the tail, body, and part of the head; here, th islets are glucagon rich and pancreatic polypeptide (PP) poor. Roughly, the α and pancreatic polypeptide cells substitute for each other in number (15–25% of the islet cells); the percentages of β cells (70%) and δ cells (5%) remain the same.

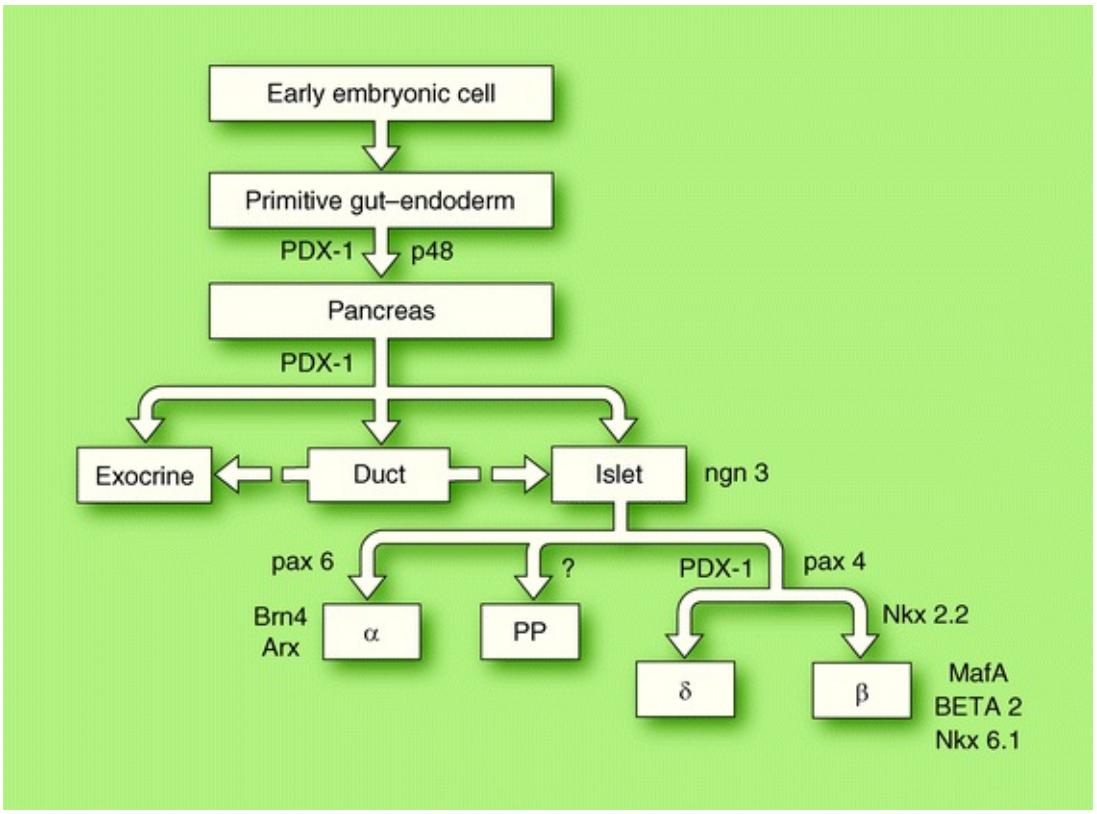

Figure 1-2. Pancreatic and islet cell differentiation. The complex control of differentiation of the pancreas and its three major components (exocrine acinar cells, ducts, and islets of Langerhans) is being elucidated by genetic analysis [1–3]. At present, only some of the transcription factors that are involved in the transition from endoderm to pancreas and then to final mature pancreatic cell types a known; several of them (BETA 2, Nkx 2.2, Nkx 6.1, and ngn 3) are also involved in the development of the nervous system. One that is clearly necessary, but not sufficient, is PDX-1 (ipf-1, stf-1, idx-1); without it, no pancreas is formed, and later it seems to be needed for β-cell differentiation. Exocrine and islets differentiate from the embryonic pancreatic progenitor tubules, but whether they arise fron the same precursor pool or even whether all the islet cells share a cell lineage remains unanswered. *IAPP* islet amyloid polypeptide; *mGPDH* mitochondrial glycerol phosphate dehydrogenase, *PEPCK* phosphoenolpyruvate carboxykinase (adapted from Edlund [4]).

Unique β-Cell Differentiation	
Increased expression	**Decreased expression**
MafA	Glucose-6-phosphatase
Glucokinase	Hexokinase 1
mGPDH	Lactate dehydrogenase
Pyruvate carboxylase	PEPCK
Insulin	MCT1
IAPP	
pdx-1	
Nkx 6.1	

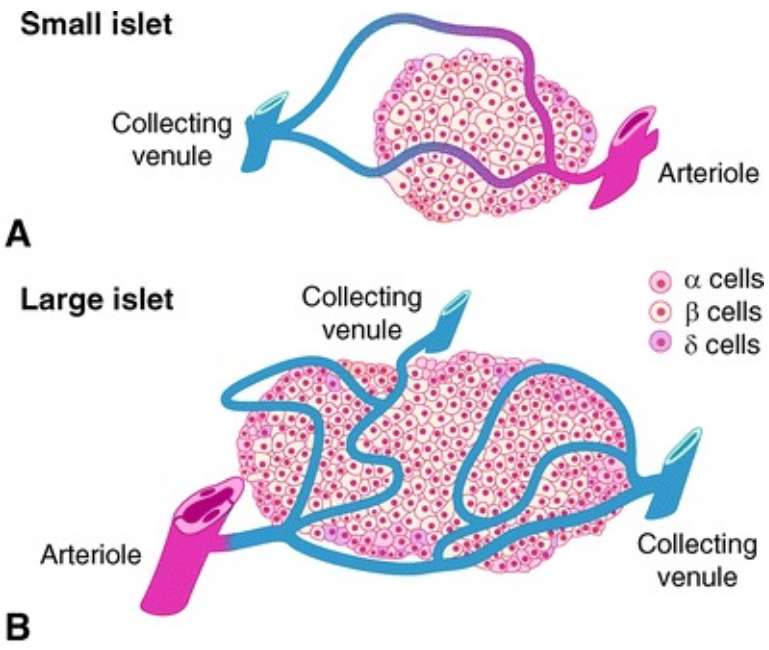

Figure 1-3. Islet vasculature and core/mantle relations. A diagrammatic summary of combined data from corrosion casts and the serial reconstructions of rat islet cells [5]. In small and large islets, β cells make up the central core and the non-β cells (α, PP, and δ cells) form the surrounding mantle. The α cells containing glucagon are found mainly in islets of the dorsal lobe of the pancreas, PP cells are found mainly in ventral lobe islets, and δ cells containing somatostatin are found in the islets of

both lobes of the pancreas.

Short arterioles enter an islet at discontinuities of the non-β-cell mantle and branch into capillaries that form a glomerular-like structure. After traversing the β-cell mass, capillaries penetrate the mantle of non-β cells as the blood leaves the islet. The vascular pattern of human islets has not yet been defined but is likely to have similarities. (**a**) In small islets (<160 μm in diameter), efferent capillaries pass through exocrine tissue before coalescing into collecting venules. (**b**) In large islets (>260 μm in diameter), capillaries coalesce at the edge of the islet and run along the mantle as collecting venules

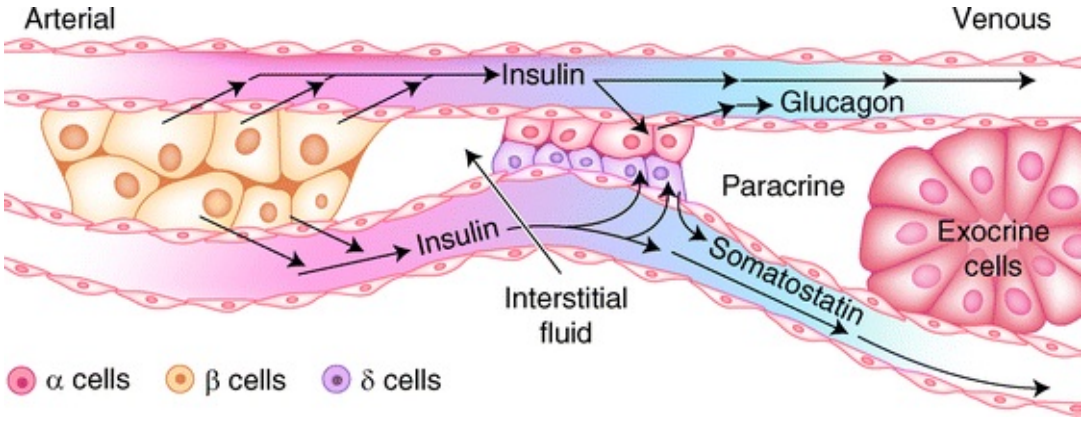

Figure 1-4. The relationship between islet core and mantle, indicating potential intraislet portal flow and paracrine interactions. This formulation is based on the known vascular anatomy and studies with passive immunization [5, 6]. These relationships suggest that β cells, being upstream, are unlikely to be very much influenced by the glucagon and somatostatin produced by the α cells and δ cells of the islet mantle, respectively. The downstream α cells, however, may be strongly influenced by insulin or possibly other secreted factors from the upstream β cells, which have a suppressive influence on glucagon secretion. This helps explain why glucagon secretion cannot be suppressed by the hyperglycemia of diabetes, which means that glucagon is secreted in excessive amounts, thus further contributing to the hyperglycemia of diabetes. This vascular pattern is known as the islet-acinar portal circulation, which means that islet hormones are released downstream directly onto exocrine cells; insulin in particular is thought to have a trophic effect on the exocrine pancreas. The relationship between β and non-β cells in human islets is more complex in that α cells can be found in the islet centers. However, there are still β-cell and non-β-cell domains that appear to maintain the physiological intraislet relationships [7].

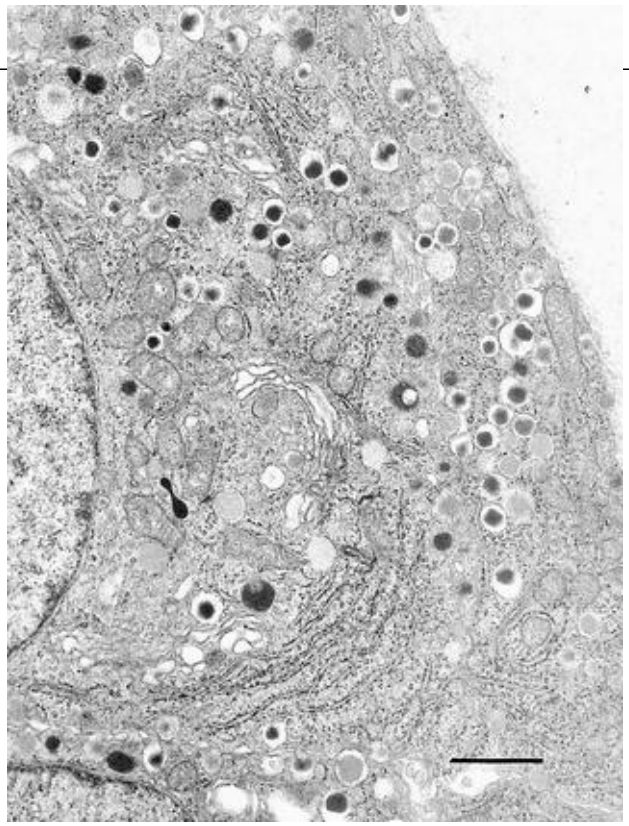

Figure 1-5. Electron micrograph of a β cell. The four major endocrine cell types in mammalian islet cells are the insulin-producing β cell, the glucagon-producing α cell, the somatostatin-producing δ cell, and the *PP* producing PP cell. Recently, the ε cell expressing ghrelin has been identified as a consistent small population of cells in the islet [8]. Ultrastructural and immunocytochemical techniques are used to distinguish these cell types. β cells are polyhedral, being truncated pyramids about 10 × 10 × 8 μm, and are usually well granulated with about 10,000 secretory granules. The tw forms of insulin granules (250–350 nm in diameter) are (1) mature ones with an electron-dense core that is visibly crystalline in some species and a loosely fitting granule-limiting membrane giving the appearance of a spacious halo; and (2) immature granules with little or no halo and moderately electron-dense contents. Immature granules have been shown to be the major, if not the only, site of proinsulin to insulin conversion [8]. In each granule besides insulin, there are at least 100 other peptides, including islet amyloid polypeptide (amylin) [9].

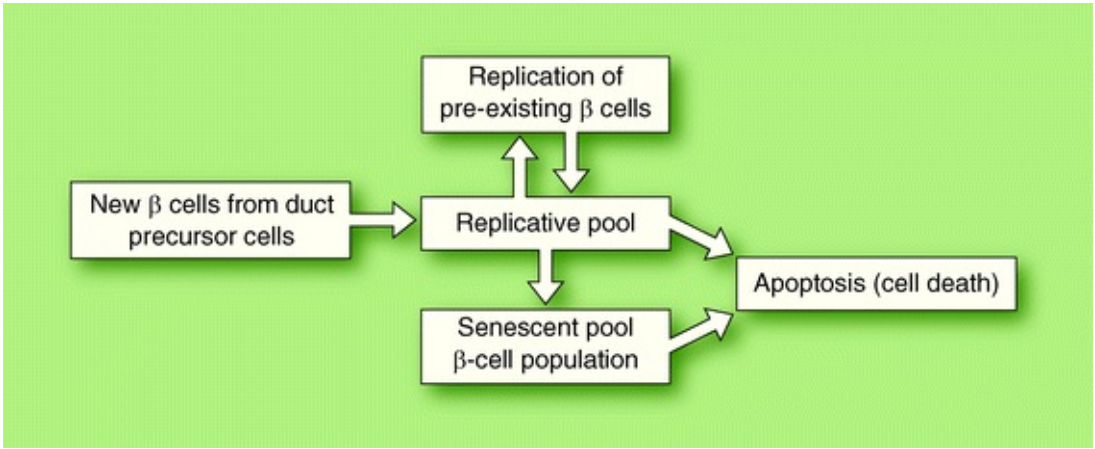

Figure 1-6. Mechanisms responsible for maintenance of β-cell mass. In normal development and in experimental studies, it has become apparent that the population of β cells within an adult pancreas is dynamic and responds to metabolic demand with changes in mass and function in an effort to mainta

euglycemia. The mass of β cells can change by cell number or cell size. The cell size or volume can change markedly in moving from an atrophied to a hypertrophy state. Two mechanisms add new β cells: differentiation from precursor or stem cells in the ducts (often called *neogenesis*) and replication from preexisting β cells [10, 11]. It has been suggested that most cell types have a limited number of replications, after which the ability to respond to replication signals is lost and they are considered senescent cells. These terminally differentiated senescent cells can be long lived and maintain good function. β-cell replication rates have been found to slow in older experimental anima [12]. Additionally, as with all cell types, β cells must have a finite lifespan and die by apoptosis [13]. The turnover of β cells implies that there are differently aged β cells at any stage of development. In adult rodents, β-cell replication is the major mechanism for expansion in response to demand. In humans, the relative contributions of replication and neogenesis remain to be defined.

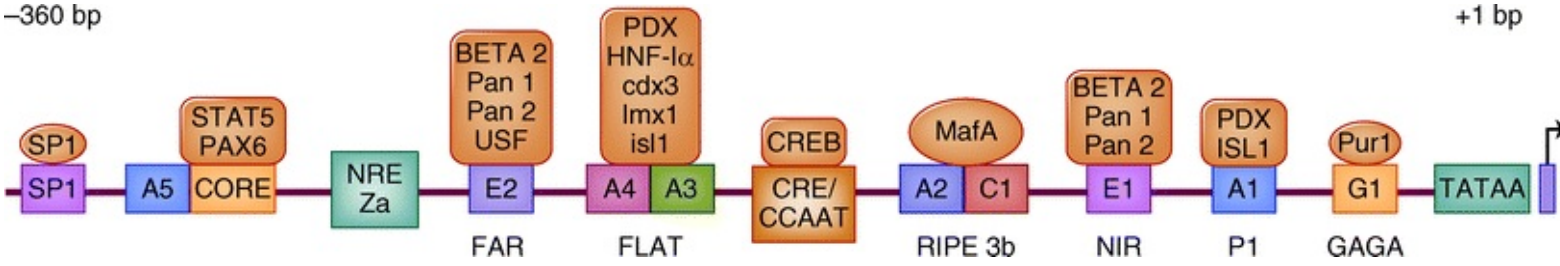

Figure 1-7. The promoter region of the insulin gene showing key enhancer elements and known binding transcription factors. Insulin gene expression is regulated by sequences at least 4 kb upstrean from the transcription start site (represented by an *arrow* and designated as +1 bp) of the insulin gene In adult mammals, insulin is selectively expressed in pancreatic β cells. A small (<400 bp) region of insulin promoter that is highly conserved in various mammalian species can regulate this selective expression and contains the major glucose control elements. This region can also recapitulate glucos responsive insulin gene expression.

In the figure, the organization of the proximal portion (−360 to +1 bp) of the insulin promoter is shown. Functionally conserved enhancer elements are illustrated as boxes. New names for these elements are shown within the boxes, and old names are shown below each box. Above the boxes are shown the names of cloned transcription factors that can bind corresponding elements. Enhancer elements E1, A2-C1, A4-A3, and E2 have been implicated in β-cell-specific expression of the insulin gene. The cell type-specific expression is mediated by the restricted cellular distribution of the transcription factors (such as BETA 2, MafA, and PDX-1) that bind these elements [3]. Furthermore, these elements, along with element Za, are also responsible for glucose-regulated insulin gene expression. Other enhancer elements, CRE/CCAAT and CORE, regulate insulin gene expression in response to other signals, such as cAMP (cyclic adenosine 3′,5′-monophosphate) by regulating cAMP response element-binding (CREB) protein and growth hormone or leptin (via signal transducer and activator of transcription [STAT] factor 5).

In addition to their role in regulating cell-specific and glucose-responsive expression insulin gene transcription factors are involved in pancreatic development and differentiation of β cells. Lack of transcription factors, such as PDX-1, BETA 2, PAX6,

hepatocyte nuclear factor (HNF)-1α, and isl1 results in the complete absence of, or abnormal, pancreatic development. Although humans with a mutant allele for PDX-1, BETA 2, or HNF-1α develop maturity-onset diabetes of youth, individuals with mutations in both PDX-1 alleles show pancreatic agenesis (adapted from Sander and German [14]).

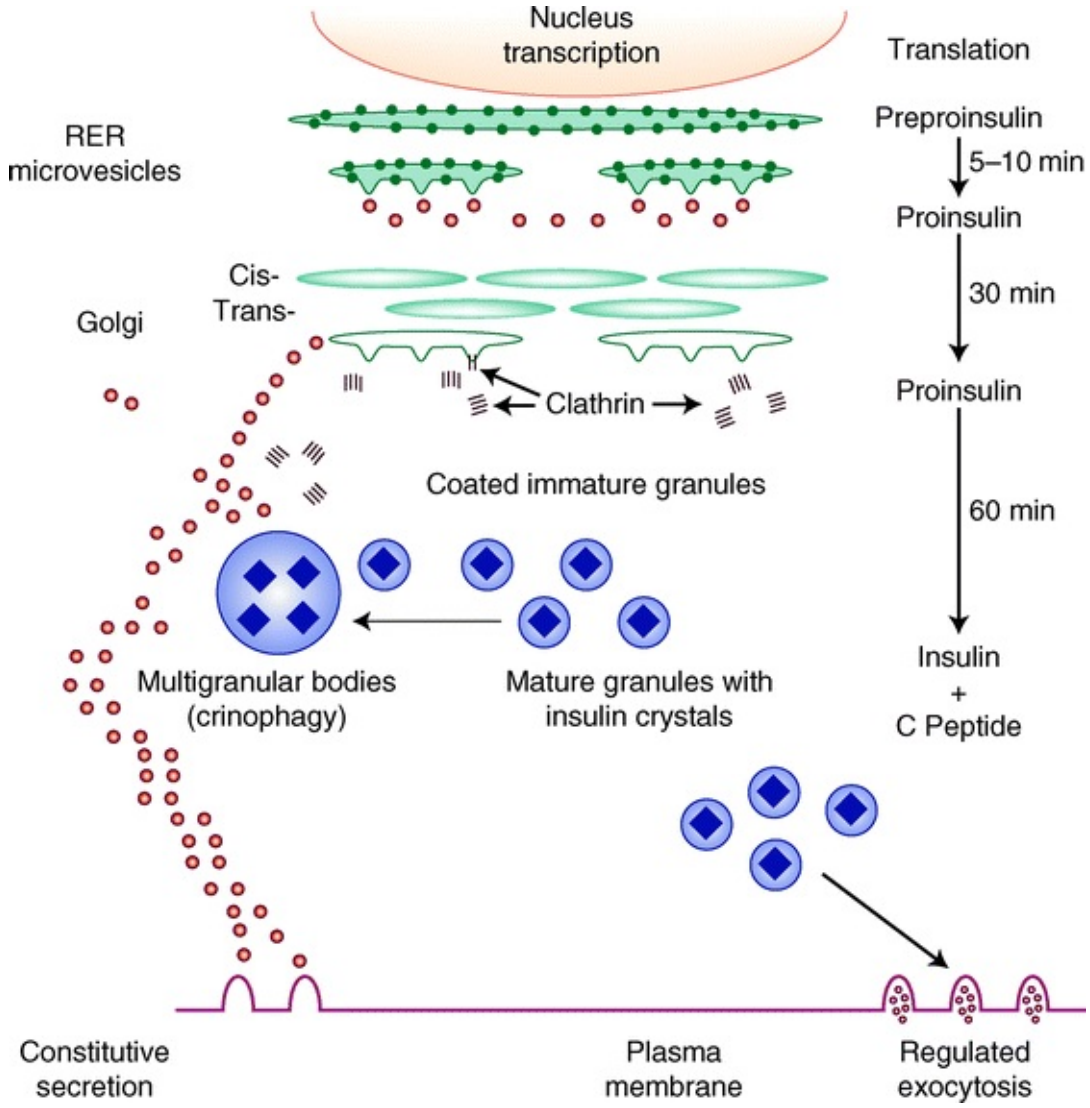

Figure 1-8. Pathways of insulin biosynthesis. Glucose stimulates the production of preproinsulin through effects on transcription and even stronger influences on translation. Shortly after its inceptio preproinsulin is cleaved to proinsulin, which is then transported through the Golgi and packaged into clathrin-coated immature granules, where proinsulin is further processed to proinsulin-like peptides, insulin, and C peptide. Granules containing crystallized insulin can either remain in a storage compartment; be absorbed into multigranular bodies, where they are degraded by the process of crinophagy; or be secreted via the regulated pathway of secretion, the final event being exocytosis. Although the vast majority of insulin is secreted through the regulated pathway, a small amount can be released from microvesicles through the pathway of constitutive secretion [8, 9, 13–15].

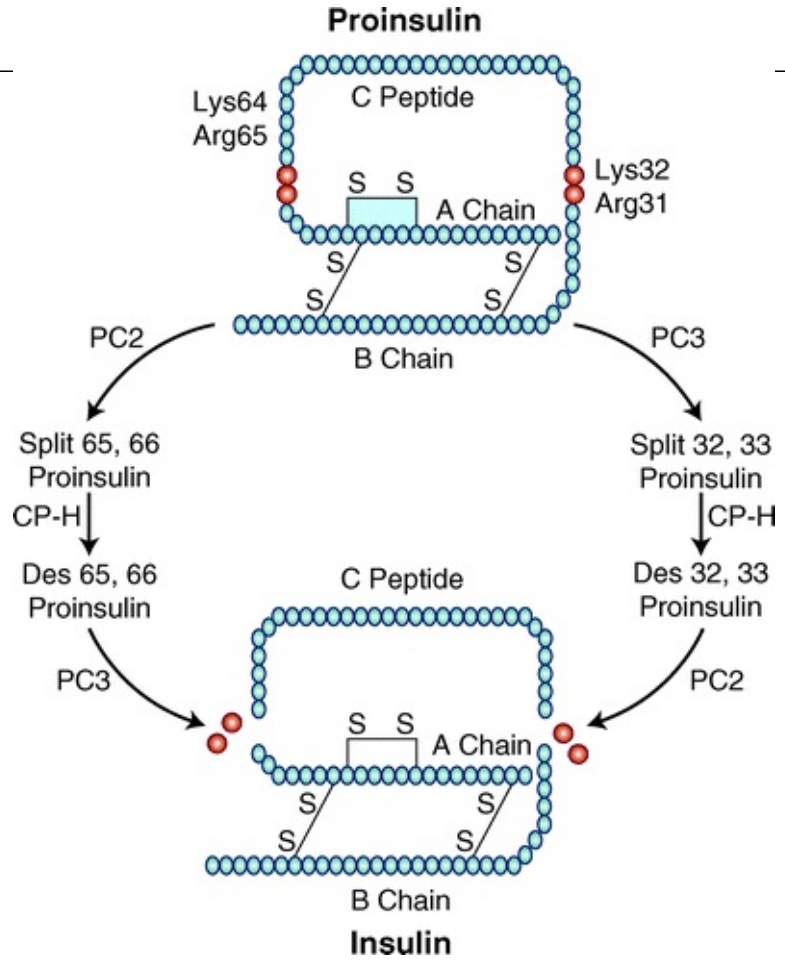

Figure 1-9. Proinsulin processing. Proinsulin is cleaved by endopeptidases contained in secretory granules, which act at the two dibasic sites, Arg31, Arg32 and Lys64, Arg65. PC2 also is known as type 2 proinsulin-processing endopeptidase, and PC3 is the type 1 endopeptidase. After cleavage by either PC2 or PC3, the dibasic amino acids are removed by the exopeptidase carboxypeptidase H (CP H). Insulin and C peptide are usually released in equimolar amounts. Of the secreted insulin immunoreactivity, about 2–4% consists of proinsulin and proinsulin-related peptides. Because the clearance of these peptides in the circulation is considerably slower than that of insulin, they account for 10–40% of circulating insulin immunoreactivity. About one third of proinsulin-like immunoreactivity is accounted for by proinsulin, and most of the rest by des 32–33 split proinsulin, with only small amounts of des 65–66 split proinsulin being present. In type 2 diabetes, the ratio of proinsulin-like peptides to insulin is increased; in impaired glucose tolerance, this finding is less consistent. The increased proportion of secreted proinsulin-like peptides is thought to be caused by depletion of mature granules from the increased secretory demand by hyperglycemia, leading to the release of the incompletely processed contents of the available immature granules [13, 14] (adapted from Rhodes et al. [16]).