The Islets of Langerhans

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The Islets of Langerhans

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This book is dedicated to the living memory of
Henrik Kindmark, M.D., Ph.D., (1964–2009)

Preface

When new fellows join my lab, I give them some reading materials so that they can orient themselves in their assignment in a new field. When fellows leave my lab, some after writing their dissertations, I prefer to give them a book as a symbolic present. I was longing for a book that contained something on more or less everything about the islets. At the same time, I wished it contained information as recent as possible. There are a few such books in the market but they are pretty outdated. I started picking islets myself from October 1990, when I joined the Rolf Luft Center, Karolinska Institutet. Over the years my fascination for islet research remained high. Since last year, I felt a stronger urge to do more for these mysterious and hidden mini-organs that are directly or indirectly involved in the pathogenesis of all forms of diabetes that affects ~250 million people in the world. After I launched the *Islet* (landesbioscience.com/journals/islets) and founded the *Islet Society* (isletsociety.org), there was a momentum that could be utilized to create something equally meaningful i.e. this book.

The idea cracked in September 2008. Starting September 19, 2008, I contacted an estimated 90% of the authors who published anything on the islets during 2007–2008 and who could be traced from the internet. I asked them to propose the title of one chapter that they would like to see in this book and to propose the name of potential author(s) who could contribute the chapter. This bottom-up approach tuned the final contents of the book to the need of its potential users. The authors who contributed the chapter are understandably the ones who had time, competence, and interest to write broad and balanced overviews of the backgrounds and advances in their respective areas of research. Together, they spent thousands of hours to do the necessary research to put together their chapters and to include in these their own views, as well as directions for the future. All but three chapters went through time-consuming anonymous peer-review processes. My communications with the authors and referees were smooth and effective. The commitments and the enthusiasm of the authors kept us all steady on the track. The only chapter that was not delivered in time was my own that was completed on July 12, 2009.

In this book one will find topics on a variety of aspects of the islets and the topics are ordered in a logical way. The anatomy, development, evolution, histology, ultra-structure, regulation of hormone secretion, electrophysiology, mathematical modeling, intracellular signaling mechanisms, apoptosis, mitochondrial functions,

islet transplantation, mechanisms of immune destruction, and prospects for regenerative medicine are examples of topics that have been included in this book. But it is by no means complete. For instance, I could not persuade any one to contribute a chapter on islet amyloid polypeptide and amyloids. By the time the book reaches the readers, other exciting new areas may emerge in this fascinating field of research. Readers will benefit maximum if they take the contents of this book as starting points, take everything they read with a pinch of salt, reflect, and do their own research into the respective subject matters. This is what active learning is.

"A man would do nothing, if he waited until he could do it so well that no one would find any fault with what he has done" – Cardinal Newman. There are certainly some mistakes that I am not aware of. Prospective readers may see this book as a beta version and register the bugs at http://isletbook.islets.se, so that they can be fixed in the next (beta) version.

I admire the authors who have put their hearts and minds into their respective chapters. Other potential authors, amongst them, Susan Bonner-Weir, and Michael Dabrowski, to name a few, could not contribute a chapter, but helped out by recommending others who did contribute. I am thankful to the reviewers whose comments were extremely helpful for making decisions and revisions. Thanks to Melania Ruiz who handled the practical aspects so efficiently. Thanks to our near and dear ones who perhaps did not receive enough attention because of our intensive engagement with the writing but were still tolerant and supportive. Finally, I am grateful to the Karolinska Institute, my alma mater, for ensuring the infrastructure that supports creativity. The preface was written on a boat, as it was cruising her way across the beautiful archipelago that symbolizes islets so well.

July 18, 2009
On board Silja Serenade between
Stockholm and Helsinki

Md. Shahidul Islam

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Chapter 1
Microscopic Anatomy of the Human Islet of Langerhans

Peter In't Veld and Miriam Marichal

Abstract Human islets of Langerhans are complex micro-organs responsible for maintaining glucose homeostasis. Islets contain five different endocrine cell types, which react to changes in plasma nutrient levels with the release of a carefully balanced mixture of islet hormones into the portal vein. Each endocrine cell type is characterized by its own typical secretory granule morphology, different peptide hormone content, and specific endocrine, paracrine, and neuronal interactions. During development, a cascade of transcription factors determines the formation of the endocrine pancreas and its constituting islet cell types. Differences in ontogeny between the ventrally derived head section and the dorsally derived head, body, and tail section are responsible for differences in innervation, blood supply, and endocrine composition. Islet cells show a close topographical relationship to the islet vasculature, and are supplied with a five to tenfold higher blood flow than the exocrine compartment. Islet microanatomy is disturbed in patients with type 1 diabetes, with a marked reduction in β-cell content and the presence of inflammatory infiltrates. Histopathological lesions in type 2 diabetes are less pathognomonic with a more limited reduction in β-cell content and occasional deposition of amyloid in the islet interstitial space.

Keywords Pathology · Type 1 diabetes · Type 2 diabetes · Morphology · Anatomy · Insulitis · Amyloid · β-cell · α-cell · δ-cell · PP cell · Autoimmunity · Innervation · Vasculature · Non-endocrine cells

1.1 Introduction

The human pancreas is an unpaired gland of the alimentary tract with mixed exocrine–endocrine function. It is composed of four functionally different, but interrelated components: the exocrine tissue, the ducts, the endocrine cells, and

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the connective tissue. These elements are intimately related through ontogeny, anatomy, histology, and function. Because the scope of this chapter is the microscopic anatomy of the islet of Langerhans, the other components will only briefly be mentioned.

1.2 The Islets of Langerhans

The pancreas has an elongated shape, and somewhat resembles a 17th century pistol with a curved handle and thick barrel. The handle is formed by the head of the gland, which is closely attached to the distal two-thirds of the duodenum, the barrel is formed by the body region, which is overlaid by the posterior wall of the stomach, and by the tapering tail region that ends near the splenic hilus. Macroscopically, the pancreas has a yellowish-pink aspect and a soft to firm consistency depending on the level of fibrosis and fat accumulation in the organ. It has an average weight of 68 g (range 45–120 g) [1] and is composed of small lobules measuring 1–10 mm in diameter. Microscopically, the lobules are formed by a mixture of ductules and well-vascularized epithelial cell clusters that reflect the two main functions of the pancreas: digestion and glucose homeostasis. Exocrine cells (98% of the parenchyma) release a mixture of digestive enzymes and bicarbonate into the duodenum. They are organized into acini that open into intercalated ducts, to which they are connected via centro-acinar cells. The intercalated ducts fuse into intralobular ducts, interlobular ducts, and finally into the main pancreatic ductus of Wirsung, which together with the common bile duct, opens into the duodenum at the papilla of Vater (papilla major). The secondary ductus of Santorini ends in the papilla minor, a few centimeters above the papilla major. Endocrine cells (1–2% of the parenchyma) release nutrient-generated hormones into the portal vein. Clusters of endocrine cells form islets of Langerhans, micro-organs that lie scattered throughout the exocrine parenchyma in between the acini and ductal structures. The islets of Langerhans are of vital importance to the body as they produce insulin, a prime regulator of glucose homeostasis. The name 'islets of Langerhans' was coined by Edouard Laguesse (1861–1927), a histologist working at the University of Lille, who, in a seminal paper in 1893, correctly deduced that they are involved in endocrine secretion. He named them after Paul Langerhans (1849–1888), who was the first to describe these cell clusters in his doctoral thesis in 1869 but who was unable to attribute them with a specific function [2]. The adult human islet of Langerhans has a mean diameter of 140 μm [3]. It is pervaded by a dense network of capillaries [4] and is (partly) surrounded by a thin collagen capsule [5] and glial sheet [6] that separates the endocrine cells from the exocrine component. Islets vary in size and range from small clusters of only a few cells to large aggregates of many thousands of cells. Depending on the exact manner in which an 'islet' is defined, the estimate of islet number in the adult human pancreas varies from several hundred thousand to several million. Total beta mass appears to be highly variable between subjects, ranging from 500 to 1500 mg [7], corresponding to an estimated 10^9 β-cells and 1–2% of

mean pancreatic weight. Adult islets contain four major endocrine cell types: α-cells (also referred to as A-cells), β-cells (also referred to as B-cells), δ-cells (D, formerly also called A1), and PP cells (pancreatic polypeptide cells, formerly also called F or D1 cells). A fifth cell type, the Epsilon or Ghrelin cell has recently been described.

1.3 Embryology and Fetal Development

The pancreas is derived from two primordia in the distal embryonic foregut [8, 9]. At 3–4 weeks of gestation, a dorsal primordium is formed opposite the hepatic diverticulum and a ventral primordium (sometimes bi-lobed) in close apposition to the diverticulum. At 6 weeks of gestation the ventral pancreas rotates, and fuses with the dorsal pancreas around week 7. The ventral primordium gives rise to part of the head region of the gland ('ventral head'), while the dorsal primordium gives rise to the dorsal head, the body, and the tail. This difference in ontogeny is reflected in significant differences in endocrine cell composition, vascularization, and innervation between the ventral and dorsal pancreas. The ventral head is drained of exocrine secretion by the ductus of Santorini and is supplied with blood via the mesenteric artery. The dorsally derived head, body, and tail are drained by the ductus of Wirsung and irrigated by the coeliac artery. The differences in ontogeny are mirrored by differences in islet composition [10, 11].

Pancreas development is controlled by a complex cascade of transcription factors [12]. Pancreatic and duodenal homeobox 1 (Pdx1) induces early (primary) progenitor cells to expand and form duct-like outgrowths into the surrounding mesenchyme. In a second wave of differentiation (secondary transition), cells at the duct tips differentiate into acini, and cells in the duct walls give rise to endocrine cells, a process driven by another key transcription factor Neurogenin3 (Ngn3). Endocrine cells are first detected at 8–9 weeks at the basal side of the ductal epithelium where they grow out to primitive islets. Exocrine acini are observed from 10 to 12 weeks. Growth of the endocrine mass during fetal life follows that of the total gland, with endocrine tissue forming 2–5% of the parenchyma [13]. Growth of β-cell mass in fetal and adult life appears to be partly by neogenesis from endogeneous Ngn3+ progenitor cells [14] and partly by replication of existing β-cells. β-cell replication peaks around 20 weeks of gestation after which replication levels decrease exponentially reaching near zero values a few years after birth [15–17].

During early development the percentage of the various endocrine cell types changes: at 8 weeks approximately 50% of endocrine cells express glucagon, decreasing to 15–20% in the adult. Similarly, the percentage of D-cells decreases from 20 to 25% in neonates to approx 5% in adults [18–21].

1.4 Endocrine Cell Types

Adult human islets contain at least five different endocrine cell types. α and β-cells were both first described in 1907 by Lane [22] on the basis of their histochemical

staining characteristics, while D-cells were first recognized by Bloom in 1931 [23]. Both PP cells [24] and Ghrelin cells [25] were discovered with the aid of immunocytochemistry.

1.4.1 α-Cells

α-cells secrete glucagon, a 29-aminoacid peptide with hyperglycemic action [26]. The peptide is derived from proglucagon (180-aminoacids) through proteolytic cleavage. Other cleavage products that can be derived from the precursor are GLP-1, GLP-2, and glicentin [27, 28]. Glucagon is stored in secretory granules that have a typical morphology with an electrondense core and a grayish peripheral mantle [29]. Glucagon was immunohistochemically localized to the α-cells by Baum et al. [30]. The number of α-cells is estimated at 15–20% [31, 32], although the relative volume taken up by α-cells can vary significantly between islets with some islets containing up to 65% of α-cells [33]. α-cells are most prominent in the dorsally derived part of the pancreas and virtually absent in the ventrally derived part (Table 1.1).

1.4.2 β-Cells

β-cells form the bulk of the pancreatic endocrine cell mass. Depending on the morphometric techniques that were used, the type of samples analyzed, and the extent of the analysis, a relative islet β-cell mass was found between 50 and 80% [31–34]. β-cells secrete insulin, a 51-aminoacid peptide with strong hypoglycemic action. Insulin is essential for cellular nutrient uptake and thus for the survival of the organism. Its isolation and immediate successful clinical application in 1923 by Banting, Best, and Collip was one of the major medical breakthroughs of the 20th century [35, 36]. Like virtually all peptide hormones, insulin is proteolytically derived from a precursor molecule, proinsulin. This biologically inactive precursor is split into

Table 1.1 Cell types in the adult human endocrine pancreas

	Cell type				
	A	B	D	PP	Epsilon
Peptide hormone	Glucagon	Insulin	Somatostatin	Pancreatic polypeptide	Ghrelin
Molecular weight	3500	5800	1500	4200	3400
Number of amino acids	29	51	14	36	28
Volume % (adult)					
Dorsal	15–20	70–80	5–10	<1	1
Ventral	<1	10–20	2	80	1
Total	15–20	70–80	5–10	15–25	1

three parts, an A and a B chain, which remain connected by two sulfur bridges, thus forming the biologically active insulin molecule, and a C chain (Connecting peptide), which is released together with insulin in a 1:1 molar ratio [37]. The β-cell also co-secretes Islet Associated Polypeptide (IAPP, also called amylin), a 37-aminoacid peptide related to calcitonin gene related peptide (CGRP) [38]. Under pathological conditions IAPP molecules may polymerize and form large intraislet amyloid deposits that are characteristic for type 2 diabetes and for insulinoma.

Insulin was first immunohistochemically localized to the β-cell by Lacy [39]. It is stored in cytoplasmic secretory vesicles that have a characteristic morphology with an electrondense core and a clear peripheral mantle (Fig. 1.1). Within the 350 nm granule, insulin (but not proinsulin) is complexed to zinc, forming insulin–zinc hexamers and crystalline granule cores. Depending on the maturation stage of the granule, the mantle may contain unprocessed proinsulin; when the proteolytic enzymes (prohormone convertases PC1-2, carboxypeptidase-H) present in the newly formed secretory granule have not yet resulted in sufficient cleavage of the precursor molecules, the granule core may be absent and typical immature 'gray' granules are found [39]. The biological reason for Zn complexation is not well understood, but its presence is of practical benefit in islet isolation procedures, where zinc-chelating dyes like dithizone [40] are helpful in determining islet yield and purity.

A β-cell is estimated to contain 9–13.000 secretory granules [41, 42]. With an average daily insulin requirement of 40 IU and an average insulin content per granule of 8 fg, it can be estimated that approx 10^{12} secretory granules are released from β-cells each day. Release may occur via a nutrient-regulated pathway or via a constitutive pathway. Nutrient-induced release is initiated via closure of ATP-dependent

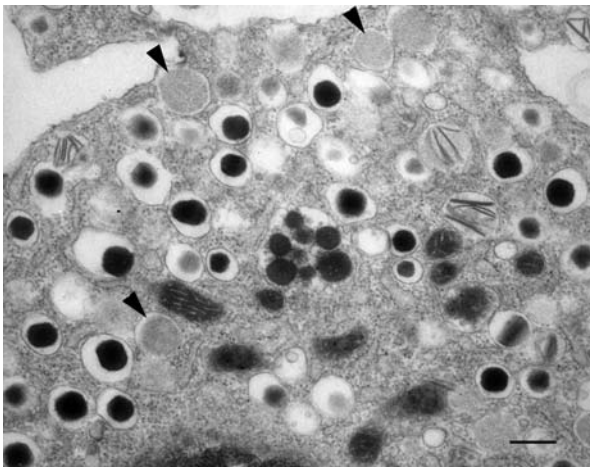

Fig. 1.1 Electron-microscopic image of an islet β-cell with mature dense-cored secretory granules and immature gray granules (*arrowheads*) (bar 300 nm)

potassium-channels, membrane depolization, opening of voltage-dependent calcium channels, and calcium-induced fusion of the secretory granules with the plasma membrane. The process of insulin release is complex and may partly consist of granule fusion with the plasma membrane and partly of temporary opening of small pores between the granule lumen and the extracellular milieu [43].

In addition to (pro)insulin, C-peptide, IAPP, zinc, and proteolytic enzymes, the secretory granule contains calcium, adenine nucleotides, biogenic amines, and a series of additional peptide (pro)hormones including chromogranin A and beta-granin [44, 45]. Several granule (membrane) proteins have been implicated in humoral autoimmunity in type 1 diabetes, like the zinc transporter ZnT8 [46], insulinoma-associated protein 2 (IA-2; ICA-512) [47], and glutamic acid decarboxylase (GAD65) [48].

β-cells in the human pancreas may show marked variation in granulation, cell size, and size of the nuclei (Fig. 1.2). Differences in granulation and cell size may reflect a heterogeneity in glucose responsiveness and biosynthetic activity [49], while differences in nuclear size may reflect polyploidy with nuclear DNA content of up to 8n being relatively common [50]. β-cells in the aging human pancreas display multiple prominent lysosomes with lipid-like content (Fig. 1.3). These strongly autofluorescent organelles resemble the lipofuscin inclusions in aging neurons and linearly increase with age [51].

1.4.3 D-Cells

The D (or δ) cells release somatostatin (formerly called somatotropin release inhibiting factor), first isolated from in the hypothalamus [52]. This peptide hormone is a

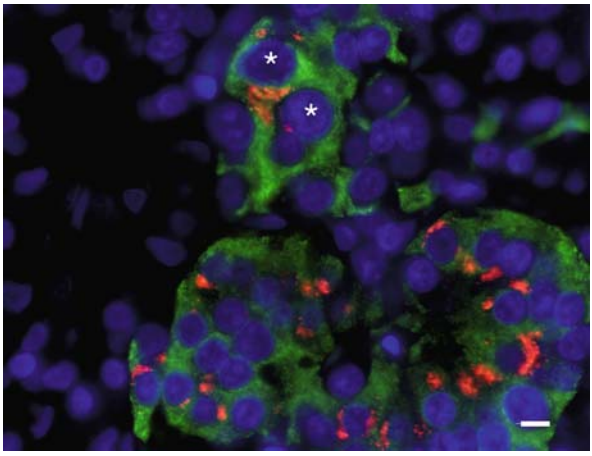

Fig. 1.2 Two-color fluorescent imaging for insulin (*green*) and proinsulin (*red*) of a human islet of Langerhans. Proinsulin has a predominantly perinuclear localization. Note the significant differences in nuclear size between islet β-cells (*asterix*) (Bar 10 μm)

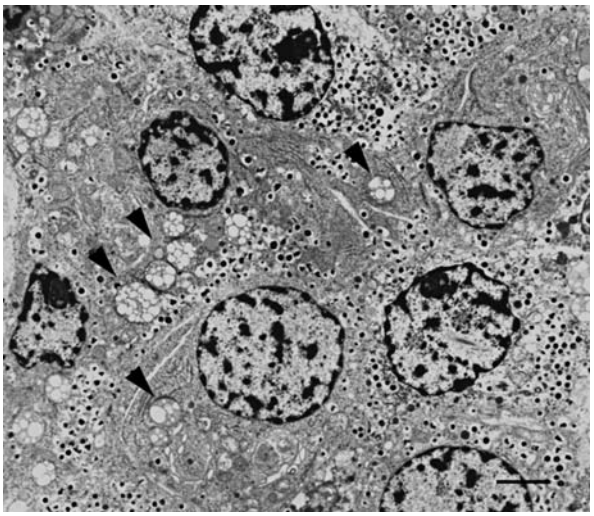

Fig. 1.3 Electron-microscopic image of aging human β-cells with multiple cytoplasmic inclusions (bar 5 μm)

potent inhibitor of glucagon and insulin release and was first immunohistochemically located to the D-cell by Luft et al. [53]. The hormone exists in a 14-aminoacid form and in a 28-aminoacid form [54]. Although all islet cells have neuron-like characteristics, the D-cells resemble small neurons most, as they often form long slender processes with a secretory-granule rich knob-like ending near a capillary suggesting focal and possibly paracrine secretion [55]. D-cells form 5–10% of islet volume (Table 1.1).

1.4.4 PP Cells

The least well studied of the islet hormones is PP, secreted by the PP cell. The peptide has been found immunocytochemically in two morphologically distinct cell types: PP immunoreactive cells (formerly designated as F-cells), characterized by round to angular secretory granules, were found in the ventrally derived head of the pancreas, while cells with small granules, formerly called D_1 cells, were found in the dorsally derived part [56]. In the human pancreas the relative PP cell mass in the ventral pancreas is considerable, constituting up to 80% of the cells (Table 1.1).

1.4.5 Epsilon Cells

The latest cell type that was added is the Epsilon or Ghrelin cell. The hormone ghrelin was first isolated from rat stomach and later localized to a specific cell type in the

adult human islet [25]. Adult islets contain less than 1% epsilon cells. The hormone is thought to be of importance in growth hormone release, metabolic regulation, and energy balance, but its exact role in islet cells has yet to be established.

1.5 Islet Anatomy

Endocrine cells in the pancreas form aggregates of various sizes and microscopic aspect. Larger aggregates, the islets of Langerhans, form small, ellipsoid or spherical structures dispersed throughout the exocrine part. The islet size and number of β-cells increases from birth to adulthood [16]. In fetuses, islets are in close contact with ducts, but they become more separated from the ducts in neonates and adults. In adults, 50% of the islets remain close to the ducts [57]. Size and distribution of islets vary widely from individual to individual, but without recognizable pattern, except that their number seems to increase towards the tail of the pancreas [58, 59]. On light microscopy, the epithelial cells of the islets of Langerhans form trabecular structures, separated by a dense network of anastomosing capillaries [4]. Two architecturally different types of islets are recognized: the diffuse and the compact islet. In the postero-inferior (ventral) head of the pancreas, the islets are of the 'diffuse' type, because the trabeculae seem more loosely arranged than in the islets occurring in the rest of the pancreas and which are known as 'compact islets'. The diffuse islets are very rich in PP cells and are larger than the compact islets. They also contain substantially less A, B, and D cells than the compact islets [60], which are primarily found in the body and tail and have sizes ranging from 50 to 280 μm. Compact islets are well circumscribed and separated by a thin layer of collagen from the surrounding acini. This is less the case in the diffuse islets, which are often irregular. Though occasional islets can measure 1–2 mm in diameter, compact islets larger than 250 μm are generally considered hyperplastic [61].

In humans, the endocrine cells are distributed throughout the islets without apparent organization; this contrasts with murine islets, which show a clear topographical separation of β and α-cell mass. It cannot be excluded that such topographical differences between human and rodent islets are paralleled by differences in endocrine and paracrine islet cell interactions. The cytoarchitecture of the human islet, with its random islet cell distribution, does not support functional islet domains in which the direction of blood flow determines intraislet endocrine signaling [34]. The relative proportion of the various endocrine cell types in the human islets can vary considerably; in one study [33] the percentage of β-cells ranged from 28 to 75%, that of α-cells from 10 to 65% and that of somatostatin cells from 1.2 to 22%. Not all endocrine cells in the pancreas occur in classical islet structures: 15% of all β-cells are found in units with a diameter of <20 μm (1–3 cells) and without associated glucagon, somatostatin, or PP cells [62]. These units, referred to as 'single β-cells' are equally distributed throughout the whole gland and in close association with acini and ductules; they are significantly smaller than β-cells located in larger islets. It has been speculated that these cells are an early stage in the formation of new

islets, although recent studies in rodents using β-cell lineage tracing were unable to confirm this [63].

The different islet cell types can be distinguished with special stains. Nowadays immunohistochemistry is used almost exclusively, but several cell-type-specific histochemical stains are available as well. The best known are Gomori's aldehyde fuchsin for β-cells [64, 65] and Hellman–Hellerström for δ-cells [66]. The Mallory-Azan stain distinguishes between the three major cell types.

1.6 Non-endocrine Islet Cells

Between the islet cell trabeculae, small amounts of connective tissue are present, with blood vessels being most prominent. Other non-epithelial elements present in the islet are nerve fibers, pericytes, macrophages [67], and dendritic cells; the latter express major histocompatibility complex (MHC) class II molecules on their cell surfaces, which may play a role in graft rejection and the initiation of type 1 diabetes.

Pancreatic lymphatics are found in the interlobular septa of the exocrine portion, but are seldom in contact with the islets [68].

1.7 Islet Vasculature

The islet vasculature is critical for adequate glucose homeostasis, not only because of the high oxygen consumption of pancreatic β-cells, but also because of timely responses to changes in plasma glucose concentration and the release of islet hormones into the circulation. Islet perfusion is mediated by neural, hormonal and circulatory signals [69]. The islet capillary network has a density five times higher than the exocrine capillary network [70, 71] and its vasculature is akin to the glomerular system of the kidney: 1 to 3 afferent arterioles provide the islet with oxygenated blood, which leaves through efferent venules; these empty into exocrine capillary networks or collecting venules that in turn empty directly into larger veins. Another similarity to glomeruli is that a variant of nephrin (a podocyte marker) has recently been shown to mark the islet vasculature [72]. The islet endothelium contains 95 nm fenestrations closed by a diaphragm and arranged into sieve plates (Fig. 1.4). Islet capillaries display up to tenfold more fenestrations than exocrine capillaries [73], further illustrating the close interaction between islet cells and the circulation. VEGF-A released from pancreatic β-cells was shown to be a determining factor in inducing islet capillaries and their fenestrated endothelial cells [74]. Islet β-cells are usually bordered by at least one capillary and show polarity in their cytoplasm with the secretory granules at the apical pole towards the blood vessel [75]. Islet capillaries are surrounded by a double basement membrane, each characterized by its own laminin subtypes. One basement membrane is derived from a peri-islet membrane that accompanies the capillary along its winding path throughout the islet; the

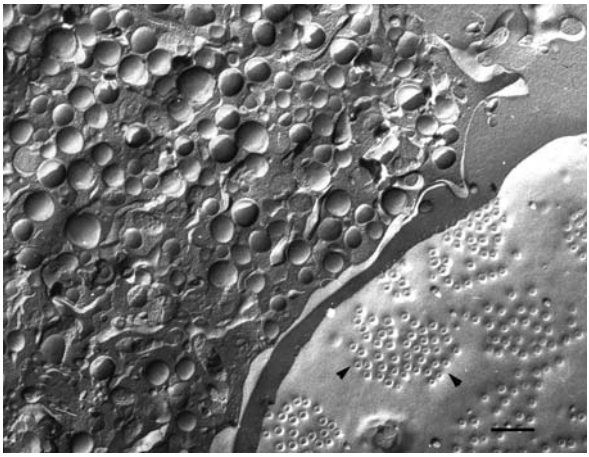

Fig. 1.4 Freeze fracture replica of a rat islet showing a fenestrated capillary with fenestrations arranged into sieve plates (*arrowheads*). Adjacent to the capillary is an endocrine cell with multiple secretory granules in the cytoplasm (bar 300 nm)

endothelial basement membrane constitutes the other. This situation differs from that in rodents where only a single basement membrane was found [76].

1.8 Innervation

Islets have sympathetic, parasympathetic, and sensory innervation; the nerve fibers contain acetylcholine, noradrenaline, and several neuropeptides. The fibers accompany the vasculature and are embedded in non-myelinating Schwann cells. They end blindly in the pericapillary space in close proximity to the islet cells; true synaptic contacts on islet cells have not been described but close nerve–islet cell interactions appear to be mediated by CADM1 (cell adhesion molecule 1) [77]. The ventral and dorsal parts of the pancreas have different innervation, with the dorsal pancreas receiving its sympathetic innervation from the celiac ganglion and the ventral pancreas from the superior mesenteric ganglion. Insulin secretion is stimulated by the parasympathetic system and inhibited by the sympathetic system [78]. It has been postulated that thin peri-islet Schwann cell sheets and sensory afferent neurons may play a role in the initiation of type 1 diabetes [79].

1.9 Islet in Type 1 Diabetes

Patients with recent onset type 1 diabetes (DM1) usually present with a pancreas that is macroscopically normal in appearance and weight. This contrasts with findings in patients with chronic disease in whom the lack of endogenously released insulin

leads to the atrophy of the acinar cells and a decrease in overall pancreatic weight [80, 81].

The characteristic lesion in recent onset DM1 is formed by the presence of inflammatory infiltrates in the islets of Langerhans. In a seminal study in 1965 [80], Willy Gepts described the presence of insulitis in 15/22 young patients with a duration of the disease of <6 months. He observed that the inflammatory lesions were limited to islets in which β-cells were still present and that most remaining islets were pseudoatrophic and contained only non-β-cells (Fig. 1.5), resulting in an overall decrease in β-cell mass to 10% of normal values. He concluded that DM1 was probably the result of a protracted inflammatory disease of autoimmune or viral etiology. Subsequent studies using immunohistochemical staining and precise morphometric methods have confirmed these initial histopathological findings [82], but the use of more sensitive techniques also indicated that residual β-cells are still present many years after clinical onset, especially in older individuals. Our knowledge of the disease processes leading to overt diabetes is still fragmentary due to the fact that only a few dozen cases of very recent onset diabetes could

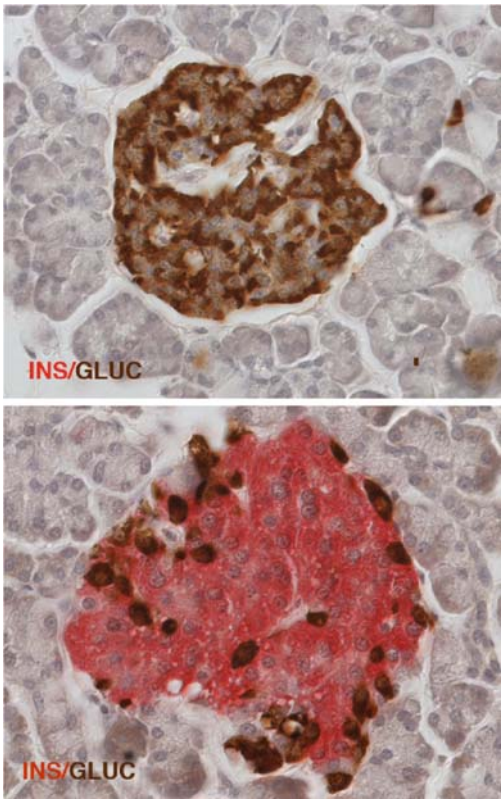

Fig. 1.5 Islets stained for insulin (*red*) and glucagon (*brown*). Islets from chronic type 1 diabetics are pseudoatrophic and consist primarily of α-cells (*top panel*), in contrast to islets from a normal control with both α and β-cells