# The PANCREAS

## AN INTEGRATED TEXTBOOK OF BASIC SCIENCE, MEDICINE, AND SURGERY

EDITED BY HANS G. BEGER, MARKUS W. BÜCHLER, RALPH H. HRUBAN, JULIA MAYERLE, JOHN P. NEOPTOLEMOS, TOORU SHIMOSEGAWA, ANDREW L. WARSHAW, DAVID C. WHITCOMB, and YUPEI ZHAO

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## An Integrated Textbook of Basic Science, Medicine, and Surgery

**Fourth Edition**

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## Preface

The fourth edition of *The Pancreas* presents the most comprehensive and latest knowledge about the genetic and molecular biological basis of embryology, anatomy, physiology, pathophysiology, and pathology for all disorders of the pancreas. Compared to the first edition, published in 1998, the fourth edition contains three newly addressed diseases of the pancreas: autoimmune pancreatitis, benign and premalignant cystic neoplasms, and neuroendocrine tumors. The understanding of the functions and dysfunctions of the exocrine and endocrine pancreas is derived from increasingly profound molecular biological data on the actions of compounds in subcellular compartments and intracellular transcription pathways. In the respective chapters, the presentation of the inflammatory (acute or chronic) and oncological diseases (benign, premalignant, or advanced cancer) is based on molecular biological understanding of pathomorphological processes and clinical phenomena. In clinical pancreatology, new and improved technical devices enable the gastroenterologist and the gastrointestinal surgeon to identify lesions by high-resolution imaging techniques, imaging of metabolic processes, and intrapancreatic ductal morphologic processes. The molecular profiling of pancreatic ductal adenocarcinoma has provided a deeper understanding of the genomic alterations that drive pancreatic ductal adenocarcinoma, including driver genes, actionable mutations, copy number alterations, patterns of genomic aberrations, structural variations, and mutational signatures. These findings have transformed our biological genomic understanding, but are still of limited clinical utility. Significant progress has been made in understanding the molecular pathogenesis of pancreatic cancer and identification of various molecular subtypes. However, this improved understanding has unfortunately not yet led to relevant progress for the patient's cure, although survival gain after radical cancer resection in addition with neoadjuvant chemotherapy is significant for selected groups of patients.

The synergistic interaction of basic scientists, pathologists, gastroenterologists, and gastrointestinal tract surgeons in the field of investigative and clinical pancreatology has led to a better understanding of pancreatic diseases through combining the knowledge of each to achieve the best management. Most importantly, the decision-making for patients with an option to be successfully treated for pancreatic disease is increasingly based on high-evidence data from clinical trials on treatment. New technical devices—endoscopic visualization of cellular abnormalities, laparoscopic minimally invasive surgical approaches, and robotic surgery—have led to significant clinical improvement. The establishment of local, parenchyma-sparing surgical approaches for the increasing number of benign tumors, cystic neoplasms, and neuroendocrine tumors have significantly improved the patient's outcome compared to classical pancreatic resections.

The goal of this fourth edition is to provide the clinician with the most current evidence-based synthesis of understanding of pancreatic diseases, functional assessment, diagnostic and technical devices, treatment options, and outcome results. All chapters are written by leading international experts on the topic. A major part of this edition has been contributed by international basic scientists, who provide an understanding of the molecular basis of pancreatic functions and dysfunctions. The editors acknowledge and are deeply indebted to all authors who have contributed to this edition. Their diligent efforts have provided state-of-the-art knowledge, particularly in regard to decision-making based on clinical evidence.

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This book is accompanied by a companion website.

**www.wiley.com/go/beger/thepancreas4**


This website includes:

- PowerPoints of all figures from the book for downloading
- List of Contributors
- List of Abbreviations

# Section 1

# Anatomy of the Pancreas

# 1

# Development of the Pancreas and Related Structures

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## Anatomy of the Pancreas

The pancreas is a unique exocrine and endocrine organ located in the retroperitoneal region of the upper abdominal cavity. In humans, when fully formed, the organ has a distinct head, body, and tail, with the head of the pancreas contacting the duodenal region of the intestines (the main pancreatic duct drains into the duodenum) and the tail of the pancreas abutting the spleen. The greatest mass of the organ is present in the head, which is composed of tissue derived from two independent anlagen (see later). In other mammals, such as dogs and mice, the organ has a far less distinct structure and is identified as an amorphous pink tissue adjacent to the mesentery that runs along the upper intestinal wall.

The cells of the pancreas are arranged into distinct lobules composed primarily of the digestive enzyme-producing cells of the exocrine pancreas, which are arranged into acini (so-called acinar cells), the ductal structures that conduct these digestive enzymes to the intestines, and distinct clusters of endocrine cells, the islets of Langerhans, that secrete hormones and function to regulate glucose uptake and release and serum glucose levels. There are five recognized cell types within the islets, the α, β, δ, ε, and PP cells, which produce the hormones glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide, respectively. The majority of the pancreatic tissue mass (more than 90–95%) is present within the exocrine compartment of the organ, with the islets of Langerhans, scattered throughout the tissue. The pancreas also has connective tissue, derived from the embryonic mesenchyme, which forms the septa that separate the many lobules of the organ. Mesenchyme-derived stromal cells are also present in the interlobular regions surrounding the pancreatic ducts, blood vessels, and nerves. In the following sections, we explore how these disparate cell types come together to form the pancreas.

## Organogenesis in the Region of the Pancreas

Around day 14, the embryonic bilaminar germ disk is composed of a layer of epiblast and a layer of hypoblast. At this time, a faint groove appears along the longitudinal midline of the germ disk that develops into a structure called the primitive streak [1]. Around day 15, epiblast cells near the primitive streak undergo a morphologic change and migrate through the primitive streak into the space between the epiblast and hypoblast in a process known as gastrulation (Fig. 1.1). Some of the ingressing epiblast cells invade the hypoblast, which is eventually replaced by a new layer of epiblast-derived cells known as the definitive endoderm. Additional migrating epiblast cells occupy the space between the epiblast and the definitive endoderm to form a third layer of cells called the intraembryonic mesoderm (Fig. 1.1). As cells of the germinal disk migrate anteriorly to form a head process and lateral regions roll underneath to form an approximately cylindrical body shape, the endoderm is rolled into a tube that projects into the developing head region of the embryo surrounded by the mesoderm layer. This is the primitive digestive tube. The pancreas is specified by two separate outgrowths that arise on the dorsal and ventral surfaces of the primitive digestive tube. The epithelial cells of the pancreas originate from the interior lining of the primitive gut tube, which consists of a single layer of endoderm. A layer of mesenchyme, from which the muscle and

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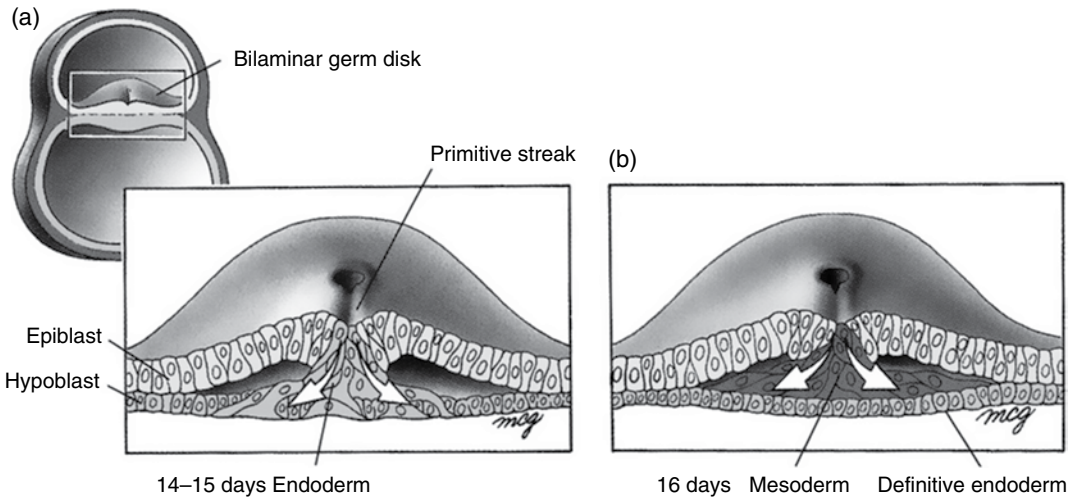


**Figure 1.1** Germ disks sectioned through the region of the primitive streak, showing gastrulation. (a) On days 14 and 15, the ingressing epiblast cells replace the hypoblast to form the definitive endoderm. (b) The epiblast that ingresses on day 16 migrates between the endoderm and epiblast layers to form the intraembryonic mesoderm. *Source:* Larsen 2001 [1]. Reproduced with permission of Elsevier.

connective tissue of the gastrointestinal organs are derived, surrounds the endoderm.

The anterior regions of the endoderm form the foregut; regions posterior to the foregut form the midgut and hindgut. The most anterior regions of the foregut give rise to the esophagus and stomach. Just posterior to the foregut, the endoderm is continuous with the yolk sac, which extends outside the embryo, in a region known as the anterior intestinal portal. Endodermally derived cells close to the anterior intestinal portal specify the pancreas. The duodenum and liver are also specified by foregut endoderm in this region.

Thus, many gastrointestinal tissues are specified at the same time from a fairly restricted region of the gut endoderm. How are each of these organs specified in the appropriate anatomic location, and how do they differentiate properly into mature functional organs? The epithelial organs of the developing embryo originate as buds from the endoderm as the appropriate temporal and spatial cues are received. Thus, proper initiation and location of endodermally derived organs are regulated by the activation status of important signal transduction pathways involved in animal development, including the hedgehog, Notch, and fibroblast growth factor (FGF) signaling pathways.

## Early Pancreatic Development

During the fourth week of gestation, two buds appear on the dorsal and ventral sides of the foregut near the anterior intestinal portal. These epithelial buds indicate the specification of the pancreas. These buds initially grow and differentiate independently, but later fuse to form a single organ. The anlage on the dorsal side, the dorsal pancreatic bud, appears first and gives rise to the dorsal pancreas. The cells of the dorsal pancreas will give rise to the head, body, and tail of the mature pancreas. The second pancreatic anlage appears shortly after the appearance of the dorsal pancreatic bud. This bud, which appears on the ventral side of the gut tube, is appropriately called the ventral pancreatic bud and develops into the ventral pancreas, which forms part of the head of the pancreas. Both pancreatic buds develop simultaneously, and the proliferating epithelial cells grow as projections into the surrounding mesenchymal tissue. During this time, the development of the intestines, and importantly the duodenum, continues. Rotation and asymmetric growth of the duodenum move the originally ventral part to a dorsal location, carrying with it the ventral pancreas and the primordial common bile duct. As the duodenum begins to rotate into its appropriate anatomic location, the ventral pancreas also rotates around the gut tube such that the ventral and dorsal pancreata lie adjacent to each other. These pancreatic rudiments then fuse to form a single organ. While both developing pancreatic buds independently form pancreatic ducts, the lumens of which are continuous with the lumen of the primitive gut, after they fuse their primary ducts anastomose to form the main pancreatic duct (Fig. 1.2). The region of the primary duct of the ventral pancreas proximal to the duodenum fuses with the primary duct of the dorsal pancreas and becomes the primary drainage into the duodenum, entering the duodenum immediately adjacent to the common bile duct. The proximal region of the primary duct of the dorsal pancreas sometimes

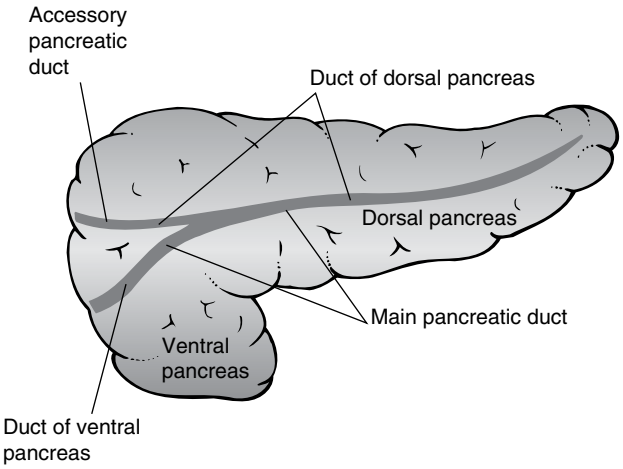


**Figure 1.2** Contributions of the dorsal and ventral pancreas to the definitive organ. The ventral pancreas becomes most of the head. The dorsal pancreas becomes the remainder of the head, plus the body and tail. The duct of the dorsal pancreas contributes a large part of the main pancreatic duct plus the accessory duct. The duct of the ventral pancreas becomes the part of the main duct nearest the duodenum.

remains as an accessory drainage but often regresses. The ducts sometimes fail to fuse, in which event two independent duct systems drain into the duodenum.

### Signaling Governing Early Pancreatic Development

Early pancreatic development and establishing pancreatic identity are governed by the interplay between several critical transcription factors and intercellular signaling pathways. PDX1 and PTF1A are among the earliest transcription factors expressed in the pancreatic progenitor populations, and their functions are critical for pancreatic development [2–5]. In mice, PDX1 expression is first detected in the primitive gut tube at embryonic day 8.5 (E8.5), which corresponds to ~25–27 days in humans. PDX1 expression demarcates the prospective pancreatic domain, which is then followed by PTF1A expression in pancreatic endoderm at E9.5 [5–7]. Mice lacking either transcription factor display pancreatic agenesis [2,3,5,8].

In addition to the transcription factors, several key intercellular signaling pathways between gut endoderm and mesenchyme, including the hedgehog, FGF, Notch and Hippo pathways, play important roles in establishing the pancreatic identity and controlling the expression of these transcription factors. Research studies have shown that sonic hedgehog (SHH), the ligand of the hedgehog pathway, is excluded from the prospective pancreatic region, but is present in the region of foregut that becomes the duodenum, and ectopic expression of SHH in the pancreas induces an intestinal fate, suggesting that SHH signaling may specify a duodenal versus pancreatic fate in the posterior foregut [9,10]. Another well-understood pathway mediating the mesenchymal–epithelial interaction is the FGF signaling pathway, in particular the FGF10–FGFR2 ligand-receptor pair. During early pancreatic development, FGF10 is highly expressed in the primitive mesenchyme, whereas its receptor FGFR2 is present in the pancreatic epithelium [11]. Mouse genetic experiments demonstrated that FGF10 provides the pro-proliferative signal to promote the expansion of the progenitor pool in the pancreatic epithelium [11]. In addition, FGF10 signaling from the mesenchymal cells is critical for maintaining the epithelial expression of SOX9 [12]. SOX9 is another transcription factor critical for early pancreatic development, and it exerts its function in part by controlling the expression of the FGF10 receptor FGFR2 [12,13]. Together, the complex regulatory loop between these signaling pathways and transcription factors in the epithelium and mesenchyme coordinates early organ growth and the establishment and maintenance of pancreatic identity.

## Differentiation of Pancreas Cell Types

The acinar, ductal, and endocrine cells of the pancreas are all produced through the proliferation and differentiation of the epithelial cells of both pancreas primordia. The cells appear homogeneous during the early stages of development as they proliferate and grow into the surrounding mesenchyme as finger-like projections. The epithelial cells form undifferentiated tubules that branch and anastomose as they penetrate into the mesenchyme to generate a tubular network, which resembles an immature (and nonfunctional) duct system. The acinar cells appear as clusters of cells at the ends of branches of this tubular network. The endocrine cells appear as cells that delaminate from the tubular epithelium and reaggregate in isolated clusters embedded within the developing parenchyma. The existing cells within these small isolated endocrine clusters proliferate, and these clusters therefore expand to form the islets.

Apparent differentiation of pancreas epithelial cells into endocrine cells can be identified beginning at 12 weeks of gestation with the detection of endocrine granules. Most of the endocrine differentiated cells identified at this time express glucagon and are therefore believed to be α cells. Importantly, lineage-tracing experiments performed in mice demonstrated that these early α cells do not act as endocrine progenitors, as β cells, the predominant cell type in the mature islet, are derived from glucagon-negative cells [14]. Differentiation of

acinar cells is detected at approximately 16 weeks, as identified by the appearance of zymogen granules. Interestingly, not all enzymes are elaborated at once—detection of trypsinogen does not occur until approximately 22 weeks. The digestive enzyme-positive cells arise as clusters from the undifferentiated tubules, the expansion of which is rapid such that the acinar cells become the dominant population within the organ. Although they are not yet mature acinar cells, the cells in the acinar clusters display some of their hallmark features, including basolaterally located nuclei. As differentiation continues, the cells become arranged in recognized acini and defined lobules surrounded by connective tissue. The ductal system arises after maturation of the immature tubular network. The specific morphologic changes that accompany this change are unclear, although some work suggests that Wnt signaling is involved in this transition [15].

## Transcriptional Mechanisms Underlying Pancreatic Cell Fate Decision

Much information about pancreatic cell fate determination and cell type differentiation has been obtained from studies in animal models. Elegant genetic and cell-based experiments in mice have identified a gene regulatory network controlled by many transcription factors to specify different cell lineages in the developing pancreas.

### Development of the Endocrine Lineage

Endocrine cell specification begins with the expression of NGN3, a bHLH (basic helix–loop–helix) transcription factor, in a subset of progenitor cells within the trunk region of the pancreatic bud [16–18]. The NGN3-expressing cells eventually give rise to all endocrine cell types: insulin-producing β cells, glucagon-producing α cells, somatostatin-producing δ cells, ghrelin-producing ε cells, and pancreatic polypeptide-producing PP cells [16–18]. NGN3 initiates endocrine lineage specification by inducing the expression of downstream transcription factors, including NeuroD, NKX2.2, PAX4, and ARX. Among them, NKX2.2, NeuroD, and PAX4 play key roles in the specification of β cells [19–21]. Mutant mice lacking any of these transcription factors display a phenotype of dramatic or total loss of β cells [19–21]. Further studies revealed that the opposing actions of PAX4 and ARX determine the fate choice between α and β cells. During endocrine differentiation, loss of ARX leads to a complete loss of α cells, but a concomitant increase in β and δ cells [22], whereas loss of PAX4 results in an opposite phenotype with loss of β and δ cells and expansion of α cells [20,22]. It is believed that this effect on cell fate choice is mediated by the reciprocal transcriptional repression between these factors.

### Differentiation of Acinar Cells

Pancreatic acinar cells are primarily derived from precursor cells in the tip region, and their differentiation is coordinated by the transcription factor PTF1A, a master regulator of pancreatic development. Prior to exocrine differentiation, PTF1A forms a complex with the bHLH transcription factor RBP-Jk, and is required for activation of RBP-Jl, an acinar-specific paralog of RBP-Jk [23,24]. The more active RBP-Jl then replaces RBP-Jk to form the complex with PTF1A, thereby directly inducing the expression of many acinar-specific genes, including secretory peptides and digestive enzymes [23,24]. Interestingly, PDX1, another factor important for early pancreatic morphogenesis, is also involved in acinar differentiation. Although not essential for initial acinar specification, it appears that PDX1 is required for terminal differentiation of acinar cells [25]. Other transcription factors, such as NR5A2 and MIST1, are also required for acinar differentiation and homeostasis, likely through the interaction with the PTF1A/RBP-Jk/l complex [26,27].

### Ductal Cell Differentiation and Lineage Plasticity

During development, NGN3-positive cells in the trunk region of the pancreatic bud give rise to endocrine cells, whereas NGN3-negative trunk epithelial cells contribute to the ductal system [28,29]. A number of transcription factors, such as SOX9, PROX1, HES1, and HNF6, are expressed in the ductal lineage and play various roles in ductal differentiation, including primary cilia formation in the ductal epithelial cells [30–33]. The Notch signaling pathway is the main determinant for promoting and maintaining the ductal cell identity [31]. Although the three lineages (endocrine, exocrine, and ductal) are specified during early development, the adult pancreatic cells from different lineages show remarkable plasticity and trans-differentiation capacity in pancreatic injury, pancreatitis, and tumorigenesis, which may shed light on the mechanisms underlying these pancreatic pathologies.

## Development and Disease

Molecules important in the development of the pancreas are also causally associated with pancreatic disorders. Several of the signaling pathways involved in normal

pancreas development, such as the Notch, hedgehog, Hippo/YAP and Wnt signaling pathways, are commonly dysregulated in pancreatic ductal adenocarcinomas [34–40]. Aberrant activation of Wnt signaling drives the development of other pancreatic tumor types such as acinar carcinomas, pancreatoblastoma, and mucinous cystic neoplasms [41–43].

In diabetes, mutation of the transcription factor PDX1, which is important for pancreas specification and for proper β-cell maturation and function, is a cause of maturity-onset diabetes of the young (MODY) [44]. Other transcription factors that are critical for β-cell development (as determined by genetic studies in the mouse), such as hepatocyte nuclear factor 1α (HNF1α), HNF1β, HNF4α, and NeuroD, are all also mutated in additional MODY complementation groups [44]. More recently, scientists have utilized our growing understanding of normal pancreas development to promote the differentiation of induced pluripotent stem cells into insulin-producing cells in a new potential therapeutic approach for diabetes [45–47].

Collectively, these findings illustrate the importance of key regulators of pancreas development and differentiation in pathologic disease states and how knowledge of normal pancreas development may drive new therapeutic strategies for pancreatic diseases.

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# 2

# Anatomy, Histology, and Fine Structure of the Pancreas

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## Introduction

This chapter reviews the anatomy, histology, and ultrastructure of the pancreas, including both the exocrine and endocrine portions. The exocrine pancreas produces and secretes digestive enzymes (e.g., trypsin, chymotrypsin, amylase, lipase) into the duodenum. The exocrine portion includes acinar cells and ducts with associated connective tissue, vessels, and nerves that comprise more than 95% of the pancreatic mass. The endocrine pancreas (islets of Langerhans) makes and secretes insulin, glucagon, somatostatin, and pancreatic polypeptide into the blood. The islets comprise 1–2% of pancreatic mass.

When the anatomic terms *anterior* and *posterior* are used in this chapter, they pertain to relationships in the human, standing erect. Similarly, *superior* and *inferior* mean toward the head and toward the feet, respectively. We will adopt the convention that *right* and *left* (unqualified) indicate the subject's right-hand and left-hand sides. However, when describing the location of structures within an image, *image right* and *image left* are used to denote relationships without reference to the subject's right or left side.

The organization and content of this chapter are based in part on a recent Pancreapedia chapter on pancreatic anatomy and histology [1].

## Gross Anatomy

The pancreas (meaning all flesh in Greek) lies in the posterior portion of the upper abdomen behind the stomach. It is largely retroperitoneal and is covered by peritoneum on the anterior surface of the head and body and is surrounded by fat in this region. It is customary to refer to various portions of the pancreas as head, body, and tail. The head abuts the C-shaped second portion of the duodenum in the right upper quadrant of the abdomen. The tail emerges into the peritoneal cavity (covered by peritoneal serosa) and extends toward the hilum of the spleen in the left upper quadrant. The pancreas weighs about 100 g and is 14–25 cm long [2]. Figure 2.1 shows a human pancreas that has been dissected to isolate it from surrounding fat and adjacent organs and Fig. 2.2 is a drawing depicting a pancreas that has been dissected to reveal the pancreatic and common bile ducts.

The pancreas is intimately associated with several adjacent organs. Relationships of the pancreas to surrounding organs and structures are depicted in Figs 2.3, 2.4, 2.5, and 2.6. As noted above, as the duodenum exits the stomach it loops around the head of the pancreas. The tail of the pancreas lies near the hilum of the spleen. The body of the pancreas lies posterior to the pyloric region of the stomach.

The portion of the pancreas that lies anterior to the aorta is somewhat thinner in the anterior–posterior axis than the adjacent portions of the head and body of the pancreas. This region is designated as the neck and marks the junction of the head and body (Fig. 2.1b). The proximity of the neck of the pancreas to major blood vessels posteriorly, including the superior mesenteric artery, superior mesenteric-portal vein, inferior vena cava, and aorta, limits the options for a wide surgical margin during pancreatectomy (Fig. 2.5).

There is no anatomic landmark for the junction between the body and tail of the pancreas [3]. Hellman defined the tail as one-fourth of the pancreas from the tip of the tail toward the head [4] whereas Wittingen and

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.

Companion website: www.wiley.com/go/beger/thepancreas4e

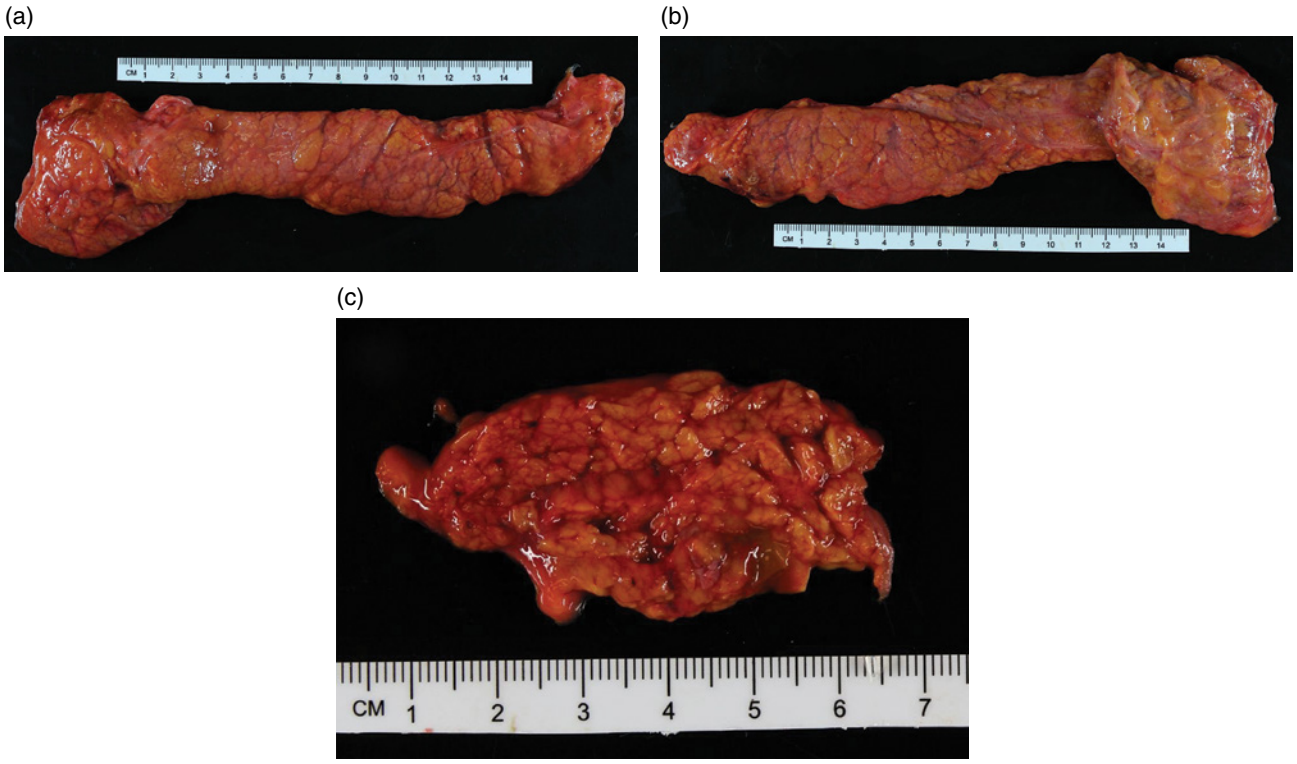


**Figure 2.1** This pancreas, from the autopsy of a 47-year-old woman, measures 22.5 cm in length and has been dissected free of most surrounding fat. (a) Anterior view with the head at image left. (b) Posterior view. A thin layer of fat (translucent yellow) covers a portion of the head at image right. Note the thin neck region just to the left of the head. (c) Cut surface of a transection through the head of the pancreas showing the lobular pancreatic parenchyma. *Source:* Dissection and photo by Catherine M. Nicka, MD.

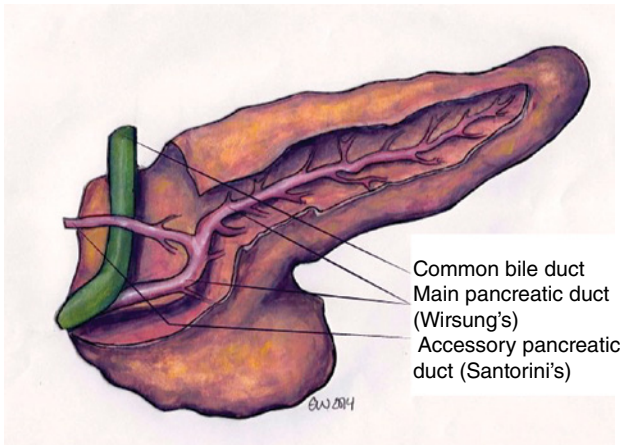


**Figure 2.2** A pancreas dissected to reveal the pancreatic ducts and common bile duct as it traverses the head of the pancreas, ending as it joins the main pancreatic duct near the ampulla of Vater. Interlobular branches of the main duct are depicted but smaller ducts (intralobular ducts and ductules) are not. Eponyms identify the anatomist, embryologist, or physician who is credited with first describing a structure. Wirsung and Santorini were such scientists. *Source:* Drawing by Emily Weber.

Frey defined the junction between the body and tail as the point where the gland sharply narrows [5]. This point is difficult to define in some pancreases.

The common bile duct passes behind the upper portion of the head and then runs through the pancreas to join the main duct in the duodenal wall (Figs 2.2, 2.5, and 2.7b). The accessory pancreatic duct drains into the duodenum at the minor papilla in most humans, and the main pancreatic duct enters the duodenum at the major papilla (ampulla of Vater, Fig. 2.3). See Chapter 3 for discussion of pancreas divisum and other anomalies with possible clinical significance.

Typically, the bile duct and main pancreatic duct join into a "common channel" referring to the fused portion of the bile and pancreatic ducts proximal to its entry into the duodenal lumen. The common channel varies in length from a few millimeters to about 1 cm. A long common channel due to junction of the bile and pancreatic ducts proximal to the duodenal wall is regarded as an anomaly [6]. Less often, there is no common channel because the ducts open separately into the duodenum at the major