The Endocrine Pancreas and Its Tumors
Sylvia L. Asa, M.D., Ph.D.

Abstract
The endocrine pancreas is a complex and important gland that is essential for fuel metabolism. Morphological investigations have an important role in the study of the normal and pathological endocrine pancreas. Endocrine tumors of the pancreas represent a group of hormone-producing neoplasms that can give rise to a variety of clinical manifestations. Their cytodifferentiation and hormonal activity can be determined using a number of sophisticated morphological techniques, including immunohistochemistry, electron microscopy, and ultrastructural immunocytology. In some cases, tissue culture has a role in the analysis of their hormonal profile. Recent advances in molecular biology have paved the way for studies of the factors that underlie cytodifferentiation and pathogenesis of these lesions. Transcription factors may determine hormonal activity and differentiation of cell types in the endocrine pancreas, and transgenic mouse models have shed light on the development of endocrine tumors in the pancreas.

The Normal Endocrine Pancreas
The endocrine pancreas is a major regulator of fuel metabolism. The spectrum of its effects is analogous to that of the pituitary, which controls many bodily functions. The endocrine pancreas is composed of multiple cell types, primarily within the islets of Langerhans. Morphological investigations have an important role in the study of the endocrine pancreas and its pathology.

History of the Endocrine Pancreas
The small clusters of morphologically unique cells scattered in the pancreas were first described in 1869 by Langerhans [44], whose name has since characterized these structures. Their endocrine nature was not initially recognized; in 1889, however, von Mering and Minkowsky suggested that they function by the release of endocrine humors, and this concept was supported by Laguesse in 1895 [42].

Although the islets initially were thought to be composed of a uniform population of cells, Diamare [15] recognized in 1899 that there were 2 distinct islet cell types. In 1907, Lane [43] proposed the Greek letters \( \alpha \) and \( \beta \) to identify 2 cell types based on differences in the solubility of their secretory granules in alcohol. The Nobel prize–winning work of Banting and Best [4], culminating in the discovery of insulin in 1922, confirmed the endocrine function of the pancreatic islets and led to the use of insulin in the therapy of diabetes.

The tremendous advances in morphology that allowed recognition of multiple cell types and hormones that emanate from these microscopic structures began in 1931 with the description of the D cell by Bloom [9]. This description was followed by specific staining of B cells with aldehyde fuchsin by Gomori [23] and the use of silver stains proposed by Hellerström and Hellman [33] and Grimelius [25] to distinguish subpopulations of A cells. Application of electron microscopy allowed recognition of the ultrastructural features of the distinct cell types in the islets [6, 24, 26, 40]. The advent of immunohistochemical methods...
permitted specific localization of hormones in those various cell types [5, 41, 55].

**Phylogeny of the Endocrine Pancreas**

A primitive endocrine pancreas is present in cyclostomes, such as the Hagfish and Lamprey, and the homology of porcine and hagfish insulin suggests that all the important properties of the molecule have been preserved during vertebrate evolution [71]. In lower species, specialized insulin-containing cells are dispersed throughout the gut wall.

In cyclostomes, insulin-containing cells comprise 99% of pancreatic endocrine cells, and somatostatin-producing cells make up the other 1% of the population [13, 71]. In cartilagenous fish, glucagon joins the family of pancreatic peptides. Pancreatic polypeptide is the most recently evolved of the 4 main islet hormones and is found in higher species of fish [13, 71].

The mammalian pancreatic islet is composed of a compact mass of cells with a dense network of anastomosing capillaries [23]. Each islet contains 4 cell types, each with a particular hormonal product. The A cells are the source of glucagon, B cells produce insulin, D cells are responsible for the synthesis of somatostatin, and PP cells produce pancreatic polypeptide. Each cell type has a specific distribution, both anatomically in the head, body, and tail of the pancreas (Table 1), and within the individual islet (Fig. 1) [20, 28]. Each also has a highly characteristic ultrastructural appearance [6]; common features are illustrated in Figure 2.

The reason for localization of the islets of Langerhans in the pancreas is not known. It may be simply that both the exocrine and the endocrine components of the pancreas are involved in regulation of nutrient absorption and utilization. It has been shown that pancreatic hormones are trophic to exocrine pancreatic elements, and feedback regulation may be important in the maintenance of exocrine pancreatic mass [8].

**Ontogeny of the Endocrine Pancreas**

Although much work has been invested in analysis of the developing endocrine pancreas of various experimental animal species, space does not permit a review of all the species-specific ontological profiles. This review concentrates on the human situation that provides insight into human pathology.

In the developing human fetus, by 4 to 5 weeks’ gestation, 3 diverticula are recognizable at the level of the bile duct; these are the one dorsal and the two ventral primordia of the pancreas [12, 37, 38, 61]. At the earliest stages, the primitive organ is

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**Table 1. Cell distribution in the mammalian endocrine pancreas**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Hormone</th>
<th>Body, Tail</th>
<th>Head</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (alpha)</td>
<td>Proglucagon-derived PYY</td>
<td>15–20%</td>
<td>5%</td>
</tr>
<tr>
<td>B (beta)</td>
<td>Insulin</td>
<td>60–70%</td>
<td>20%</td>
</tr>
<tr>
<td>D (delta)</td>
<td>Somatostatin</td>
<td>5–10%</td>
<td>5%</td>
</tr>
<tr>
<td>PP</td>
<td>Pancreatic polypeptide</td>
<td>2–5%</td>
<td>70%</td>
</tr>
<tr>
<td>EC</td>
<td>5HT</td>
<td>Occasional</td>
<td>Occasional</td>
</tr>
<tr>
<td>G</td>
<td>Gastrin</td>
<td>Fetal</td>
<td>Fetal</td>
</tr>
</tbody>
</table>

**Figure 1.** Immunohistochemistry identifies 4 cell types in the normal human islets of Langerhans. The A cells, containing glucagon, are found preferentially at the periphery of the cell cords (A), whereas the insulin-containing B cells fill the center of the cords (B). Somatostatin in D cells (C) and pancreatic polypeptide in PP cells appear to be random in distribution; the somatostatin cells are actually carefully interposed between A and B cells (ABC technique, original magnification × 71).