The Nobel Pancreas: A Historical Perspective

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For everyone interested in the pancreas, it is truly a noble organ. Known to the ancient Greeks, its name in Greek "pan kreas" translates as "all flesh." Aristotle believed its function was to protect the great vessels and 4 centuries later Galen claimed it to be a cushion for the stomach.[1] The Renaissance anatomists, beginning with Vesalius, defined its structure with its ducts, first shown by Johann Wirsung in 1642, to empty into the intestine. Regnier de Graaf, of the Graafian follicle, was the first to study pancreatic secretion in 1664, using a goose quill inserted into the duct. In the 19th century, Claude Bernard in Paris, and others, showed the digestive capabilities of pancreatic juice for fat, carbohydrate, and protein.[1,2] Paul Langerhans, a medical student in Berlin, described the eponymous islets in 1869 and in 1889, Miring and Minkowski described experimental diabetes in the dog after pancreatectomy.[3] In addition to understanding the anatomy and physiology of the exocrine pancreas, Hans Chiari had described the autodigestion of the pancreas that accompanies pancreatitis in 1896. By 1900, the histology and general understanding of the function of the pancreas was in place. The 20th century was to be occupied first with understanding the control of pancreatic secretion and then the understanding of specific cell types of the pancreas as molecular machines evolved to carry out specific functions. A timeline for this increase in understanding of the pancreas and its diseases is shown in Figure 1. More detailed coverage of the last 160 years is shown in Figure 2.

In 1896, the Swedish inventor Alfred Nobel died, and in his will he left much of his fortune—earned in the manufacture of explosives, including dynamite, which he invented—to establish prizes that bear his name in different areas of knowledge to be chosen by different academies in Stockholm or Norway. One of these prizes in Physiology and Medicine and another in Chemistry will be discussed here. The first Nobel Prizes were awarded in 1901 and they have been awarded annually since then to one to three individuals in a specific area. In this Commentary, I will review the advances in scientific knowledge in which the pancreas led the way to the extent that it was recognized by the awarding of 5 Nobel Prizes for work that either related directly to products of the pancreas or used the pancreas as a cellular source to understand fundamental physiological and cell biological processes. I will also note some omissions and controversies.

The early years of the 20th century were marked by understanding of the neural and hormonal control of the pancreas. One of the early giants of modern physiology was Ivan Petrovich Pavlov who, before studying the conditioned reflexes for which he is best known, studied the neural control of gastric and pancreatic secretion. Pavlov, working in St Petersburg, Russia, developed the first modern physiology laboratory with multiple staff who worked together as a team. They showed that psychic stimulation or putting food in the stomach led to secretion from the pancreas, which was collected via a pancreatic fistula.[4] Acid and fat were especially good stimulants and carbohydrate was not. His laboratory also identified enterokinase, the intestinal activator of trypsin, and described the cephalic phase of pancreatic secretion. Pavlov's work was first summarized in a series of lectures and then in a book published first in Russian and then in English in 1902 entitled, *The Work of the Digestive Glands*.[5] Pavlov's contribution was recognized when he received the Nobel Prize in 1904 "in recognition of his work on the physiology of digestion." Meanwhile, another famous experiment was carried out by William Bayliss and Ernest Starling at University College in London, in which they showed that an extract of the intestinal mucosa, when injected into a dog with its pancreas completely denervated, led to copious secretion of pancreatic juice.[6] This was, in fact, the first demonstration of a chemical messenger or "hormone," a term coined by Starling in his Croonian Lecture of 1905 to the Royal College of Physicians. Thus was born the field of Endocrinology. Starling, probably the most

Abbreviations used in this paper: ER, endoplasmic reticulum; RER, rough endoplasmic reticulum.

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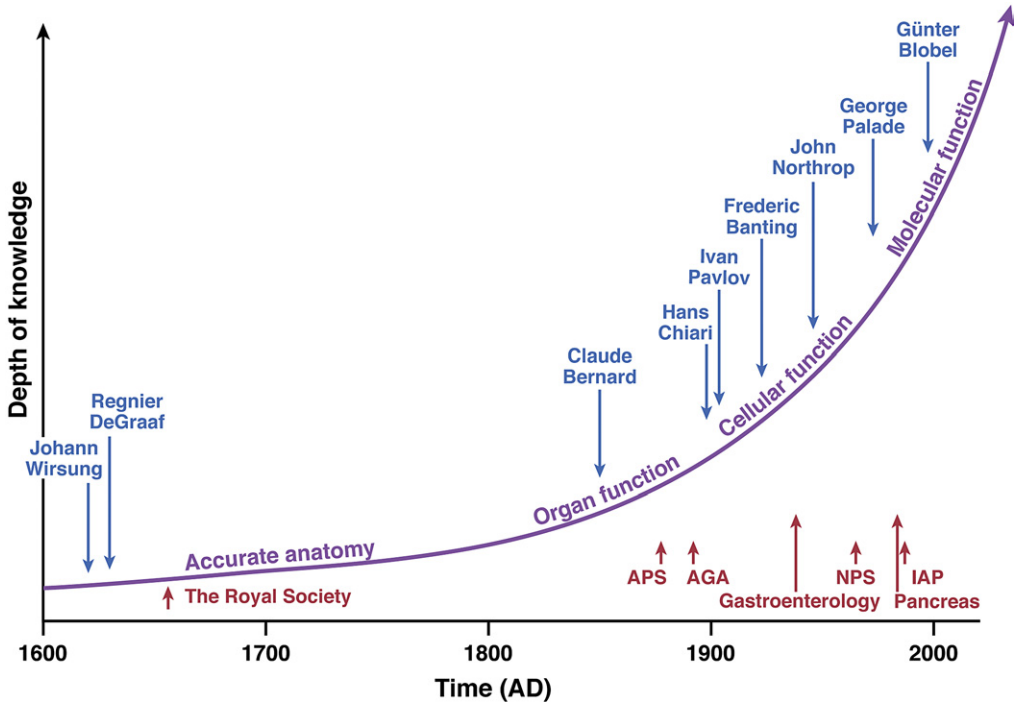

Figure 1. Depth of knowledge of the pancreas and pancreatic disease has accelerated during the last 150 years. Above the curved line are placed major discoveries and awarding of Nobel Prizes for work on or using the pancreas. Below the line are indicated the founding of organizations and journals associated with study of the pancreas: AGA, American Gastroenterological Association; APS, American Physiological Society; IAP, International Association of Pancreatology; NPS, National Pancreatic Societies (American, European, Japanese, etc). The *Philosophical Transactions of the Royal Society*, the first forerunner of today's scientific journals, was initiated in 1662 shortly after the founding of The Royal Society in London. *Pancreas*, the first journal devoted to the pancreas started in 1986; *Pancreatology*, published by the IAP began in 2001 (not shown). For lack of space, American organizations and journals are indicated.

famous physiologist not to win the Nobel Prize, also discovered "Starling's Law of the Heart" and described the physical forces regulating capillary fluid exchange. However, in his youth, he had fallen in love with German culture and was a vocal German supporter in the period just before WWI, which might have affected his chances at the prize.[7]

The second Nobel Prize awarded for the study of the pancreas went to Frederic Banting and John Macleod in 1923 for the isolation of insulin.[3] By the early 1900s, it was widely believed that the islets of Langerhans produced an internal secretion into the blood that regulated carbohydrate metabolism. A number of investigators around the world tried to make extracts of the pancreas to treat diabetes, but failed. Banting, a young physician in Toronto without research training, was aware of work showing that ligation of the pancreatic duct caused the acinar cells to atrophy, and he realized that removing their proteolytic enzymes would help to isolate intact insulin. In 1921, Banting discussed his approach with Macleod who,

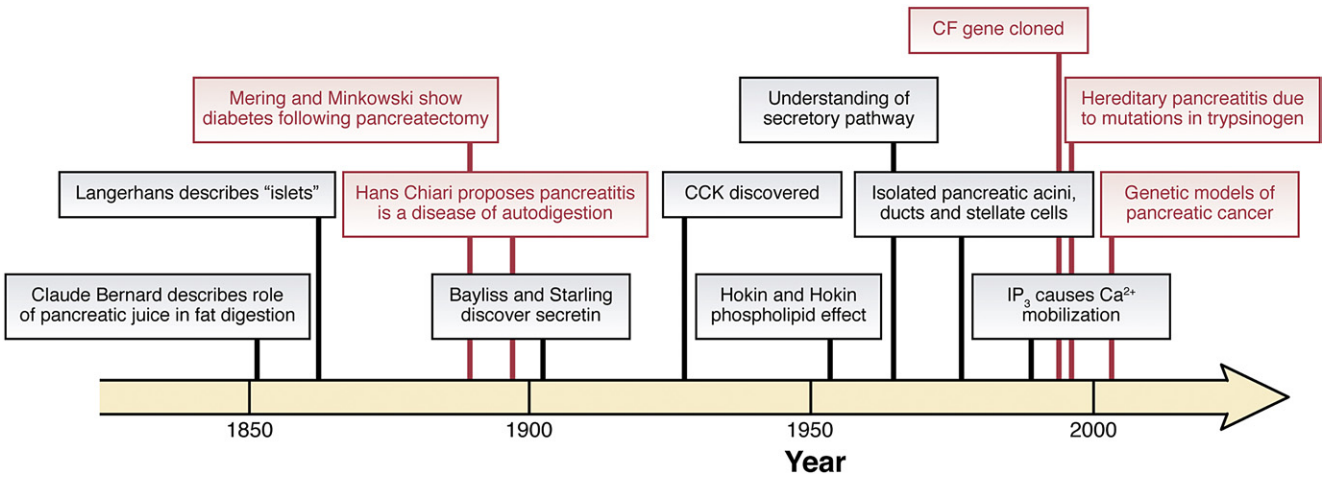

Figure 2. Recent timeline of major events in understanding of pancreatic function (*black*) and pancreatic disease (*red*).