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History of Pancreas Transplantation

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On December 20, 1893, 3 years after von Mering and Minkowski showed that total pancreatectomy in dogs resulted in diabetes mellitus, Dr. P. Watson Williams in Bristol, England, grafted three fragments of a pancreas obtained from a freshly slaughtered sheep into the subcutaneous tissue of a 15-year-old boy in extremis, 5 months after clinical onset of diabetes. The recipient died 3 days later, not of complications from the unsuccessful transplant but of unrelenting acidos, a sequela of basically untreated diabetes. At autopsy, the recipient's own pancreas was shrunken and sections showed little but fibrous stroma. According to Williams, the history and the postmortem examination left little doubt that the patient had "pancreatic diabetes" a case that "presented all the conditions that might lead one to hope for beneficial results from successful grafting of the pancreas, if anything can be hoped for in this direction at all." He was not discouraged, and further stated that "failure was possibly due to obtaining the graft from a sheep that had been killed by bleeding. . . . If ever I felt justified again in resorting to pancreatic grafts in a similar case, I should obtain them from a living animal anesthetized or dispense with the anesthetic altogether."

Williams' use of the term "pancreatic diabetes" reflected the prevailing aversions at classification by etiology and the concept that not all cases of diabetes are secondary to an abnormality of the pancreas. He commented on the large share of attention that diabetes received at the hands of clinicians, pathologists, and chemists; the diverse opinions that were advanced; and on recent facts that at first sight seemed to justify important conclusions as to the real nature of diabetes and indicating fresh lines of treatment, at least for pancreatic diabetes, by extracts or grafts of the pancreas. Williams recalls the canine pancreatic extirpation experiments of Minkowski (not naming von Mering) that resulted in diabetes (no citation, implying it was general knowledge) and the clinical cases of diabetes associated with severe pancreatic atrophy secondary to calcareous ductal obstruction reported by Freylan (Berl Klin Woch 1893;6). On the other hand, he cautions not to overlook the results of the investigations of the pancreas in cases of diabetes by Williamson (again, no citation, but probably R.T. Williamson, author of Diabetes Mellitus and Its Treatment. Edinburgh; 1878), which showed that in 50% the gland was normal in structure, "rendering it evident," in Williams view, "that we must guard against attributing a too important position to the pancreas as a factor in diabetes mellitus."

Even without mentioning the instances of gross pancreatic pathology in which diabetes was absent, Williams' 1894 article conveys the prevailing confusion over the relation of the pancreas to diabetes. Before grafting the sheep pancreas, Williams gave extracts of sheep pancreas, first orally and then by injection (without effect, a failure that he noted duplicated that of others), actions that reflected the uncertainty over whether an external or internal pancreatic secretory product was crucial in maintaining glucose homeostasis.

The tone of Williams' 1894 article suggests that his reference to Minkowski was to the 1890 publication coauthored with von Mering that dealt strictly with pancreas extirpation—and not to the canine pancreas autotransplant work Minkowski published in 1892, which made an internal secretion the most tenable hypothesis.

Similarly, as also published in 1892, Hedon did a partial pancreatectomy in dogs and transposed the pancreatic remnant (uncinate process)—totally disconnected from the duodenum but on a vascular pedicle—to the subcutaneous tissue with creation of a ductocutaneous fistula, so that reconnection to the intestine was impossible (thus addressing a criticism of earlier experiments). Diabetes did not ensue, proving that an internally secreted substance must exist.

In addition, in 1893 Lagesse named the nonacinic clusters of cells scattered throughout the pancreas the "islets of Langerhans," after Paul Langerhans, who first described these formations (Zellhaufen) in his doctoral thesis at the University of Berlin in 1869. Undoubtedly, Williams was not aware of the post-1889 experiments of Minkowski in Strasbourg (then in Germany) or of Hedon in Montpellier, nor of the suggestion of Lagesse that the islets were the source of the postulated internal secretion (indeed, Lagesse coined the term endocrine secretion and later, in animal experiments, was one of the first to show that ligation of the pancreatic duct was followed by atrophy of the acinar cells, usually without destruction of the islets or without development of diabetes).

Lagesse's insight shifted the focus of correlating diabetes and pancreatic pathology from the gross and general to the microscopic and particular. Several investigators, using advances in techniques leading to distinction of cell types (with the ß-cell ultimately identified as the source of the internal
secretion named insulin), clearly described islet lesions, or even the absence of islets in the face of no other abnormalities, in association with diabetes mellitus.\textsuperscript{9-14} However, there were also cases of diabetes where no islet pathology was discerned, and there were examples of islet pathology in the absence of diabetes.\textsuperscript{8} Thus, the clinical–pathologic correlation of diabetes and the pancreas was confusing at both a microscopic and gross level.

In Williams’ day, the clinical classification of diabetes was little more than a general recognition of mild and severe forms. The mild form was seen more commonly in adults and associated with obesity (\textit{diabetes gras}); the severe form was more common in children and associated with leanness (\textit{diabetes maigre}).\textsuperscript{15} However, at the end of the 19th century it was clear that there was a form of diabetes that should be amenable to treatment by pancreatic extracts or transplants. Both extracts and transplants were successfully applied in the 20th century\textsuperscript{16,17} and remain as treatments in the early part of the 21st century. The development of both these treatments—exogenous insulin and transplants (\textit{β}-cell replacement)—depended on the persistent efforts of individuals who built on the cumulative knowledge and technical advances of preceding generations in multiple disciplines.

### Nature of the Pancreas

Long before organ or tissue transplants (or surgery of any kind) could be considered by physicians for treatment of a specific disease, the anatomy and function of the identified organ had to be understood (to at least some degree) and pathologic correlation with various disease states had to be established. It took centuries to figure out, but we now know that the pancreas is a nearly unique organ with dual components that function more or less independently: (1) the exocrine portion (98% of the gland), connected by a ductal system to the intestine, secretes enzymes that aid in digestion; and (2) the endocrine portion, comprised of about 1 million separate cellular spheres scattered throughout the gland—called islets because of their appearance when sliced in histologic section (the flatlander’s perspective). The islets secrete hormones into the blood stream, of which one, insulin, is essential to sustain life by its promotion of carbohydrate metabolism in nearly all tissues of the body. End-stage disease can occur simultaneously in both components of the pancreas (endocrine or exocrine), but more often one component is affected and the other is not.

Given its dual nature, the entire pancreas can be transplanted as an immediately vascularized graft to correct endocrine deficiency alone (most common), exocrine deficiency alone (rare), or both. Or, the endocrine portion (islets) can be isolated and transplanted as a free graft to an ectopic site in a diabetic recipient, restoring autoregulated insulin secretion after neovascularization occurs. Within the islets, \textit{β}-cells synthesize and-secrete insulin. Insulin acts at the cell membrane level, facilitating entry of glucose into the cell for metabolism. The role of the \textit{β}-cell is to maintain blood sugar levels within a narrow range. The brain does not require insulin to drive glucose into the cells, but does require a sufficient level of glucose in the blood so that enough is constantly available for metabolism. Thus, \textit{β}-cells are not only synthesizers and secreters but also glucostats (analogous to mechanical thermostats or humidists). They turn on to secrete insulin when the blood sugar rises above the threshold level (about 83 mg/dL) and shut off when the blood sugar reaches or is below this level.\textsuperscript{18} The \textit{β}-cell is the ultimate in a close-looped insulin pump.

### Discoveries About the Pancreas and Diabetes

The highlights of discoveries about pancreatic anatomy and physiology were described by Busnardo,\textsuperscript{19} by Child in his history of pancreatic surgery,\textsuperscript{20} and by Wellman and Volk in their historical review of the diabetic pancreas.\textsuperscript{8} Landmarks in the evolution of our understanding of the nature of diabetes were summarized by Papaspyros\textsuperscript{21} and Levine\textsuperscript{22} and put in perspective by Gale.\textsuperscript{23}

In early English writings, the pancreas was called “sweet-bread,”\textsuperscript{24} and the term has persisted in the language of the abattoir. The pancreas was grossly described by the anatomist Herophilus of Chalcedon around 300 BC. Two centuries later it was given its name (pan=all; creas=flesh) by Ruphos of Ephesus. Galen (ca. AD 130 to 201) referred to the pancreas in his writings but without an understanding of its function.\textsuperscript{20}

However, even the exocrine function of the pancreas was not understood until Claude Bernard performed his experiments in the mid-19th century.\textsuperscript{25} The realization that the pancreas must have a dual nature, with both external and internal secretions, did not occur until the end of the 19th century.\textsuperscript{26} Diabetes mellitus, as a syndrome with clinical characteristics, was described in ancient medical writings of several cultures.\textsuperscript{21} Yet, it was centuries before an association with pancreas pathology was described—sketchily in the 18th century but not definitively until the 19th century.\textsuperscript{8}

From the time Galen described the pancreas as a cushion for the stomach, virtually no references to the organ were recorded until the Middle Ages.\textsuperscript{8,19,20} The fact that the pancreas had a duct was mentioned by Luzzi in 1275. But, the first accurate description of the pancreas and its anatomic relations was not published until 1543, in the monumental \textit{De Humani Corporis Fabrica Libri Septem} by Vesalius and his student Fallopio. In the 17th century, Thomas Wharton noticed the structural similarity of the pancreas and salivary glands. The main pancreatic duct was described by Wirsung in 1642, the accessory duct by Santorini in 1724, the termination of the main duct in a papilla by Vater in 1728, the vascular relationships by Walther in 1729, and the musculature surrounding the papilla by Oddi in 1887.\textsuperscript{25} The descriptions of anatomy were paralleled by physiologic studies.\textsuperscript{20}