Pancreas and Diabetes Mellitus: The Relationship between the Organ and the Disease

Saumya Menon, Gopalakrishna Rajesh, Vallath Balakrishnan

Abstract
Diabetes mellitus has been a fascinating disease from the dawn of medical history. The first breakthrough in its treatment came in 1922, with the discovery of insulin which was extracted from the pancreas of a dog. Even earlier, a relationship between pancreas and diabetes mellitus had been suspected by medical scientists. However, the study of diabetes mellitus is much more than its relationship with the pancreas. On the other hand the pancreas has been known to be a very reclusive organ that is hidden away from physicians and surgeons for centuries. In recent times, it has become more accessible and has yielded some of its secrets. The relationship between the pancreas and diabetes mellitus is a story full of complexities and surprises. This article attempts to reveal some of the important events and persons in the story and the controversies surrounding them.

Introduction
The pancreas, hidden in a posterior recess of the abdominal cavity, with its relative inaccessibility, rightly fits into the description of “a riddle wrapped in an enigma” having shyly evaded the attention of meddling anatomists and surgeons for several centuries. From its secretive nature it could very well be a Scorpio! This mysterious organ has been having a long-standing affair with diabetes mellitus, part of which has been revealed to us now. On the other hand, the story of diabetes mellitus is one of the most fascinating chapters in the history of medicine. One of the major events in its history was the way its relationship to pancreas was brought out in 1922, by Banting and Best, a story in itself with the punch of a ‘cloak and dagger’ mystery. In this article we attempt to capture some of the exciting people and events of the story of the complex relationship between this little organ and a disease that is today overwhelming mankind.

Anatomy
The earliest recognition of the pancreas is believed to be by the Greeks. The first description of the organ has been attributed to Herophilus of Chalcedon, born in 336 BC on the Asiatic side of the Bosporus. He has been considered “Father of anatomy” who practiced dissection, even on living criminals, in Alexandria in ancient Egypt. Rufus of Ephesus (1st or 2nd century AD), the Greek physician and anatomist gave the name pancreas to the organ (pan=all; creas=flesh, derived from the Greek) since there was no bone or cartilage in it and its uniform consistency. In the thirteenth century there was mention of the organ in the “Anathoma” of Mondino de Luzzi published in 1487 in Padua, Italy.

When Greek civilization gave way to the Romans, many Greek physicians flocked to the capital of the New Empire. Galen, physician of the gladiators and to the Roman Emperor, was notable among them. Once a year, he and his students cut open a dead pig to study its anatomy. Galen viewed the pancreas as a cushion overlying and protecting the large vessels behind it. Because of his formidable reputation as a medical authority, his views, many of them disproved later, were to hold sway for the next several centuries and blocked independent scientific thinking and pursuits till nearly the 18th century.

Andreas Vesalius, who in 1531, at the age of seventeen, left his home in Brussels to study medicine in Paris provided a more realistic description of the pancreas. Sylvius a disciple of Galen was his teacher. Vesalius wished to dissect the human body, but would have been burned or hanged if he did. While working in Padua, he completed his medical masterpiece De humani corporis fabrica - Fabric of the Human Body, divided into seven volumes. Vesalius in his illustration of the pancreas, seemed to be more impressed with the vessels running through the gland since he had cut away most of the gland to expose the vessels. He thought that the gland afforded a protective cushion for the stomach.
Vesalius was assisted in his work by his student Gabriele Fallopio (1523-1562). Even though the term pancreas is not mentioned by Vesalius in his book, the English translation mentions the synonym “sweetbread”.  

Johann George Wirsung, a German émigré, living in Padua, described in 1642, the structure of the main duct of the pancreas. He wondered whether it was an artery or a vein. A colleague gave his name to the duct. It seems he got the idea from his student Hoffman who had noticed such a duct in the rooster. The first known picture of pancreas was produced by the Roman anatomist Bartolomeo Eustachio (1520-1574). He showed the posterior aspect of dog’s pancreas with duodenum and the common bile duct. The discovery of the pancreatic duct established the role of pancreas as a secretory gland nullifying the previous theories such as cushion of stomach and a pad supporting vessels. His pictures were published 140 years after his death by Lancisi. The credit for the discovery of the accessory pancreatic duct is usually given to Giovanni Domenico Santorini (1681-1737). However, there were at least 8 observations of the minor duct prior to Santorini. Santorini wished to publish a book on his findings of the minor pancreatic duct. However he died before his work could be published. Michele Girardi, 38 yrs after Santorini’s death, published the drawings under the title Jo. Dominci Santorini anatomici summii septemdecim tabulae which means- Giovanni Domenico Santorini, the excellent anatomist’s seventeen drawings. D.Moyse, (1852) a French student was the first to pictorially depict the microscopic structure of the pancreatic acini in a dissertation he submitted.  

Physiology  

The famous Dutch physician Franciscus de Le Boe (Sylvius) did several experiments on digestion and on the role of pancreatic juice and bile in the digestive process. Many of his hypotheses were later questioned by John Conrad Brunner who believed that the duodenal glands secreted the main digestive juice, and is the first recorded person to resect a pancreas. His experiments were published in a book entitled Experienta nova circa pancreas [New experiments on the pancreas]. Regnier de Graaf (1641-1673) was a student of Sylvius who assisted Sylvius in his studies of the digestive process. De Graaf investigated the pancreatic juice of a dog by collecting it though a quill inserted into the pancreatic duct. He tasted the pancreatic juice and observed that the juice was insipid and of an acid-salt (acidic) type. He collected the pancreatic juice from a dead sailor later, and noticed it was similar to that of the dog.  

Leopold Gmelin and Friedrich Tiedemann discovered in 1826, that the pancreatic juice was alkaline and not acidic like gastric juice and that it contained proteins. It was the classic work of Claude Bernard (1813-1878), the great French physiologist that brought out the dominant role of the pancreatic juice in digestion. He clearly demonstrated that gastric digestion was only a preparation, and that further breaking up of starch and proteins took place by the effect of the pancreatic juice. Bernard’s complete studies including the anatomic studies, comparative anatomy and physiology, and his experiments with the pancreatectomized dogs were published in 1856.  

It was the celebrated Russian physiologist, Ivan Petrovich Pavlov from St. Petersburg, who through his studies of pancreatic fistulae in dogs, demonstrated the vagal control of pancreatic secretion. Pavlov’s group found that introduction of acids into the duodenum stimulated pancreatic juice secretion and also described ‘enterokinase’ that activated pancreatic juice. Pavlov’s book, “The Work of the Digestive Glands” comprising his lectures at the Imperial Institute for Experimental Medicine in St. Petersburg was first published in 1897 and remains a classic work in physiology. His work on “conditioned reflexes” earned him outstanding acclaim and reputation. Pavlov was awarded the Nobel Prize in Physiology or Medicine in the year 1904.  

Bayliss along with Starling, who was his brother-in-law, working in University College, London, discovered a chemical substance released from the proximal small intestine in response to acid which stimulated secretion from the pancreas. They named this substance ‘secretin’ and suggested the term hormone, from the Greek word meaning “I set in motion”. Secretin was the first hormone to be discovered and Bayliss and Starling’s epoch-making paper appeared in the Journal of Physiology in 1902. The second hormone to be released from the duodenum and the intestinal mucosa was cholecystokinin, discovered years later in 1928-29 by Ivy and Oldberg which stimulated the contraction of gall bladder and also increased pancreatic protein secretion. In the year 1928, Ivy and Oldberg had demonstrated a hormone with the action of contracting the gallbladder and relaxing the sphincter of Oddi. This was labeled cholecystokinin (CCK) in 1943. Harper and Raper discovered pancreozymin, a hormone that influenced pancreatic enzymatic secretion. A few years later, Jorpes and Mutt proved that cholecystokinin and pancreozymin were the same substance, which is now known as cholecystokinin.  

Diabetes Mellitus  

The term diabetes is derived from Latin and ancient Greek and literally means “a passer through; a siphon”. The term “diabetes,” meaning running through a siphon is based on traditional belief that
in this disease all fluids consumed rapidly run through the body to be passed in urine, thus causing polyuria. The word mellitus comes from Latin and means honey-sweet. It was Thomas Wills in 1675 who added the word mellitus to diabetes as the urine of diabetic patients had a sweet taste. This sweet taste had however been previously commented upon by ancient Greeks and Indians.

In 1552 BCE, the Egyptian physician Hesy-Ra of the 3rd Dynasty makes the first known mention of diabetes – found on the Ebers Papyrus – and lists remedies to combat the ‘passing of too much urine. Demetrius of Apamaia, a Hellenistic physiologist of the Herophilian school, seems to have used the name diabetes towards the beginning of the Common Era. Aretaeus of Cappadocia (81-138 CE), a Greek physician, follower of Hippocrates, who practiced in Rome and Alexandria, gave a detailed description of the disease which went by the name diabetes. Aretaeus believed the cause of diabetes lies in the stomach, Galen implicated the kidneys and Claude Bernard, the celebrated French physiologist, in the middle of the 19th century, favored the liver.

Johann Conrad Brunner (1653-1727), who studied medicine in the University of Strasbourg, in his studies observed that dogs could survive partial pancreatectomies. Brunner also found that the dogs suffered from polyuria, polydypsia, polyphagia and bulimia but did not associate it with diabetes. This had to wait another 200 years for Oskar Minkowski and Joseph von Mehring to describe it. It took a few more years before the pancreas - diabetes connection was established. In 1674, Thomas Willis, a physician, anatomist and professor of natural philosophy at Oxford, discovered, by tasting, that the urine of diabetic persons was sweet. However, Charaka and Susruta of India had predated him by nearly fifteen centuries when they described “Madhu Meha” (diabetes) in their Samhitas (Treatises). The Susruta Samhita deals with diabetes, and its symptoms in detail. It elaborates on the symptoms such as overabundance and sweetness of urine, weight loss, impotence and ulcers. It also differentiates between the early onset ‘thin’ diabetes and later-onset ‘fat’ diabetes, thus being forerunners to type 1 and type 2 diabetes.

In 1776, Mathew Dobson of England showed that diabetics excrete sugar in their urine. Cawley reported in 1788 the observation of a shrunken pancreas in a diabetic at autopsy, perhaps the first autopsy in a diabetic. Eteienne Lancereaux (in 1877) was the first to recognize that diabetes mellitus was definitely related to pancreas. Before insulin was discovered, treatment for diabetes consisted of a diet low in carbohydrates and by feeding fresh veal pancreas by mouth. John Rollo, Surgeon-General to the Royal Artillery treated a patient by dietary restriction in 1806.

In 1899, Joseph von Mehring and Oscar Minokowski of Strasbourg, demonstrated that extirpation of the pancreas of the dog caused diabetes. The two were arguing whether dogs would survive pancreatectomy, when their chief Naunyn suggested that they better try out the experiment and verify it. After the experiments, a laboratory attendant noticed the presence of flies over the urine of the depancreatectomized dogs, but not over the urine of the control dogs. Following this tip, Minkowski found out that the urine of the depancreatectomized dogs contained sugar. It was the first practical demonstration that pancreatectomy in dog caused diabetes.

Paul Langerhans (1849-1888), a medical student working in Rudolf Virchov’s institute in Berlin, presented a thesis on clear cell clusters (“Zellhaufen”) in the gland in 1869, describing the structure of the pancreatic islands. In the forward to his doctoral thesis, which was entitled ‘Contributions to the microscopic anatomy of the pancreas’, Paul Langerhans wrote: “the purpose of these lines can be at best to help in drawing greater attention to the pancreas than has so far been paid by anatomists”. There was no follow-up to Langerhans’ work during the next few decades, so that Naunyn stated: ‘Nothing is more boring than the autopsy of a diabetic- except the autopsy of two diabetics’ (Schadewaldt, 1975). It was not until 1893 that Laguesse, a French worker, suggested, probably under the influence of the epochal work of Mehring and Minkowski, that the assumed internal secretory function of the pancreas may be ascribed to the “islets of Langerhans”. In the year 1893, Laguesse described the granules of the islet cells of the pancreas. Eugene Opie (1901), a US pathologist proposed the “common channel theory” and the role of bile reflux in the causation of acute pancreatitis. He also described consistent hyaline changes in the islets of Langerhans in diabetic patients, the first evidence of islet cell damage in diabetes. About the same time as Opie’s observation on the islets, Ssobolew and Schulze independently demonstrated that following ligation of the pancreatic duct, the gland atrophies, but the islets are spared and diabetes did not develop. Moses Barron (1883-1974) in a paper “The Relation of the Islet of Langerhans to Diabetes with special Reference to Cases of Pancreatic Lithiasis” made the landmark observation that in pancreatic disease without islet involvement, there was no diabetes.

Sir Edward Albert Sharpey-Schafer (1850-1935) theorized that diabetes resulted from deficiency of a single substance produced by the pancreas. He, in the year 1910, dubbed the chemical produced by the pancreas “insulin”. The great break-through came in diabetes with the discovery of insulin in
1921. Frederick Grant Banting studied in Toronto for his MB and during the war became a private in the army and won a Military Cross for gallantry in action in 1918. Afterwards he tried to establish a practice while lecturing part time. It was while working as a lecturer in pharmacology in Toronto University that he got interested in diabetes after reading a paper on the pancreas in diabetes. He approached John James Rickard Macleod, the professor of physiology at the University of Toronto, a leading diabetes researcher, for facilities to work on diabetes. Macleod provided him with a few dogs and basic facilities. Charles H Best a medical student was assigned to assist him. When Macleod was on leave, Banting and Best prepared “isletin”, an extract prepared from the pancreas of a dog whose duct had been ligated earlier. The extract was injected into another depancreatectomized diabetic dog in a moribund condition and in diabetic coma. Following the injection, the dog dramatically recovered. By now Macleod had returned from leave and he too got excited by the results and provided the young workers better facilities. The new substance was purified and standardized by J.B.Collip, a biochemist who had joined their team. The pure extract was labeled “insulin”. A 14 year-old boy, Leonard Thompson, dying of diabetes was saved by giving an injection of the newly discovered hormone. In 1923, the Nobel Prize in Medicine was jointly awarded to Banting and Macleod. Banting was furious that Best was left out; he shared his prize money with Best. Macleod shared his part of the prize money with Collip. This award and subsequent comments by the key players led to a bitter controversy about who really deserved the credit for the discovery of insulin and have been the substance of several conflicting articles. Banting died in 1941 in a plane crash in Newfoundland. Best later succeeded Macleod as Professor of Physiology in the University of Toronto and died in 1978 after a long and a productive scientific career. Since 2007, Banting’s birthday (14th November) has been observed as World Diabetes Day.

There was great excitement and tremendous demand for the new drug. The researchers gave the patent rights to the University of Toronto and refused financial gain. The university laboratory could not cope up with the demand. Commercial production of insulin on a large scale started and was soon made available in the market.

There was further controversy surrounding the discovery of insulin by Banting and Best. In 1916, Nicolae Paulescu, a Romanian scientist had developed an aqueous pancreatic extract which normalized the blood sugar level in a diabetic dog. His experiments were interrupted by the event of the World War I. However, in 1921 he published a research paper ‘Research on the Role of the Pancreas in Food Assimilation’. His discovery was even patented on April 10, 1922 by the Romanian Ministry of Industry and Trade. Thus Paulescu’s work preceded that of Banting and Best. Despite this fact, sufficient acknowledgement was not recorded by the Toronto group to Paulescu’s work in any of their writings.

Frederick Sanger of England received the Nobel Prize in chemistry (1958) for his discovery of the complete sequence of the two polypeptide chains of the insulin molecule. Sanger later developed the “dideoxy” method for sequencing DNA, also known as the Sanger method, for which he was awarded a second Nobel Prize in chemistry in 1980. Radioimmunoassay of plasma insulin was reported by Solomon Berson and R.A. Yallow in 1977.

In the 1923, Kimball and Murlin studied pancreatic extracts and found an additional substance with hyperglycemic properties. This substance was identified as glucagon. The amino acid sequence of glucagon was described by Bromer et al in 1957. A more complete understanding of its role in physiology and disease was not forthcoming until the 1970s, when a radioimmunoassay was developed.

Type 1 diabetes was distinguished from type 2 diabetes by Sir Harold Percival Himsworth in an article in Lancet in 1936. He was the Professor of Medicine in London University and delivered the Goulstonian Lecture at the Royal College of Physicians on “Mechanisms of Diabetes Mellitus” in 1936.

Diabetes in Pancreatitis

Harley in 1862, reported a case of acute pancreatitis exhibiting glycosuria; and Atkinson in 1895, and Korte, in 1911, described several similar cases. Fitz, curiously enough, made no mention of diabetes in his original contributions to the literature of acute pancreatitis, but Shumacker, in 1940, estimated that 11 per cent of patients with acute pancreatitis had glycosuria during some phase of the acute attack.

De Graaf in the second edition of his book in 1668 described pancreatic calculi which was probably the first pathological description of chronic pancreatitis. The first association of diabetes with pancreatic calcification was described by Thomas Cawley in 1788 after observations at the postmortem of a very obese man. However, he considered kidneys to be the cause for this disease. The significance of the association between the disease and the organ was reported by Richard Bright in a patient having pancreatic cancer and diabetes. Arnaldo Cantani observed that fatty changes and shrinking was more common in the pancreas of a diabetic than non-diabetics. Diabetes due to chronic pancreatitis is characterized by the
low incidence of ketosis and the high incidence of insulin-induced hypoglycemia.\textsuperscript{25}

### Insulins

The last 90 years have witnessed tremendous progress in insulin therapy, from the initial crude, yet life-saving, animal insulin extracts to novel human insulin analogues.\textsuperscript{26} In 1922, bovine insulin was first given to humans. For more than six decades, insulin from different animal sources was used, until the breakthrough in biotechnology made it possible to produce human insulin in sufficient amounts. The first insulin was a quick and short acting ‘soluble’ or ‘regular’ insulin. In 1936, protamine was used to develop slow-release insulin. The effect of protamine zinc insulin (PZI) lasted for 24-36 hours. In 1950 isophane NPH (neutral protamine Hagedorn) insulin was developed with maximal effect of 24 hours. In 1951 the amorphous lente insulins (IZS) – semilente, lente, and ultra-lente – were developed. The following decades were to witness the development of human insulins and analogues. Recombinant DNA human insulin was first used in the 1980s. The advances in insulin delivery systems – syringes, pens, pumps, patches, etc. over the years have also been remarkable. Efforts are currently focused towards developing non-invasive insulin delivery systems, and there are several competing technologies in different stages of development. Novel approaches to mimic the endogenous release and kinetics of insulin, and also many improved analogues designed to achieve better control and effective treatment of diabetes are anticipated.

### Oral Anti-diabetic Drugs

The most widely used antidiabetic drugs are insulin secretagogues which stimulate beta cells to release insulin.\textsuperscript{27} Insulin secretagogues can be divided into two subclasses: sulfonylureas and non-sulfonylureas. The first oral hypoglycemic agent, sulfonylurea was identified in 1942. These drugs were found to stimulate insulin secretion by residual beta cells in type 2 diabetes. Sulphonylureas have been used since the 1950s and their efficacy is well-established. However, they are being superseded by newer agents. First-generation sulfonylurea compounds became widely available in 1955. The second-generation sulfonylureas were introduced in 1984. Sulfonylureas that are currently available are gliclazide, glimepiride, glyburide, and the older agents: chlorpropamide and tolbutamide. The last two are now rarely used. In 1970, during the University Group Diabetes Program, the largest and longest diabetes research project at the time it was found that patients taking the oral diabetes medication tolbutamide had a higher rate of cardiovascular death than patients on placebo or insulin. Non-sulfonylureas are a relatively new class of medications: repaglinide is a benzoic acid derivative, and nateglinide is a phenylalanine derivative. The mechanism of action of these drugs is similar to that of the sulfonylureas but they act at a different receptor. The glinides have a faster onset and shorter duration of action than the sulphonylureas. They are associated with a reduced risk of hypoglycaemia, cause less weight gain, and are metabolized and excreted by the liver, and so can be used in patients with impaired renal function.

Some other agents besides sulfonylureas (including biguanides and alpha-glucosidase inhibitors) have been available for the treatment of type 2 diabetes for a long time. Acarbose and miglitol are drugs in the class of alpha-glucosidase inhibitors which lowers postprandial glucose levels. In the 1950s various biguanides (e.g., metformin, phenformin, buformin) were used in different countries for the treatment of diabetes. All but metformin were removed from the international market in the 1970s because of the associated high risk of lactic acidosis. Metformin is the sole agent in clinical use in this class. Metformin improves insulin sensitivity especially in skeletal muscle, and is an ideal first-line agent particularly in overweight patients. Metformin may also improve other cardiovascular risk factors; and may have a role as a novel anti-cancer drug.

Thiazolidinediones were identified as an effective insulin sensitizer in 1990s. While metformin acts mainly on the muscle and the hepatocyte, TZDs act predominantly on the adipocyte and the muscle. The 2 thiazolidinediones currently available in are rosiglitazone and pioglitazone. Troglitazone, an earlier thiazolidinedione was removed from the world market in 1997 because of an unacceptable risk of fulminant hepatic failure. Thiazolidinediones improve insulin sensitivity, particularly in the peripheral tissues. Scientists from the Cleveland Clinic analyzed data from more than 15,000 patients and 12,000 controls. They discovered an increased risk of cardiovascular events among patients taking rosiglitazone. Furthermore, increased risk of cancer of urinary bladder has been reported in patients using pioglitazone. There has been a decline in popularity of TZDs and currently pioglitazone is third-line of treatment in many guidelines.

### Incretins and DPP4 Inhibitors

After the discovery of secretin by Bayliss and Starling, oral administration of extracts of intestinal mucosa failed to help several patients with type 1 diabetes. In 1932 La Barre proposed the name incretin for a hormone extracted from the upper gut mucosa, which caused hypoglycemia and proposed possible therapy for diabetes. Incretins are gut-derived peptides...
secreted in response to meals. The two major incretins are glucagon-like peptide (GLP-1), which is produced by the neuroendocrine L cells of the ileum and colon, and glucose-dependent insulinotropic peptide, which is produced by the K cells of the duodenum and jejunum. In 1970, JC Brown isolated and sequenced GIP from intestinal mucosa. Originally named gastric inhibitory peptide, GIP was renamed glucose-dependent insulinotropic peptide in 1973 after Brown and Dupre showed that GIP stimulates insulin secretion. (GLP)-1 is a gut hormone that stimulates insulin secretion, gene expression, and β-cell growth. Together with the related hormone glucose-dependent insulinotropic polypeptide (GIP), it is responsible for the incretin effect, the augmentation of insulin secretion after oral as opposed to intravenous administration of glucose. The effects of endogenous incretins are short-lived because of rapid degradation and inactivation by the enzyme dipeptidyl peptidase-IV (DPP-4). Endogenous GLP-1 has a short half-life (<2 min). To counteract this, agents that are resistant to DPP-4 degradation such as exenatide and liraglutide have been developed. There are two commercially available GLP-1 agonists—exenatide and liraglutide. Exenatide is derived from the naturally occurring peptide, exendin-4, which was isolated from the salivary secretions of the lizard Heloderma suspectum (Gila monster). This lizard eats once a month and the function of exendin-4 is to rapidly increase the production of insulin in response to nutrients entering the gut. Liraglutide provides greater improvements in glycaemic control, induces weight loss, improves obesity-related risk factors, and reduces pre-diabetes. Animal studies have shown an increased occurrence of thyroid medullary cancer with high doses of liraglutide but the clinical relevance is unclear. In 2007 a question was raised about the causal relationship between the first of the glucagon-like peptide 1 receptor agonists, exenatide, and pancreatitis, as postmarketing reports of pancreatitis in patients treated with this agent had been received by the Food and Drug Administration (FDA). Early clinical trials of liraglutide suggested an increased incidence of pancreatitis.

Another approach was the development of Inhibitors of DPP-4 to prevent the inactivation of GLP-1 and prolong the activity of the endogenously released hormone. In contrast to GLP-1 receptor agonists, these drugs are available orally and have a longer duration of action, requiring only once daily dosing. The drugs currently available are sitagliptin, saxagliptin, and vildagliptin. There have been reports of acute pancreatitis in patients receiving sitagliptin.

Incretin therapy appears to offer an effective alternative to the currently available hypoglycaemic agents. Continued evaluation and further long-term studies will confirm its safety and clinical role.

Recently sodium-glucose transporter 2 (SGLT-2) inhibitors like dapagliflozin and sergliflozin have been developed to produce glucosuria and reduce the plasma glucose concentration. Inhibition of the SGLT2 transporter is an effective and novel strategy to control the plasma glucose concentration in T2DM subjects. These oral antidiabetic agents have the potential to improve glycemic control while avoiding hypoglycemia, to correct the glucotoxicity, and to promote weight loss. Because these agents have a distinct mechanism of action that is independent of insulin secretion or the presence of insulin resistance, the efficacy of this class of drugs is not anticipated to decline with progressive β-cell failure or in the presence of severe insulin resistance. Furthermore, this class of drugs can be used in combination with all other antidiabetic medications with anticipated additive efficacy on glycemic control. The SGLT2 inhibitors are also effective as monotherapy in newly diagnosed diabetic patients. Currently available data indicate that the SGLT2 inhibitors have a good safety profile.

Other therapies in development include glucagon receptor antagonists, glucokinase activators and sirtuins.

Bariatric Surgery

An exciting development has been the increase in popularity of bariatric surgery procedures initially started as treatment for morbid obesity. Bariatric surgery results in significant weight loss and remission of diabetes in most patients. After surgery, glycemic control is restored by a combination of enforced caloric restriction, enhanced insulin sensitivity, and increased insulin secretion. An enhanced incretin effect was found to contribute independently to improved glucose levels after bariatric surgery. Prospects of reversal of diabetes and freedom from hypoglycemic agents after bariatric surgery are very bright for obese patients with type 2 diabetes.

Pancreatic and Islet Cell Transplantation

After the discovery that pancreatectomy leads to diabetes, Ssobolew had speculated that transplantation of the pancreas can be a treatment for human diabetes. In 1893, Hedon from France, performed the autotransplant of a free, nonvascularised fragment of pancreas in a 10 kg dog. This dog was induced to have diabetes after doing a total pancreatectomy. This lead to a reduction in glucosuria as well as blood glucose levels. The first successful pancreatic transplant was done on December 17, 1966 at University of Minnesota by Kelly et al. The recipient was a 28 year old lady, diabetic.
since the age of 9 who developed terminal renal failure. However, the still functioning graft had to be removed because of rejection and sepsis, and she died shortly after.

Moskaleweski in 1965 showed that islet cell could be separated from the exocrine tissue by collagenase in 1967 Lacy suggested that for separation, mechanical mincing of the pancreas was a much better method. The Minneapolis group in 1977-78 did the first islet cell transplant in ten patients. Seven out of them required insulin in lesser doses; however none of them could do away with insulin completely. In 1978 another new approach was carried out by the Minnesota group. They resected around 96% of the pancreas of a 39 year old woman with chronic pancreatitis. This tissue was then minced, digested with collagenase, islets separated and re-injected into the spleen of the woman. She showed significant improvement during the follow up period of six months. From December 16, 1966, through December 31, 2010, more than 37,000 pancreas transplantations have been reported to the International Pancreas Transplant Registry (IPTR), including more than 25,000 from the US and more than 12,000 from outside the US.

Pancreatic islet transplantation is a minimally invasive treatment that has the potential to prevent diabetes after total pancreatectomy for chronic pancreatitis (islet autotransplantation) and to reverse diabetes in those with type 1 diabetes (islet allotransplantation). While pancreas transplantation is not considered experimental anymore, there is often reluctance to recommend this procedure to patients because of its complexity and risks, especially for solitary pancreas transplants. However improved surgical techniques and newer immunosuppressive regimens contributed significantly to better graft survival. Exocrine pancreas transplantation is a treatment of choice for patients with diabetes mellitus complicated by end-stage renal disease. Pancreas transplantations in diabetic patients may be divided into 3 categories: those performed simultaneously with a kidney (SPK), those given after a previous kidney transplantation (PAK), and pancreas transplantation alone (PTA). Recently, the performance of pancreas transplant was shown to be feasible laparoscopically under robotic assistance using the da Vinci Si high definition (SiHD) surgical system.

**Stem Cell in Pancreas**

Since the discovery of embryonic stem cells, several researchers have been studying the possibility that human embryonic stem cells could be developed as a therapy for treating diabetes. In 2000, Spanish workers engineered mouse embryonic stem cells to allow selecting cells that were differentiating into insulin-producing cells. Ron McKay (in 2001) and his colleagues described a series of experiments in which they induced mouse embryonic cells to differentiate into insulin-secreting structures that resembled pancreatic islets.

The world’s first study on cell therapy for type 1 diabetes on humans was performed by a research team (2003) from the Divisions of Immunology and Endocrinology, University of Sao Paulo, Brazil. The Scientists at University of Wisconsin isolated stem cells from the inner cell mass of human blastocysts and grew them in culture for prolonged periods of time. In 2006, a Chinese group from the University of Naijing, infused stem cells, 50% into the peripheral vein and 50% directly into the pancreas through arterial catheterization. Five patients were treated by following this protocol, 4 became insulin-independent (2 for short time) and one improved requiring 50% decrease in the insulin dose. The scientists from the University of North Carolina at Chapel Hill School of Medicine in 2008, transformed cells form human skin into cells that produce insulin.

Mario Capecchi and Eugenio Sangiorgi from the Catholic University of Rome in 2009 reported a method for marking and isolating stem cells in the pancreas. This involved use of a special fluorescent protein, produced in the pancreas under the stimulus of a molecular switch, a piece of DNA. Capecchi was the co-winner of the Nobel Prize for Physiology or Medicine, for his discovery of a method for introducing homologous recombination in mice using embryonic stem cells along with Martin Evans and Oliver Smithies.

The modern era in diabetes mellitus owes a lot to that grand man of diabetes, Elliot P Joslin. He, more than anybody else in our times, has contributed to the practice, teaching, education and research on diabetes mellitus. He maintained a database of all the patients he began to see in large books, which was the first of its kind ‘diabetes registry’. He compiled the first textbook on diabetes, ‘The Treatment of Diabetes Mellitus.’ The International Diabetes Federation (IDF) is one of the biggest non-governmental organizations involved in a mission to promote diabetes care, prevention and a cure worldwide since 1950. The campaign for a United Nations Resolution on diabetes was a response to the diabetes pandemic. The United Nations passed Resolution 61/225 ‘World Diabetes Day’ on December 20th 2006. Since 2007, Banting’s birthday (14th November) has been observed as World Diabetes Day. The IDF brought out the blue circle symbol as a global symbol for diabetes in 2006.
Conclusion

The hide and seek relationship between this small organ and an all encompassing disease are the stuff of mystery and suspense. Diabetes is not all about the pancreas. The metabolism of glucose and the actions of insulin in the human body are far more complex and are still to be unfolded fully. Diabetes leaves its foot prints on all the tissues and organs of the body that it touches. The future should be pregnant with many more surprises.

References


2. Fitzgerald PJ. Medical anecdotes concerning some diseases of the pancreas; in Fitzgerald PF, Morrison AB (eds): The pancreas, Baltimore, Williams & Wilkins, 1980, pp 1-29.


30. Ssobolew LW. Zur normalen und pathologischen Morphologie der inneren Sekretion der Bauchspeicheldruse [Contribution to the normal and pathologic morphology of endocrine secretion of the pancreas], Arch Path Anomat 1902; 168:91.


