

The pancreas and Diabetes Mellitus

A few historical observations

There is one organ in the human body that has kept itself hidden in the posterior abdomen retroperitoneally, wrapped in mystery for centuries – the pancreas. This recluse was fondly nicknamed “the hermit organ” by abdominal surgeons of the early 20th century who rarely attempted to meddle with it.

The earliest recognition of the pancreas has been attributed to the Greeks. The first description of the organ has been credited to Herophilus of Chalcedon (300 BC). He has been considered “a father of anatomy” who practiced dissection in the then flourishing city of Alexandria, including those done on living criminals. Rufus of Ephesus (100 AD), the 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 because of its uniform consistency.

When Greek civilization was conquered by Rome, many Greek physicians flocked to the capital of the new empire. Galen was one of them. His views and teachings of medicine were unquestioned and accepted as gospel truth. Once a year, he and his students cut open a dead pig to study anatomy. Galen never dissected a dead man, because Roman religious beliefs forbade it. 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 were to hold sway for the next several centuries, though many of these have been proved wrong.

In the 16th century, another famous anatomist dared to challenge the dogmas of Galen. He was Andreas Vesalius, who in the year 1531, at the age of seventeen left his home in Brussels to study medicine in Paris. Sylvius was his teacher, who himself was a disciple of the great Galen. The students were expected to believe and learn everything that Galen had written.

Young Vesalius did not comply. He wished to dissect the human body, but would have been burned or hanged if he did. So he, along with a friend, started collecting bones from cemeteries and studied them. By the time he was twenty two, he was teaching in the University of Padua in Italy, while working there, 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 function for the stomach. The term pancreas is not mentioned by Vesalius in his book, but an English translation supplied the synonym “sweetbread”. Fitzgerald observes that today, in the United States, the delicacy sweetbread sold in the restaurants is really the thymus gland of pigs and not the pancreas.

Johann George Wirsung, in 1642 described the main duct of the pancreas, which bears his name. It seems he got the idea from his student Hoffman who had noticed such a duct in the rooster.

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. Regnier de Graf was a student of Sylvius who assisted Sylvius in his studies of the digestive process. De Graf investigated the pancreatic juice of a dog by collecting it through 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 did not chemically analyze it. He managed to collect the pancreatic juice from a dead sailor subsequently, and noticed it was similar to the dog's pancreatic juice.

Brunner, in his further studies, observed that dogs could survive pancreatectomies for periods upto one year. Brunner also found that the dogs suffered from polyuria, polydypsia, and bulimia, but did not describe sugar in the urine. It took another few years before the pancreas – diabetes connection was established. In 1674, Thomas Willis, a physician, an anatomist and a professor of natural philosophy at Oxford, discovered, by tasting, that the urine of diabetic persons was sweet. Charaka and Susruta of India had predated him by nearly fifteen centuries when they described “Madhu Meha” (Diabetes) in their Samhitas (Treatises). In 1776, Mathew Dobson of England showed that diabetics excrete sugar in the urine. Cawley reported in 1788 that he observed a shrunken pancreas in a diabetic at autopsy, perhaps the first autopsy in a diabetic.

It was the classic work of Claude Bernard (18130-1878), 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.

Paul Langerhans (1869), a medical student, published his dissertation describing the structure of the pancreatic islands, which were later christened the “islets of Langerhans” by Laguesse, a French worker who described the histological changes in the islets of atrophied pancreas that resulted from ligation of the pancreatic duct.

It fell to the lot of another celebrated physiologist, this time Russian, Ivan Petrovich Pavlov from St. Petersburg, through his studies of pancreatic fistulae in dogs, to demonstrate the vagal control of pancreatic secretion. Pavlov's group found that introduction of acids into the duodenum stimulated pancreatic juice secretion and also described ‘entero kinase’ 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.

By the time of the second English edition of Pavlov's work, 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.

In the year 1892, it was suggested by Laguesse that the islet cells of the pancreas, described by Langerhans in 1869, were the histological units involved in the pancreas of the diabetic patient. Eugene Opie (1901), who proposed the "common channel theory" and the role of bile reflux in the causation of acute pancreatitis, described by a hyaline changes in the islets of diabetic patients, the first evidence of islet cell damage in diabetes.

In another experiment, around the same time as Opie's observation on the islets, Ssobelow and Schulze demonstrated that following ligation of the pancreatic duct, the gland atrophies, but the islets are spared and diabetes did not develop. Moses Barron in a paper "The Relation of the Islet of Langerhans to Diabetes with special Reference to Cases of Pancreatic Lithiasis" made the critical observation that in pancreatic disease without islet involvement, there was no diabetes.

As early as 1899, two workers, Joseph Von Mering and Oscar Minkowski 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.

Friedreich, in 1878, confirmed the role of alcohol in pancreatitis. However, the Harvardian pathologist Reginald Fitz was the person to describe in 1889 succinctly the clinical features of pancreatitis and described its gangrenous, hemorrhagic and suppurative aspects.

The great break-through came in diabetes with the discovery of insulin in 1922. Frederic Banting studied in Toronto and was a private in the army before he

completed his Medicine and was commissioned. He won an MC for gallantry in action in 1918. After his practice failed to take off, he approached Macleod, the professor of physiology at the University of Toronto for facilities to pursue his studies on diabetes. Charles H. Best, a medical student was assigned to assist him. Macleod was on sabbatical leave at the time. 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. The new substance was purified and standardized by J.B. Collip, a biochemist. The pure extract was labelled insulin. A 14 year-old boy 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. He shared his prize money with Best. Macleod shared his portion of the prize money with Collip. There was great excitement and tremendous demand for the new drug. The university laboratory could not cope up with the demand. The Connought antitoxin laboratories in Toronto and the pharmaceutical company Eli Lilly jointly met the challenge by starting large-scale production of insulin, which was made available in the market.

Meanwhile, advances in other areas were also taking place. Alessandro Codivilla of Imola, Italy, 1898, had performed a pancreatico-duodenectomy for pancreatic cancer. William S. Halstead, professor of Surgery in Johns Hopkins operated on a case of carcinoma of ampulla of Vater. Allen Whipple was born in 1881 in Persia and in 1897 migrated to United States with his missionary parents. He studied at Princeton University and later, became Chairman of the department of Surgery at Columbia University. He, along with his colleagues, performed in 1940 the first successful one-stage resection of an islet-cell carcinoma of the head of the pancreas. The surgery of pancreatico-duodenectomy goes by his name.

Patrick J. Broe in the year 1981 suggested that the definite treatment of diabetes mellitus should be pancreatic transplantation, which carries the hope of preventing the secondary complications of diabetes mellitus and their devastating consequences. Today, pancreas transplantation is a reality and islet cell transplantation in its infancy.

Several years ago, Bard and Pic pointed out that the islet cell was a potential candidate for the development of cancer. A.G. Nichols in 1902 reported the first single adenoma of the pancreas arising from the islet tissue. Between 1911 and 1926, several cases of islet cell adenoma were reported in the European and American literature. However, no clinical signs or symptoms were reported to suggest functional disturbances.

The first case of hyperinsulinism associated with a tumour of the islet cells was reported by Russel M. Wilder and colleagues. The cells of this cancer bore a

striking resemblance to the cells of the islets of Langerhans, and alcoholic extracts made from the cancer tissue in the liver acted like insulin when injected into rabbit. The first successful operation for a functioning islet cell tumour of the pancreas was performed by Roscoe R. Graham of Toronto, and reported by Goldwin Howland, Walter Campbell, Ernest Maltby, and W.L. Robinson in 1929.

In 1938, Whipple described the symptomatology of hypoglycemia and prompt recovery from the attack after the administration of glucose.

Zollinger and Ellison, in 1955, suggested the possibility of a non beta-cell tumour of the pancreas, which secretes a factor that could cause peptic ulcers. The hormone that was responsible for the ulcer production was identified as gastrin, which was sequenced by H. Gregory (1964) and synthesized by R.A. Gregory (1964). In fact, the hormone gastrin had been discovered at the beginning of the 20th century (1905) by Eddins. Radio-immuno assay of gastrin was reported by S.A. Berson and R.A. Yalow. Subsequently, many other hormones have been identified and cloned. Modern tools of radio-immuno assay and immunocytochemistry have contributed greatly to the identification and elucidation of the structure of many of these hormones.

In the year 1928, Ivy and Oldberg had demonstrated a hormone, Cholecystikinin, with the action of contracting the gallbladder and relaxing the sphincter of Oddi. In 1943, Harper and Raper discovered another hormone, Pancreozymin, that influenced pancreatic enzymatic secretion. A few years later, Jorpes and Mutt proved that cholecystikinin and pancreozymin were the same substance, which is now known as cholecystikinin (CCK).

In the year 1952, M. Comfort and A. Steinberg described a pedigree of a family with hereditary chronic relapsing pancreatitis. After more than 40 years (1996), Whitcomb and colleagues described the genetic defect (Cationic Trypsinogen gene- (PRSS 1) mutation) underlying hereditary pancreatitis. The cystic fibrosis gene (CFTR) had already been mapped to the long arm of chromosome 7 and had been cloned, and mutations that account or the defects in cystic fibrosis described (Kerem and colleagues 1989, Riordan and colleagues, 1989). Witt and colleagues described the association between SPINK1 mutations and pancreatitis.

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. His name has become synonymous with diabetes. All modern diabetologists are, in one way or other, his students.

Diabetes mellitus is not just about the pancreas. It touches all the organ systems in the body and all tissues, and leaves its footprints on the tissues it has touched. It can be said that to know diabetes mellitus is to know medicine.