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Brief History of Diabetes Mellitus - From Sushruta to Banting –

Orlando Mejía-Rivera

Professor of Internal Medicine and Medical Humanities, Medicine Program, University of Caldas, Manizales, Colombia

ABSTRACT

This text makes a brief historical tour of the knowledge of diabetes mellitus, showing the sequence of ancient discoveries and the effort of several generations of physicians and researchers to better understand a pathology than remains a challenge for contemporary medicine. It also highlights the extraordinary episode of the discovery of insulin by Banting and best, in which some serendipitous facts were exploited by the observant and brilliant mind of Frederich Banting.

***Corresponding author**

Orlando Mejía-Rivera, Professor of Internal Medicine and Medical Humanities, Medicine Program, University of Caldas, Manizales, Colombia.

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Introduction

The clinical entity known as diabetes mellitus is described in texts as old as the Egyptian papyrus of Ebers (1536 B.C.E.), in which it is inferred from prescription 274 that it is a formula to treat polyuria. In any case, there would be other different causes that do not allow us to be sure that it is only due to diabetes. Hence, there is no consensus among medical historians to accept the identification of this pathology in the medical papyri.

It also appears in the Hindu Sushruta (5th century B.C.E.), which defines a clinical picture consisting of intense thirst, drowsiness, loss of strength, bad breath, accelerated emaciation of the sick and the presence of a urine like honey that attracted ants; therefore the disease was called Madhumeha, which literally means: honey urine [1].

It was also described by the Chinese physician Zhongjing Zhang, in the second century B.C.E., in his classic and masterful work of Chinese medicine called Treatise on Febrile Diseases (Shang Han Lun); there he points out the existence of a disease (named xia-ke) characterized by intense thirst, abundant urine, so sweet that it attracted dogs, and the presence of furunculosis in most of these patients [2].

Diabetes is not mentioned in any of the fifty-three medical treatises, grouped in sixty-two books, which constitute the so-called Corpus Hippocraticum written over four centuries (V to I B.C.E.). In the first century in Rome, a writer and medical encyclopedist, known as Cornelius Celsus, compiled all the Hippocratic and Hellenistic knowledge of Greek medicine in his influential work De re médica. Here he mentions a pathological entity in which the sick eliminated more urine than water ingested. As this description is not found in the Hippocratic treatises, it must have been taken from some Alexandrian physician whose name is not known to this day [3].

It is due to the physician Areteo of Cappadocia (1st century) to have named the disease as diabetes. In an early work entitled The Causes and Signs of Acute and Chronic Diseases, he referred to an extraordinary affection, infrequent in man, which melted the flesh of the body and extremities, and turned them into urine. The term diabetes means "a passer-through, siphon," and alludes to the passage of bodily substances through the urine. Areteo tried dietary treatment in these patients by means of sweets, starches and fruits [4].

Years after Aretaeus appeared Galen, the most famous physician of the Greco-Roman era. Born in Pergamon (AD 129 – c. AD 216), he exercised his profession and authority in Rome; in a tangential reference to diabetes, Galen stated that it was a disease produced by the inability of the kidney to retain water. This hypothesis, like everything he said, was considered a dogma and, therefore, no subsequent physician, in the following thirteen centuries, dared to doubt the truths revealed in the Galenic treatises.

Arab Physicians

Rhazes (c. 864 or 865-925 or 935 CE) was the first great Arab physician known in the West. He described the treatment of diabetes based on a diet low in sugars and flour. But it was Ibn Sina, better known as Avicenna (c. 980-1037 CE), physician, philosopher, theologian, geologist and astronomer, who was the great Arab figure who had a profound influence on Western medicine. He wrote more than two hundred works on various subjects, the most important of which is his medical treatise called The Canon of medicine [5]. Here is described, in great detail, the clinical picture of diabetes, being Avicenna the first to recognize polyphagia as a frequent and important symptom and to record the association between the disease and sexual impotence in men. He also noted the presence of diabetic gangrene in the final periods of the disease and the frequency of furunculosis in these patients.

Although some historians credit him with having pointed out the sweet taste of urine, the respected and accurate historian of medicine Garrison showed that this does not appear anywhere in Avicenna's work [6]. However, perhaps, more important than the above, is his attempt to explain the origin of the disease, not as the consequence of an alteration of the kidney, but of liver damage; with this clinical intuition he anticipated, by centuries, the future experimental studies of Claude Bernard.

Renaissance and 17th and 18th Centuries

The contribution of the famous Paracelsus (c. 1493-1541) to the understanding of diabetes consisted in making the first experiments with the urine of diabetic patients, around 1520, when he tried to analyze its chemical components. By evaporating the urine, he extracted a saline residue, which led him to associate this finding with a hypothetical alteration of the kidneys, which, supposedly, were not capable of retaining the salt in the organism and when this was lost in large quantities, diabetes was produced.

Although his conclusions were wrong, they meant the subsequent conceptual opening to try to understand the origin of the disease by means of the chemical analysis of the urine of diabetics. This fact promoted a medical trend where the chemical constitution of the different secretions of the body would be considered fundamental to understand the origin of diseases.

Thomas Willis (1621-1675) reported in his book Pharmaceutice rationalis, sive Diatriba de Medicamentorum Operationibus in humano Corpore, in 1664, an important discovery in relation to diabetes: he routinely tested the urine of his patients and thus rediscovered, for the civilization of the West, that diabetics had sweet-tasting urine. In this way, he differentiated the polyuria caused by diabetes insipidus from that produced by sweet urine diabetes.

Willis tried to interpret the reasons for this sweet taste and concluded that it was caused by the presence of acids and salts in the urine of diabetics. In addition, he detected a relationship between the triggering of the diabetic episode and certain previous mood disturbances such as sadness, prolonged sorrows and depressions of the spirit.

The Swiss physician Johan Von Brunner, in 1682, performed pancreatectomies on dogs to clarify the controversy of that time as to whether or not the pancreas was an essential organ for life, and found that these pancreatectomized dogs presented a picture of intense thirst, abundant urine emission and emaciation; but he did not directly relate the absence of the pancreas to the existence of diabetes [7].

Robert Wyatt, in 1774, after evaporating the blood and urine of diabetic patients, supposed the existence of a substance analogous to sugar that was found increased in large proportions in diabetics. But it was Matthew Dobson, in a work on "Experiments and observations of urine in diabetics", published in 1775, who found and confirmed that the sweet taste of urine was due to the presence of sugar in it and also isolated it from the blood of diabetic patients after detecting its sweet taste [8].

From these findings, Dobson concluded that the decrease in weight and strength in diabetics was the consequence of the loss of nutritive material in the urine. Thomas Cawley, an English physician, published in 1778 an article in the London Medical Journal, where he relates the results of an autopsy performed on a diabetic patient [9]. There he describes multiple stones in the pancreas and significant atrophy of the pancreas. This report is the first to directly relate diabetes with a pancreatic alteration. Rollo, in 1796, described the acetonic odor in the breath of diabetics and recommended to treat them with scarce food [10].

William Cullen (1712-1790), a physician born in Edinburgh, wrote towards the end of the 18th century a book called Main Lines in the Practice of Medicine (1776) and there he gives the surname of diabetes Mellitus (sweet) and attributes its etiology to a primary disorder of the central nervous system [11].

The 19th Century

With the advent of the 19th century, medicine benefited from the incipient advances in microscopy. With the ability to examine organs under the microscope, histology emerged as an essential scientific element that helped to classify and better understand diseases. In the course of the 19th century three medical mentalities will appear in a definite way:

1-The anatomo-clinical orientation, which seeks the pathological correlation of the microscopic lesion and the clinical picture of the disease.
2- The pathophysiological orientation, which takes up the concept of understanding disease as a dynamic process, where the passage from health to pathology was a change of a quantitative, chemical and physical nature, but not necessarily qualitative.
3- The etiopathogenic orientation was stimulated by the studies of Pasteur and Koch on the existence of germs as the cause of certain infectious diseases. Throughout the 19th century, diabetes will have these three approaches, with a predominance of the pathophysiological and anatomo-clinical explanation.

Michel Eugené Chevreul (1786-1889) continued Dobson's studies on the urine of diabetics; in 1815 he identified glucose as the sugar found in the urine of diabetic patients, realizing that this substance was identical to grape sugar [12]. Home invented the foam test, to diagnose the diabetic character of urine. Eberle, in 1831, proved that the urine of diabetics fermented easily, but rotted with difficulty. Ambrosiani, in 1835, succeeded in fermenting blood sugar.

Claude Bernard, as already mentioned, also made fundamental contributions to the knowledge of diabetes and sugar metabolism. He conducted experiments with dogs subjected to sugar-free diets to try to better evaluate carbohydrate metabolism. Up to that time it was believed that animal organisms received sugar from the diet and the organism, by means of the lung, destroyed the sugar. However, on finding significant quantities of sugar in the hepatic vein of these animals, Bernard concluded that not only was there no organ that destroyed sugar, but that sugar was found in all animal blood even if the diet was free of it. He then demonstrated that the sugar-producing organ was the liver by the biochemical process of glycogenesis.

If the liver was the blood sugar producing and regulating organ and the urine of diabetics was full of sugar, Bernard thought that diabetes mellitus was produced by a primary disorder in the regulation of sugar by the liver. Thus originated the theory of increased hepatic glycogenicity as the pathophysiological explanation of diabetes. This theory was initially little accepted in the medical scientific circles of the time. In 1855, Claude Bernard himself produced glycosuria in rabbits, after the pitting of the floor of the fourth cerebral ventricle and central galvanization of the cut pneumogastric nerve.

This glycosuria lasted for a few hours and was accompanied by hyperglycemia. He concluded that this was due, in essence, to a secondary stimulation of the liver which produced an increased discharge of sugar, under the influence of the central nervous system. Bernard also described some pathology findings in diabetes, such as the presence of sugar blood, without exception, in all organs, hypertrophy of the liver and he reported finding atrophy of the pancreas on some occasions.

Until Claude Bernard's work, it was thought that the cause of diabetes was due exclusively to the influence of a certain type of food, such as insufficient or only vegetable food, or to the abuse of fermented and sweetened drinks such as cider or pear drink; also, to the very frequent use of tea. Bernard's discoveries on diabetes were recorded in Lessons in Experimental Physiology (1855-1865), although all the texts on diabetes and the pancreas written by Bernard were published in his 1870 book Leçons sur le diabète et la glycogenèse animale.

Hermann and Fehling, in 1848, perfected the diagnostic technique of determining sugar in the urine, a test that continued until the 20th century. The great clinician Thomas Addison and Sir William Gull described diabetic xanthoma. Paul Langerhans, in 1869, at the age of 22, presented his thesis on the histology of the pancreas as a requirement for his medical degree. There he pointed out the presence of a cellular conglomerate that had the shape of small islands, but he could not explain its specific function.

Chauffard and Hanot, in 1870, designated a clinical picture consisting of a combination of pigmentary cirrhosis and diabetes as bronzed diabetes. Nine years later, the famous clinician Von Recklinhausen determined the two pigments of bronze diabetes and gave the name hemochromatosis to the entity.

A disciple of Claude Bernard, Etienne Lancereaux, in 1880, was the first to differentiate the existence of two clinical types of diabetes. One he called "skinny" or acute diabetes, and showed that it occurred in young patients and was rapidly fatal. The other form he found he called "stable" diabetes and observed that it occurred in obese adults and had a better prognosis than "skinny" diabetes. Regarding etiology, Lancereaux stated that diabetes was a syndrome of diverse origins, although he related some forms of diabetes to atrophy of the pancreas [13].

Apollinaire Bouchardat, a fellow disciple of Lancereaux, was the precursor of effective dietary treatment for the disease. Bouchardat recommended fasting, the reduction of carbohydrates in the diet, the consumption of gluten bread and physical exercise as adjuvant therapy for diabetic patients. In his therapeutics he says diabetics should: "Decrease the amount of bread and starchy foods. Prescribe meats, eggs, fish and non-starchy legumes, but all in moderate quantities. More salty foods than usual. Generous wine" [14].

The Italian Julius Vassale, in 1889, had the merit of having initiated the studies on the internal secretion of the pancreas, since he ligated the excretory ducts of the pancreas of dogs, which caused the destruction of the acinous tissue, but not that of the islets of Langerhans. This finding was a precursor of later advances in the knowledge of the endocrine and exocrine pancreas.

First Serendipitous Discovery

Oscar Minkowski and Joseph Freiher von Mering, in 1889, decided to carry out joint experiments on dogs, to intervene in one of the scientific controversies of the time that had been going on since the end of the 17th century, and consisted in knowing whether the pancreas was an essential organ for life. Von Mering thought it was not, and that it was possible that certain fats, indispensable for the metabolism of the organism, could be absorbed without the presence of pancreatic ferments. Minkowski then proposed to him to demonstrate this hypothesis by means of the total pancreactectomy of a dog.

After the surgery, the laboratory assistant complained that the dog urinated too much and kept the place dirty. Von Mering and Minkowski turned their attention to the animal and discovered that the polyuria was accompanied by other clinical symptoms that were identical to those presented by patients with diabetes mellitus. This chance finding led them to completely reorient the experiment and to postulate a new hypothesis: the causal relationship between the absence of the pancreas and the onset of diabetes mellitus [15].

Minkowski performed other pancreatectomies, in addition, performed subcutaneous transplantation of pancreatic tissue in some of the dogs without pancreas, and showed that the symptoms of diabetes reversed or did not reappear [16]. In doing so, they fully confirmed the causal association between the alteration of the pancreas and the development of diabetes.

This fact is a clear finding of classical serendipity, and the shrewdness of the researchers in giving meaning to the dog's symptoms was due to the fact that, for both of them, the problem of diabetes was a known and previously investigated subject.
Minkowski was born in Alexsten (Russia) on January 13, 1853, and trained as a surgeon and internist at the Urden Hospital in the city of Cologne (Germany). At the age of twenty-six he had already made the discovery of B-oxybutyric acid in the urine of severe diabetics. He later demonstrated that there was a decreased carbon dioxide tension in the blood of diabetics, a lower alkaline reserve during diabetic coma, and therefore recommended alkaline therapy in the treatment of diabetic acidosis. In addition, Minkowski theorized that the essence of the problem in diabetes was the inability to produce sufficient carbohydrate combustion in the periphery, e.g., in the muscles.

Von Mering, a German physician born in Cologne (1849-1908), was also dedicated to the study of diabetes and before the experiments with Minkowski, in 1886 he had made the discovery of renal diabetes secondary to the use of the glycoside Floridicin, composed of apple, pear, cherry and plum root bark.

Adolf Kussmaul described in detail the clinical manifestations of diabetic coma and related the presence of acetone, the acidotic picture and the characteristic type of respiration. Theodor Von Frerichs (1819-1885), a German, was the founder of a clinical school devoted to treating diabetic patients and to research on diabetes. Frerichs is credited with the first great monograph on diabetes (1784), based on four hundred cases of his personal experience and fifty-five autopsies of diabetics.

His disciple Bernhard Naunyn wrote a therapeutics book for diabetics in 1898, and his dietary recommendations influenced all of European medicine for almost twenty years. Naunyn's diet was based on a starch-poor regimen with "125 gm of protein and fat in quantity" [17]. In addition, it promulgated continuous monitoring of glycosuria levels, adjusting the diet to these concentrations.

Naunyn postulated a theory of diabetes according to which the diabetic liver had an inability to convert sugar into glycogen, hence the high blood glucose levels. Stadelmann, a disciple of Naunyn,

introduced the concept of diabetic coma as an acidosis with a fatal prognosis; he also studied the relationship of B-oxybutyric acid to diabetic coma and the effects of alkali therapy.

Carl Von Noorden, another German, elaborated a special study about dietetics in diabetics and concluded that there was in the disturbance of the disease an overproduction of blood sugar as a consequence of liver glycogen. He related this to a progressive breakdown of glycogen due to decreased pancreatic secretion. He recommended a diet of oatmeal and the reduction of sugar elements [18].

Gustave Edouard Laguesse, in 1893, put forward the theory that the islets described by Langerhans, provided an internal secretion that perhaps influenced the metabolism of carbohydrates and this hypothesis will try to be tested by several researchers in the early twentieth century [19].

The Pre-Insulin Era

At the beginning of the 20th century, there was a consensus in the scientific community that the key to the origin of diabetes lay in trying to identify that unknown substance produced by the pancreas which, when lacking, caused the disease. Through parallel but independent studies, in 1901, the American pathologist Eugene Lindsay Opie and the Russian Leonid Sobolow described the hyaline degeneration of the pancreas of patients who had died of diabetes. In his treatise on diabetes, Lindsay Opie stated that a lesion of the pancreas could cause diabetes and this lesion would have the character of a destruction or injury to the islets of Langerhans [20].

In addition, the first decade also saw other scientific breakthroughs, which modified the conception of physiology and biochemistry. The Japanese Jokichi Takamine and the American Thomas Bell Aldrich, in 1901, isolated adrenaline. William Maddick Bayliss (1860-1924) and Ernest Henry Starling (1866-1927) discovered, in 1902, secretin, a substance formed by the action of an intestinal acid and carried by the blood to the pancreas, where it stimulated the secretion of pancreatic juice. But more importantly, they themselves defined the concept of "hormone" in 1905, and succeeded in positioning in the scientific community "the idea that certain organs could produce substances capable of exerting a powerful influence on other parts of the body" [21].

The pathophysiological understanding of the incipient endocrinology favored and reaffirmed the search for the substance of the pancreas involved in the diabetic disorder. Hence, the numerous attempts made to find it. Zuelzer, in 1908, succeeded in isolating a macerate of alcohol and pancreatic extract and injected it in some diabetic patients, but they presented convulsions and this forced to suspend the experiments. It is feasible that it was a hypoglycemic reaction, but it was interpreted, at that time, as a toxic reaction to the extract and it was speculated that it was impossible to apply it to human beings.

Other similar attempts by physicians such as Hedon and Ibrahim also failed. However, the Romanian Paulesco elaborated another pancreatic extract and after injecting it to dogs he demonstrated hypoglycemic effects in them; but the beginning of the First World War prevented him from publishing the results of his work. It was not until after 1925 that he made them known, when the findings of Banting and Best were already public.

Jean de Meyer, in 1909, gave the name Insulin to the still hypothetical pancreatic hormone, involved in the regulation of sugar metabolism [22]. Sir Edward Sharcey Schafer, in 1916, postulated that diabetes was produced by the lack of the hypothetical insulin; however, he could not isolate this substance either.

As the years went by and scientists increasingly failed to isolate the enigmatic pancreatic hormone, which supposedly acted on blood sugar, some chose to think that perhaps this substance was used very quickly by the organism and therefore did not accumulate in the blood and must also be of a very unstable nature.

However, this concept evolved into other theories that moved away from the initial search for insulin. The physiology group in Ontario (Canada), led by Macleod and other North American and European centers, began to think that perhaps the function of the pancreas consisted of purifying the blood that circulated through it, destroying toxic substances that prevented the degradation of sugar.

Thus, a special pancreatic substance such as the hypothetical insulin did not have to exist. Therefore, began the abandonment of the scientific search for the enigmatic hormone and a pessimistic mood began to prevail among researchers. At this stage, the only relatively useful advance in the treatment of diabetes was due to the dietary therapy recommended by Allen, who introduced the so-called "starvation" diets, with less than five hundred calories a day, which at that time were the only source of life support for diabetics [23]. Nevertheless, almost 100% of diabetic children died within a year of the onset of the disease and adults survived for a few years in conditions of great physical and mental suffering.

Young Professor Frederich Banting

Frederich Banting was born on November 14, 1891, on a farm near the town of Alliston, in the province of Ontario. He was an outstanding child in sports and very normal in his studies. He had a certain stammer which he retained throughout his life. He was fond of oil painting. After a fleeting period when he thought his vocation was to be a religious missionary, he entered the Faculty of Medicine at the University of Toronto.

Encouraged by his teacher Dr. Clarence Leslie Starr, a renowned children's hospital surgeon, he pursued the specialty of orthopedic surgery and obtained his degree in 1916. He enlisted as a lieutenant surgeon and participated in the first world war. In 1918 he was wounded by machine gun bullets in his right forearm and the limb was to be amputated due to the possibility of gangrene. Banting refused surgery and accepted the risk of death. However, he was cured and returned to work as a medical intern at the Ontario Children's Hospital.

Soon after, he opened his private practice in the city of London, province of Ontario. Two anxious months passed in which the young surgeon had no patients and, faced with the situation of extreme economic hardship, he decided to get some teaching hours at the University of Western Ontario, as an assistant professor of anatomy, physiology and clinical surgery. At 29 years of age, with an uncertain future and a teaching job more out of necessity than vocation, Frederich Banting could not imagine what would happen to his life in a few months.

The Strange Night of October 30, 1920

On the evening of October 30, 1920, Banting began to prepare his lecture on the physiology of the pancreas, which he would give to medical students two days later. His knowledge of sugar metabolism and diabetes mellitus was very superficial, as his

previous activity as a war orthopedist had distanced him from the study of internal medicine.

He read two texts that caused him great curiosity. The first, Minkowski and Von Mering's description of their experiments with pancreatectomized dogs and the presentation of diabetes mellitus. The second, a copy of Langerhans' thesis where he describes the islets of the pancreas and reports that they have no excretory duct to the intestine.

Both information were well known, as we already know, by the scientific community. But for the young Banting it was new knowledge and, excited, he thought for himself what others had already thought: diabetes mellitus was caused by damage to the pancreas and it was most likely that the islets with no apparent function, discovered by Langerhans, had something to do with the disease.

Tired and satisfied with his new knowledge, to be taught in class, he was ready to go to bed when he decided to leaf through the latest journal of Surgery, Gynecology and Obstetrics, to which he had subscribed and which had arrived that same day. To his surprise he found an article that had to do with the subject of the pancreas and decided to read it. The text called "Relationship between the islets of Langerhans and diabetes, with special reference to pancreatic lithiasis", was written by Dr. Moses Barron, from the city of Minneapolis. It explained that when the pancreatic ducts were blocked by the presence of stones, the gland atrophied, with the exception of the islets of Langerhans. When the pancreatic ducts were ligated in experimental animals, they did not present diabetes mellitus [24].

Banting went to bed, but it was difficult for him to fall asleep, in between sleeps he thought about the texts he had read and his motivation was no longer that of repeating some data to the students, but that of a genuine curiosity to know the origin of the mysterious and deadly diabetes mellitus. At two o'clock in the morning he woke up suddenly, turned on the light and excitedly wrote in his notebook the following: "Ligate pancreatic ducts of dogs. Wait six to eight weeks for degeneration. Remove the residue and extract." [25].

Banting, who the night before was an unqualified professor preparing a class, stood up as a researcher, convinced that the experiment he had devised and described, in a few sentences, would lead to the successful discovery of the cure for diabetes. He did not know that similar reflections had already motivated a legion of researchers to try to find the substance produced by the islets.

Inexplicably, a young doctor, with no research experience, was convinced that he could solve a problem that had remained unsolved for twenty-five years by the best medical brains of the time.

Banting's case, up to this point, is paradigmatic of bibliographic serendipity, in the classic serendipity mode, since the reader was not seeking to solve the problem of diabetes and beyond: the Banting reader did not even set out, at the beginning, to read like a scientist since he was not one. Moreover, this serendipity is of unconscious predominance, for the idea for the key experiment came to him after he went to sleep, although he went to bed overexcited with the creative possibilities of what he read.

But rather than an isolated fact of bibliographic serendipity, what emerges with Banting is a typical pattern of "serendipitous reader" who reads from his present all the information of the past and updates it through wonder and curiosity. Moreover, his method is to skim and ask creative questions about what he reads, that is, to look for a meaning to what he reads, which is not explicit in the text.

Most of the previous attempts to extract the key substance from the islets of the pancreas had failed because the macerate was made from the whole gland and the pancreatic digestive juices destroyed the insulin molecules. Banting, in his bibliographic serendipity, read the different texts and established between them an association that was not present in the isolated texts. Hence, he was able to conceive the perfect experiment, without making the mistakes of so many experienced researchers with great theoretical mastery of pancreatic metabolism. The difference was that Banting's limited knowledge was connected by him in a new context of meaning and epistemological sense.

Moreover, Banting read for the first time, i.e. as if they were new, data that, being well known to researchers, ceased to be of interest and were considered old and historical. Bibliographic serendipity presupposes a reader for whom no data is historical, its historicity being understood as data that can no longer contribute to new knowledge. Banting read all texts as present data, current, alive for reflection and not as fossil data, dead, which is common in most researchers who think that what was written in the past is no longer of real importance for the science of the present and the future.

In the following months the young Banting reaffirmed his conviction that he had to put his experiment into practice and made the decision to give up orthopedic surgery, university teaching and his future plans to become a private practice physician. He then went to visit the prestigious physiologist and researcher at the same Ontario university, Dr. J.J.R. Macleod.

A Dream Become Reality

Frederich Banting arrived at the beginning of 1921, where Professor Macleod explained his idea and asked him for twelve dogs, a laboratory, an assistant and ten weeks to show the results. Perhaps Macleod's merit lies in the fact that, although he was no longer convinced that the solution to the problem of diabetes was the search for the pancreatic substance and that he must surely have smiled at a young inexperienced surgeon who was trying to solve such a complex scientific dilemma, he decided to give Banting what he was asking for.

The reasons for this seem to be more the merits of Banting's stubbornness than some degree of Macleod's confidence in the success of the experiment, for Macleod himself related in his version of the discovery of insulin, written in 1922, that: He arrived about the middle of May, 1921. I found that Dr. Banting had only a superficial text-book knowledge of the work that had been done on the effects of pancreatic extracts in diabetes and that he had very little practical familiarity with the methods by which such a problem could be investigated in the laboratory [26].

The assigned assistant was a 22-year-old medical student, deeply knowledgeable in carbohydrate chemistry, named Charles Best. On May 16, 1921, they began the task of ligating the first pancreatic ducts, but these attempts were unsuccessful, because the ligation produced necrosis of the ducts and neoconducts were formed that protected the organ from atrophy.

However, Banting corrected his surgical technique and, demonstrating his talent as a surgeon, invented a simpler way

to perform total pancreatectomies in research dogs. On July 27, 1921, they removed the islets of Langerhans from an atrophied pancreas, cut them into small pieces, froze them in brine and then macerated them in 900 cc of saline solution.

This extract was injected into a pancreatectomized diabetic dog in agony and within a few minutes they observed that the sugar level in the dog's urine dropped until it disappeared and the animal recovered almost miraculously. Within five hours the dog was dead.

After this first success, they used liver and spleen extracts, without any result. After several similar experiments, they realized that to keep a dog alive for three days they needed the pancreas of two healthy dogs. On August 19, 1921, they succeeded in keeping a dog alive for eight days, with the sacrifice of five dogs, and convinced that the islets contained the substance they had been looking for so long, they named it Isletine [27].

By this time the money and dogs given by Macleod had run out. Banting sold his car to continue the experiments. Moreover, they were concerned about the impracticality of the method of isolating isletin. It was under these circumstances that Professor V. E. Henderson appeared and paid Banting to do a series of scientific readings for his institute of pharmacology.

Again, another bibliographic serendipity was about to emerge. Banting's readings led him to review and leaf through a classic book on diabetes written by Laguesse in 1893. There the author referred that the pancreas of newborns was rich in islets of Langerhans and poor in digestive juice secreting cells. Immediately, the "serendipitous researcher" Banting related this fact to his quest to improve the extraction of isletin and imagined another hypothesis: if the pancreases of newborns were richer in islets of Langerhans, it was to be assumed that the pancreases of embryos must have even more isletin-producing islets.

He then recalled his peasant childhood and learned that the cows that were taken to the slaughterhouse were impregnated earlier so that they would get fatter. So they went to the city slaughterhouse and obtained the pancreatic organs of nine bovine embryos rich in isletine.

A few months later they discovered that for the extraction of the pancreas it was enough to add acidified alcohol instead of salt water, and in this way the deleterious action of the digestive juice on the isletine was stopped and it was ready for use. Convinced of its total success, they inoculated themselves with portions of the extract to confirm that it was not toxic in humans. They then applied it to the diabetic physician Joe Gilchrist, a friend of Banting's, with spectacular results.

In December 1921, Banting wrote up the results of his research in a paper entitled "Internal Secretion of the Pancreas". In one of its paragraphs it is said that: “Since the extract has always produced a reduction of the percentage sugar of the blood and of the sugar excreted in the urine, we feel justified in stating that this extract contains the internal secretion of the pancreas” [28].

On December 26th Banting was invited in the company of Macleod (who realized at the end of Banting and Best's experiments the great importance of their discovery) to a medical congress at Yale University in the United States and it was there where Banting read his memorable experimental work.

On January 11, 1922, a fourteen-year-old diabetic boy named Leonard Thompson was dying in a Toronto hospital; his glycemia was five hundred mg/d, he was eliminating 3.5 liters of urine per day and was undergoing a Guelpa-Allen hyponutrition of 450 kilocalories per day. He was given a dose of insulin and to put it in Banting's own words, "the boy became smarter, looked better and said he felt strong" [29]. This was the third human being treated with insulin.

Macleod suggested changing the name of the substance from isletin to insulin, although this request was never clearly justified. The Nobel Prize in medicine, as already mentioned, was awarded to Banting and Macleod in 1923.

In summary, it was the bibliographic serendipities made by Banting that led to the successful discovery of insulin, which also changed the whole pathophysiological orientation in diabetes mellitus and contributed, later on, to other discoveries of body hormones.

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