Historical perspective

From pancreatic extracts to artificial pancreas: history, science and controversies about the discovery of the pancreatic antidiabetic hormone

IV: Frederick Banting and Charles Best

Frederick G. Banting (1891-1941)

Sir Frederick Grant Banting was born in a farmhouse of Allinston, Ontario (a small town about forty miles north of Toronto, Canada), on November 14, 1891. He was the last of five children of William Thomson Banting and Margaret Grant. John Banting, Fred’s grandfather was an Irish immigrant who arrived in Canada in the 1850s. The most relevant biography about Banting has been written by Michael Bliss, Professor of the Department of History at University of Toronto.1

Fred Banting attended the public school in Alliston, where he was seen more as an athlete than a serious student. Banting was a member of the high school baseball team winner of the league championship. Nevertheless, Banting wanted to become a medical doctor, and not a Methodist minister, what his authoritarian father wished for him to be. In the fall of 1910, in the company of his cousin Frederick Hipwell, registered at Victoria College in Toronto. After this experience, he was convinced that studying religion in order to please his father was a mistake. After being surprised by getting the support from his parents for such decision, Banting enrolled the Medical School, University of Toronto, during the fall of 1912. His cousin Fred Hipwell shared also the same initiative. Banting started to date a language student, Edith Roach, daughter of the Methodist minister of Allleston. Fred was just an average student. The Professor of Biochemistry A.B. McCallum induced Fred’s interest by the pancreatic glands and the pancreatic islets, although Banting primary choice was to become an orthopaedic surgeon.2

In the early summer of 1914, the Archduke Franz Ferdinand, heir to the Austria-Hungarian Empire, was assassinated in Sarajevo, determining the origin of the First World War. Although the schedule for his medical class was to graduate in 1917, Frederick Banting joined the Canadian Officers Training Corps in 1915. This circumstance was referred in Banting’s memoirs to be responsible of the “very deficient medical training”. His destination to the Granville Canadian Special Hospital in Buxton, England, did not al-
low marrying Edith. One year later, Banting was transferred to the Ambulance Corps in France. On September 28th, 1918, Banting was injured in the battle of Cambrai; he applied a tourniquet to his injured arm and continued working. Captain Banting was condecorated with the Military Cross, refused the amputation advised by the hospital doctors, and after a long convalescence, saved his arm.

In September 1919, Frederick Banting continued his training as Surgical Resident at the Hospital for Sick Children in Toronto, under Chief Surgeon Dr. Clarence L. Starr. Then, he moved to London, Western Ontario, in July 1920, opening a private office and accepted a part-time job as lecturer at the University.

In October 1920, Banting read an article by Moses Barron, indicating that the ligation of the pancreatic duct was followed by the degeneration of the cells of the pancreas which secrete trypsinogen, antagonistic to the internal secretion of the gland (figure 1). Since the acinous but not the islet tissue, degenerates after this operation, the hypothetic pancreatic hormone could be extracted from these intact islets. Banting became excited about the possibility of curing diabetes by the administration of pancreatic extracts developed under these premises.

For this reason, he visited Prof. JJR Macleod, the very prestigious professor of Physiology, at the University of Toronto, on November 7th. Initially, Macleod was not in his favour. Banting was a surgeon, not a basic researcher, had only a superficial textbook knowledge on experimental diabetes, and was not familiar with the adequate methodology to be used in the laboratory. Nevertheless, Macleod finally accepted to offer, in summer time, a space for laboratory, an assistant, and ten dogs, in order to facilitate the experiments. Therefore, Banting could not start right away the research project, as he wished. He returned to his unsuccessful private practice in London.

In March 1921, Banting wrote Macleod, expressing his interest to start working in Toronto already in May, which was already accepted. The Professor of Physiology explained the project to Charles Best and Clark Noble, fourth-year students of Physiology and Biochemistry, and Research Assistants in his Department. Macleod left to both students the decision about how to assist Banting in his research. They flipped a coin and Charles won the toss. Banting and Best cleaned the dirty surgical laboratory provided for the experiments. On May 17, 1921, Macleod, Banting and Best met to initiate the research project.

The fate of diabetic patients experienced an extraordinary transformation after the introduction of insulin treatment. In 1922, Banting was appointed Senior demonstrator in Medicine at the University of Toronto. In 1923, he obtained the Doctor of Sciences degree and was elected Chair of Banting and Best Institute for Medical Research, University of Toronto. Additional appointments were Honorary Consulting Physician to the Toronto General Hospital, the Hospital for Sick Children, and Toronto Western Hospital. The Banting and Best Institute was engaged in silicosis and cancer (mainly the Rous’s sarcoma), among other areas. Frederick Banting received the Reeve Prize of the University of Toronto, in 1922; the Nobel Prize in Physiology and Medicine, in 1923; and in the same year, the Canadian Parliament granted him a Life Annuity. He received honorary distinctions of many academic organizations, not only from Canada, US and England. In 1928 Banting gave the Cameron Lecture in Edinburgh. In 1934, Banting was honoured as Knight Commander of the Civil Division of the Order of the British Empire.

In 1925, Frederick Banting married Marion Robertson, a radiology technician at Toronto General Hospital. Although Fred and Marion divorced in 1932, they had a child, William, born in 1929. In 1939, Banting married Henrietta Ball, a technician of his department. Then, he rejoined the Army.

Banting strongly opposed to Hitler and showed friendship to Jewish researchers escaping from the Nazis. The Canadian Government rejected his request to combat overseas at the Second World War. He was assigned to a special research program to overcome the danger of pilots when they flew at high altitudes. He developed a flight suit, filled with fluid, to protect pilots from air bubbles forming in blood. While his colleague in the project decided to travel by ship to England with the suits, Banting decided to fly.

On February 20, 1941, he took off from Gander, Newfoundland, aboard a Hudson bomber. Shortly after the plane took off, the engines failed; the airplane crashed in a deserted site of Newfoundland. Banting was seriously injured and two other men died. While waiting for help, Banting died on February 21, at the age of 50.

Charles H. Best (1899-1978)
Charles Herbert Best was born in West Pembroke, Washington County, Maine, US. His parents, Herbert Huestis Best, a physician, and Luella Fisher, were Canadians from Nova Scotia. From childhood, Charles became an experienced horseman. He moved to Toronto, Ontario, in 1915 to become a Bachelor of Arts. One
of his aunts died in 1917 in Boston, as a consequence of suffering for diabetes.

In 1918, he enlisted in the Canadian Army, and went overseas in the First War as a Sergeant. After the war, he completed the studies for the Baccalaureate in Physiology and Biochemistry, graduating with Honours. With an appropriate background in laboratory methods, including blood-sugar measurement, his summer plans changed when Professor Macleod asked him to assist Dr. Frederick Banting’s research project. Charles Best was 22 years old. Being so young for the occasion, Best was at the right time and the right place doing research at the University of Toronto.

Banting was responsible for the surgical work. Best was responsible of the chemical assays. And, finally, James B Collip accepted the critical task of the purification of the pancreatic extracts. On March 23, 1923, the Council of the Academy of Medicine of Toronto provided a Resolution that conclusive evidence has shown that the isolation of a substance presumed to be the internal secretion of the pancreas and termed insulin by Dr. F.G. Banting and Dr C.H. Best occurred in summer of 1921 at the University of Toronto.

In 1923, the Nobel Prize Committee honoured FG Banting and JJR Macleod for the discovery of insulin. J.B. Collip and C.H. Best were ignored by the Committee. Voluntarily, Banting shared half of his award money with Best, and Macleod took the same decision regarding Collip. In 1924, Charles Herbert Best and Margaret Hooper Mahon got married. They would be succeeded by two sons.4

Then, Best completed his doctorates in both Medicine and Physiology. Sir Henry Dale, Nobel Laureate and President of the Royal Society of England, invited Best as Researcher of the National Institute for Medical Research in London, England. Other Best’s mentors were Dr. Elliott P. Joslin in Boston, US, and Dr. J.G. Fitzgerald, the first Head of the Connaught Labs, and Dean of the Faculty of Medicine, Toronto University. Charles Best joined Frederick Banting as Director of the Banting and Best Institute, and succeeded J.J.R. Macleod as Professor of Physiology at University of Toronto, in 1929.

Charles Best was Advisor for the Medical Research Committee of World Health Organization, Companion of the Order of Canada, Commander of the Civil Division of the Order of the British Empire, Companion of Honour Fellow of the Royal Society of London, and the first Canadian elected in the Pontifical Academy of Sciences. In 1933 Charles Best was offered the Chair of Physiology in Edinburgh to succeed Sir Edward Sharpey-Schafer, and in 1951 the Chair of Physiology in Cambridge, but he decided not to leave both Departments he headed, the Department of Physiology and the Banting - Best Department of Medical Research from the University of Toronto. Best received 30 Honorary Degrees, being the first presented at the University of Chicago in 1941.

As Frederick Banting, Charles Best loved to paint. Best always depicted a great deal of energy and enthusiasm for life. In 1953 he suffered a series of heart attacks. In 1964, he was bothered by a severe depression. On March 31, 1978, Charles Best died as a consequence of an aortic aneurysm. He was 79 years old. He was buried in Mount Pleasant Cemetery, Toronto.

Animal research activities at the Department of Physiology, University of Toronto, leading to the development of an active pancreatic extract

Frederick Banting and Charles Best met for the first time in mid-May, 1921. Macleod had assigned them a small room in the Department of Physiology, not having been used for more than 10 years. It was dirty and very uncomfortable. They cleaned it with their hands and knees. Banting had never before performed a pancreatocotomy. Macleod showed the surgical procedure with the first dog, leaving behind a small remnant, following the two-step protocol described by Hédon in 1909. The technique allowed the pancreatic function while the animal recovered. About a week later, the completion of total pancreatectomy will induce diabetes to the animal. Best used the Myers-Bailey technique for estimating blood sugar, a modification of the Lewis-Benedict procedure, and the Benedict’s method for the determination of glycosuria. He also measured the glucose to nitrogen (G:N) ratio, as an additional metabolic parameter of the disease (figure 2).

Macleod left for summer vacation to Scotland. The research team worked with the hypothesis that after a few weeks of having the pancreatic ducts tied off, the pancreas would atrophy but will contain intact the islands of Langerhans. The first intention was to graft pieces of the “degenerated” gland into the pancreatectomized diabetic dogs. Later on, the decision was to prepare an emulsion of the “degenerated” pancreas and to inject it, at variable doses. The injection of the extracts from this “degenerated gland” would overcome the hyperglycemia and glycosuria of depancreatized dogs.

The lack of experience of Banting was responsible of animal deaths either from the anaesthesia or the surgery. Eventually, the surgical performance improved, although Banting and Best were running out of dogs. Banting had to sell his car to
buy more animals. On July 10, 1921, after experimenting with nineteen dogs, the outcome was very poor. Fourteen animals died, and only in two animals the protocol evolved as expected. In most animals the “degenerated pancreas” showed a normal appearance, suggesting failure of the duct ligation procedure (?), and it looked almost impossible to induce experimental diabetes in depancreatized dogs.

At the end of July and early August, 1921, Banting and Best initiated to test the effects of the pancreatic extracts, following the instructions of Macleod (figure 3). On August 3, Banting and Best decided to abandon the unsuccessful and laborious Hédon procedure (?), and it looked almost impossible to induce experimental diabetes in depancreatized dogs.

On September 21, Professor Macleod returned from his summer vacation. A few weeks later he met Banting and Best, and, after being reported by them, insisted in the need of additional experiments. The results were not good enough for publication, and better results could be achieved if they were able to improve the methodology. After debating the experiments in a Journal Club meeting in the month of November, they initiated also longevity experiments.

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The first original article, describing the research activities performed up to November 10, 1921, was sent for publication with the title of “The internal secretion of the pancreas”. It was accepted by the Journal of Laboratory and Clinical Medicine, and published in the issue of February 5, 1922 (figure 5). The article contained formal errors and meaningful mistakes as disagreements between the information supplied and figures or lack of accuracy in comments regarding the achieved results. The text accounts for the administration of 75 doses of pancreatic extracts of “degenerated pancreas” to 10 depancreatized dogs (figures 6-8).

Since the extracts induced a reduction of the percentage of sugar in blood and of sugar excreted in the urine, they considered justified suggesting that this extract...
contained the internal secretion of the pancreas. A distinct improvement in the clinical condition of diabetic dogs was also observed after the administration of extracts of degenerated pancreas. Nevertheless, the investigators stated that these results did not justify the therapeutic administration of degenerated pancreas extracts to cases of diabetes mellitus in the clinic.

The researchers read a report from G.E. Laguense demonstrating that fetal pancreases were more plentiful of islet cells. Also, the ligation of the ducts required over a month to obtain a “degenerated gland”, and meant the need to sacrifice the life of one animal to save the life of another one, impractical for clinical use. Banting and Best traveled to William Davies Company’s slaughterhouse in northwest Toronto, and the owner allowed them to take what they needed. They cut up the pancreas, and left the tissue to stand in alcohol-acid solution, following the procedure explained by Macleod. The alcohol was evaporated by a warm air flow. The dry residue was dissolved in saline solution and then injected into a pancreatectomized dog (figure 9). It was observed, on November 17, 1922, that an intravenous injection of the fetal pancreas extract induced a marked reduction of the hyperglycemia after 45 minutes. Two more injections were administered that day, and at the following day. A reduction of 50% in blood sugar was achieved in one hour. The 24 hour urine collection was sugar free. It appeared that the pancreatic extract was working. They also demonstrat-
ed that tissue extracts from liver, spleen, thymus and thyroid, prepared with the same protocol that pancreatic extracts, were not effective.

For Banting and Best, after many weeks of intense, laborious work with conflicting results, they were facing a new era. Additional improvements were introduced in the longevity experiments: a) the use of the Shaffer-Hartman method (recently learned by Collip), for the determination of blood glucose; b) ethanol in the preparation of the fetal calf extract; c) subcutaneous administration; d) the advantage in sterility provided by the Berkefeld filter. Whole pancreas extracted with alcohol (as previously used by Zuelzer) showed satisfactory results. From now on, the researchers showed their preference for fresh whole pancreas. Banting and Best also initiated further steps towards purification of the extract, using dialysis, and washing with toluol after the evaporation of ethanol to get an extract free of lipid substances.

Banting and Best investigated whether frequent injections with active and potent extracts were able to prolong the life of pancreatectomized animals. One special dog subjected to such investigation was Marjorie, dog # 33 (figure 10). The pancreas of Marjorie was removed on November 18, 1921. The animal showed an excellent response to the administration of fetal calf pancreas (figure 11). On December 12, 1921 James B Collip became a member of the team, invited by Macleod to help Banting and Best in the purification of the pancreatic extract. He entered the group at the time when Banting and Best had already observed the effectiveness of alcoholic extracts of fresh whole adult pancreatic extracts.

Collip used both normal and hyperglycaemic rabbits and, also, whole beef pancreas. The experiments with normal rabbits allowed an excellent description of hypoglycemia and hypoglycemic shock (figure 12). The table displays the registry of blood glucose (BG) before/after the administration of insulin, the amount of extract given, time after injection, and symptoms developed, including the appearance of convulsions. It was commonly observed that BG fell between approximately 25 and 50% within 2 hours after the injection. For purposes of physiological assay of insulin, it was considered as most satisfactory to estimate the number of cubic centimeters which lowered the percentage of BG in the rabbits to 0.045 or from 2 to 4 hours. The administration of 4 g of dextrose in 20% solution was fol-
lowed by the recovery of the animals; injections of saline in equal quantities had no effect. This investigation was a key for both concepts the physiological assay and the unit for dosing the pharmacological preparations of the antidiabetic hormone. The final conclusions of this investigation are depicted in figure 13.

The team also investigated the effect of pancreatic extract on the various experimental conditions known to cause marked hyperglycemia in rabbits (puncture—injuring the occipital tubercle—, epinephrine, carbon monoxide poisoning, ether). Insulin, in suitable doses inhibited the development of hyperglycemia subjected to these different conditions.

Collip worked in his own laboratory, making his pancreatic extract, introducing methodological changes. Instead of evaporating the liquid phase of the alcoholic solution, decided to use a vacuum still followed by filtration obtaining a concentrated solid residue. In this way, the potency of the preparation markedly increased. Furthermore, Collip tested the effect of the extract on ketonuria and glycogen formation in the liver. In fact, Collip was the first investigator able to demonstrate in the University of Toronto the effectiveness of the extract on the ketotic state. He also measured the amount of glycogen stored at the liver in normal and diabetic animals. In a particular experiment, the
liver of a diabetic dog, treated with pancreatic extract, depicted more than 25% glycogen, demonstrating the effectiveness of the internal secretion of the pancreas on glycogen synthesis.3

JJR Macleod developed a large group of experiments with the aim to achieve potent insulin preparations from fish pancreas. He initially gave recognition to the previous reports of Rennie who discovered that islet tissue in the bony fishes (Teleostei) is collected into nodules which are often encapsulated and are, thereby, separated from the zymogenous tissue. Rennie and Fraser failed to demonstrate the presence of insulin because they administered the islets by mouth; insulin is readily destroyed by digestive enzymes.15

The general protocol was to observe from time to time the amount of blood sugar in normal rabbits injected with extracts prepared from: 1) the pancreas of representative Elasmobranchs (Squalus –dog fish–, and Raja –skate–); 2) the principal islets of representative Teleostei (Myoxoccephalus –sculpie–, and Lophius piscatorius –angler fish–); c) the zymogenous (acinar) pancreatic tissue, as free as possible from islets, in the same and other Teleostei.16 These investigations showed, quite clearly, that insulin is present only in pancreatic islets and not in the exocrine pancreas.

On December 30, 1921, Macleod, Banting, and Best, presented a scientific communication, entitled “The beneficial influence of certain pancreatic extracts on pancreatic diabetes”, at the American Physiological Society Conference at Yale University in New Haven. Macleod was the Chairperson of the meeting, being Banting the speaker. Among many other experts, Allen, Joslin, Kleiner, Scott, Carlsson and Clowes, were present.5 The conference of Banting was flat. He was unable to properly answer many pertinent questions. Macleod felt obliged to make frequent interventions, explaining that additional reports were in progress. Nevertheless, George Clowes, the Eli Lilly Research Director, told Macleod that he was impressed about the importance of the investigation and offered the collaboration of the Company in the industrial preparation of the extract. Professor Macleod answered that the stage of the process required more time to be ready for commercial exploitation.3

Although Collip was in charge of purifying and preparing the extract for clinical use, Banting was eager in being the first to try the administration to patients. Therefore, he urged Macleod to use for this purpose the extract being used by Best and himself to treat dog 33, Marjorie. This dog had survived 70 days after pancreatectomy.17 On January 27, the animal was killed by an overdose of chloroform. The autopsy, made by the pathologists Dr. W.L. Robinson at the General Hospital, Toronto, found the following:

The area formerly occupied by the pancreas showed no gross evidence of pancreatic tissue. There were a number of firm fibrous adhesions about the duodenum. These were sectioned, and on microscopic examination showed no evidence of pancreatic tissue remaining in them. The duodenum was then examined and nothing abnormal found except for a small nodule about 3 mm in diameter, situated in the wall at the mesenteric attachment and 10 cm, below the pylorus. This on microscopic examination was found to consist of what is apparent a nodule of pancreatic tissue, lying in the submucosa. Serial microscopic sections of this, however, failed to show the presence of any islands of Langerhans. No other microscopic evidences of pancreatic tissue could be found.

Duncan Graham, the Eaton Professor of Medicine, Toronto University, denied the request of Banting to try the administration of the extract to a diabetic subject, considering that a surgeon, not currently on clinical practice, was not qualified for human experimentation.

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