

## **GLIMPSES OF THE HISTORY OF INSULIN**

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### **ABSTRACT**

The discovery of the insulin which took place at Toronto, Canada in 1921-22 is one of the most important medical discoveries of the modern age. For this miracle, Prof . John James Richard Macleod and Frederick Grant Banting were Jointly awarded the Nobel Prize in 1923 for Physiology or Medicine. Frederick Sanger a British biochemist discovered the structure of Insulin in 1958 and was awarded Nobel prize for chemistry.

Diabetes mellitus is called *Madhumeha* in ancient Indian *Ayurvedic* medicine. Egyptians and Greeks knew about it. Greek physician Aretarus of Capadocia first suggested the term 'Diabetes' and described it.

Though insulin was discovered about 80 years ago research interest in it still continues unabated. This paper also gives case details of the first patient on whom Insulin was first tried and chronology of research on pancreas and Insulin.

Insulin is one of the most important medical discoveries of the modern age. It was one of the North America's first great contributions to medical science and its therapeutic armamentarium. It was not an accidental innovation nor a miracle. It was the product of the years of dedicated work by hundreds of researchers of the pancreas and diabetes, the improvements in chemistry leading to quick, accurate blood sugar tests and other developments. Many great things were being achieved in medical science during the 19th and 20th centuries. The microbe - hunters, such as Louis Pasteur (1822 - 1895 ), Heinrich Hermann Robert Koch (1843 - 1910) and

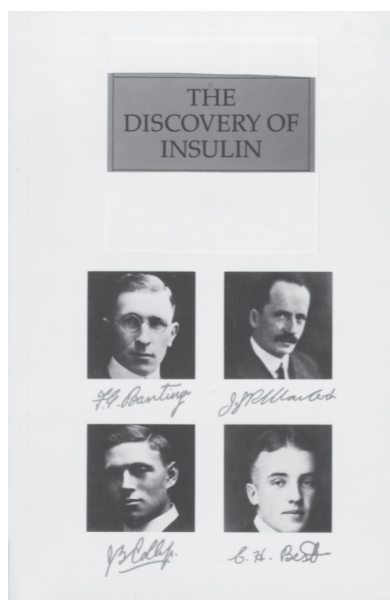
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Paul Ehrlich (1854 - 1915) had found the causes and cure of dreaded infectious diseases; surgeons like Joseph Lister (1827 -1912) had made operations a way of saving, rather than taking lives, and humanitarians ranging from Florence Nightingale (1820 - 1910) to Walter Reed (1851 - 1902) and William Osler (1849 - 1919) had shown that medicine was a healing and helping profession. Insulin was just another jewel in the crown of curative medicine.

The discovery of insulin at the Department of Physiology, University of Toronto, Canada, in 1921 - 22 was one of the most dramatic events in the history of therapeutics. Insulin's impact was so exciting and sensational because of the incredible effect it had on diabetic patients. Those who watched the first starved, some times comatose, diabetic, receive insulin and return to life, saw one of the genuine miracles of modern medicine. They were present at the closest approach to the resurrection of the body that our secular society can achieve, and at the discovery of what has become the elixir of life for millions of human beings around the world for the discovery of this "miracle" Professor John James Richard Macleod (1876 - 1935) and orthopaedic

surgeon (by training) Frederick Grant Banting (1891 - 1941) were jointly awarded the Nobel Prize for Physiology or Medicine in 1923. It is of great importance that Charles Herbert Best (1899 - 1978), while still a medical student, collaborated with Banting in experiments leading to the isolation of insulin and also that the biochemist James Bertram Collip (1892 - 1965) developed a method for extraction of substantial quantities of the hormone from bovine pancreatic tissue. Though not included in the award, Macleod shared his prize money with Collip and Banting. Undoubtedly wonderful gesture by a colleague for a colleague. The Nobel Prize turned out to be about \$24,000 dollars in 1923; division of the cash



was the prize winner's business, and there was no comment in the Nobel records about the division.

The University of Toronto recognized the Nobel Laureates with a special convocation on November 26, 1923, at which Banting and Macleod were each awarded the honorary degree of Doctor of Science.

The cradle of cure for diabetes crawled over a long track to reach its current state. The penumbra of pancreatic research is simply spectacular; myriads of minds pushed the cradle forward all along (APPENDIX -I).

British biochemist, Frederick Sanger (1918 - ) of Cambridge, England, was awarded the Nobel Prize in Chemistry in 1958 for discovery of the structure of the insulin molecule (51 aminoacids in two chains). It has been synthesized later, as well. It is of interest to note that Sanger was also a co-winner of the Nobel Prize in Chemistry in 1980 with Paul Berg (1926 - ) and Walter Gilbert (1932 - ), both of the U.S.A., for the first preparation of a hybrid of Deoxyribonucleic Acid (DNA) and development of chemical and biological analysis of DNA. Sanger is the first "double" Nobel Laureate in Chemistry. The "Sanger Centre" in Cambridge University, England, is the Mecca of advanced research in molecular biology and biochemistry.

### **The Malady**

*Diabetes* (Greek word, meaning - 'siphon' or 'pipe-like') *Mellitus* (Latin word of honey) is a disease of disturbance in the utilization of glucose by cells - the building block of the body due to lack of the internal secretion (Hormone) - "INSULIN" by the beta cells of the islets of Langerhans in the pancreas. It is also called the sugar disease or the sugar sickness. It is different from *Diabetes Insipidus* (urine is insipid - unpalatable lacking taste)- an endocrine (hormonal) disorder of the posterior pituitary gland situated inside the brain, in which a large volume of sugar-free urine is passed.

"*Diabetes Mellitus*" is called "*Madhumeha*" (*Madhu*"-meaning "honey") in ancient Indian *Ayurvedic* Medicine; ancient Egyptians and Greeks knew about it. The Greek physician, Aretaeus of Cappadocia (2nd century A.D. ) first suggested the term

“Diabetes” and described the disease as “a melting down of the flesh and limbs in urine”. Frequent urination (polyuria), constant thirst (polydipsia), excessive hunger (polyphagia), constant fatigue or weakness and rapid weight loss are the classic symptoms of diabetes. Insulin is the vehicle to carry glucose into the cell across the cell membrane. Glucose, the fuel for the body, coming from the break-down of the food we take, cannot enter the cells of the body for chemical conversion to energy due to lack of Insulin. Glucose remains in the blood-stream.

There are two clinical types of diabetes - “Juvenile-onset” (Type-I) in younger people and “Maturity-onset (Type-II) in the older.

The pancreas is the natural home of insulin. The pancreas is a large elongated glandular structure transversely at the back of the abdominal cavity, behind the stomach. Its function is primarily digestive; its secretion, the pancreatic juice, contains a variety of digestive enzymes and passes into the duodenum *via* the pancreatic duct. The pancreas also has an endocrine function, secreting hormones directly into the bloodstream. These hormones are elaborated by cells scattered throughout the gland, in clusters, called the “Islets of Langerhans”(alpha and beta cells), and are chiefly concerned with the regulation of carbohydrate metabolism: they include “Insulin”, “Glucagon” and “Somatostatin”. The word- “*insula*” originates from the 20th century New Latin word- “insulin” islet of the pancreas.

Though discovered about 80 years ago, research interest in insulin still continues unabated. Neurons (brain cells) are now known to synthesize and secrete insulin; but glucose utilization in neurons is largely insulin independent and hence it must have other functions in neuron, as growth, maturation, neuro-protection, neuro-modulation, learning and memory (Man, H. Y., Line, J. W., Ahmedin, G., Liu, L., Becker, L. E., Sheng, M. and Wang, Y. T.: Regulation of AMPA receptor - mediated synaptic transmission by clathrin - dependent internalization. NEURON, 2000, Vol. 25: 649-642). Insulin recruits GABA (Gammaaminobutyric acid) and other receptors to the postsynaptic domain, and the rate of constitutive dyamin - dependent endocytosis of AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors is accelerated by insulin.

### **The Clinical Tests**

*(Source: Michael Bliss - The Discovery of Insulin, Faber and Faber, London/ Boston, Revised Edition, 1988 .)*

Banting was a surgeon turned general practitioner at London on the outskirts of Toronto, and then got interested in pancreatic research in Prof. Macleod' physiology department. He had no clinical responsibility. He requested his clinical colleagues at Toronto General Hospital to try their pancreatic extract in diabetic patients. Collip was a biochemist. Best was a medical student-cum laboratory assistant, helping Banting. Best later became one of the authors of the well-known book: "Physiological Basis of Medical Practice". Their scope of clinical research was very limited. They had to depend on the mercy of their clinical colleagues, some sceptical about new things to try on humans.

### **The First Patient**

Leonard Thompson, age 14, Wt. - 65 lbs.

Date of Admission - Dec. 2, 1921 - Diagnosed in 1919.

Status: Public ward Patient (i. e. a charity case in the Diabetic Clinic (Ward H).

Doctors - in - charge: Dr. Walter "Dynamite" Campbell and Dr. Duncan Graham.

On admission, Leonard was pale, had his hair falling out, abdomen distended, breath smelling of acetone - dull, listless, content to lie in his bed day after day. "All of us knew that he was doomed" recalled a senior medical student in the ward. The condition was fatal. Leonard's father, on Dr. Campbell's advice, agreed to let them try Banting and Best's new extract on his son.

In December, 1921, Best made some whole beef pancreatic extract in alcohol. The solution was filtered, most of the alcohol was evaporated off in a vacuum still, the solution was washed twice with toluene, and the remaining watery solution was sterilized with a Berkefeld filter. Banting and Best tested the extract's potency on their dog -

“Marjorie” depancreatized on November 18, 1921. They might have tried in themselves to find that there was only a little redness at the injection site on the arms. The extract was “a thick brown muck” in appearance. In the afternoon of January 11, 1922, 15cc. of the extract (presumably diluted) was injected by a young house physician - Dr. Edward Jeffrey- seven and a half cc into each buttock.

The results of the injection, as reported in a publication signed by Banting, Best, Collip and Campbell, was as follows:

“Leonard Thompson’s blood sugar dropped from 440 to 320. The twenty-four hour excretion of glucose fell from 91.5 grams in 3, 625 cc of urine to 84 gram in 4,060 cc. The Rothera test for ketones continued to be strongly positive. “No clinical benefit was evidenced.” A sterile abscess, caused by the impurities in the extract, developed at the site of one of the injections.

Banting himself commented on the results in his Nobel Prize Lecture on December 10, 1923, as ‘marked reduction’ in blood sugar and urine being rendered sugar- free . The effect of the pancreatic extract on Leonard’s urinary sugar is given in appendix II.

Leonard was given further injections of Collip’s new extract daily on and from January 23 to January 26, 1922. “The boy became brighter, more active, looked better and said he felt stronger.” This was the first unambiguously successful clinical test of the internal secretion of the pancreas on a human diabetic.

Leonard Thompson - the first person brought back from the edge of the grave by insulin, died on Easter Monday, April 20, 1935, in Toronto General Hospital. He was 27 Years old. He had lived a more or less normal life, holding down a steady job as an assistant in a drug and chemical factory, taking 85 units of Insulin daily.

Leonard Thompson’s pancreas was preserved and is displayed as Item No. 3030 in the Anatomical Museum at the Banting Institute, University of Toronto, Canada.

### **The Second Patient**

Elizabeth Hughes - an American - was the second patient treated in Toronto in 1922 by Banting’s team. She had some 43,000 injections after first receiving insulin in Toronto. She died suddenly of a heart attack at the age of 60 on April 25, 1981.

Jim Havens was the first diabetic to receive insulin on the evening of May 21, 1922, in the U.S.A. He died of cancer in 1960 at the age of fifty - nine.

### **The Rival Claimants**

Insulin had not emerged out of a vacuum, but was the culmination of years of work by dozens of scientists in many countries on both sides of the Atlantic. Nicolas Paulesco, Professor of Physiology of the Romanian school of Medicine in Bucharest, Published important papers in French medical journals in 1921, describing successful experiments with pancreatic extracts which he named “Pancreine”. He got a Romanian patent on “Pancreine” in April, 1922. There is no evidence that “Pancreine” was ever used successfully to treat humans. Paulesco was trained in Paris in the 1890’s . He Published his results in French journals in 1921 and 1922.

After the Nobel Prize was awarded to Banting and Macleod in 1923, Paulesco, outraged at what he believed was Toronto’s theft of his work, demanded justice from the Nobel Committee. The protest was ignored. On the 50th anniversary of the discovery of insulin, the International Diabetes Federation, on the insistence of the Romanian School of Medicine, did establish a special Blue-Ribbon Committee to prepare a factual account of the various researches leading to the discovery of insulin. A careful report with a tightly written summary of historical knowledge about the discovery of insulin was published in 1971. It concluded that Paulesco’s “Pancreine” probably contained insulin - as did the pancreatic extract prepared by several earlier researchers, especially George Ludwig Zuelzer of Berlin in 1906, Ernst Lyman Scott, medical student at the University of Chicago (1911 - 1912), Israel Kleiner (1919) at the Rockefeller Institute - but it was the Canadians - Banting, Best, Collip and Macleod - who made insulin therapeutically suitable for the treatment of diabetes mellitus.

Zuelzer injected 8 cc of pancreatic extract under the skin of a comatose 50-year old diabetic in a private clinic in Berlin on June 21, 1906. With apparent initial improvement, the patient sank into a deep coma on June 30 and died on July 2. After the Nobel award Zuelzer made a pathetic plea for some recognition of his priority, but was ignored.

Scott worked on pancreatic extracts in animals for his thesis for a master's degree in 1911 at the University of Chicago under the noted Physiologist, Anton Carlson. The first two conclusions of his thesis were :

- (1) There is an internal secretion from the pancreas controlling the sugar metabolism.
- (2) By proper methods this secretion may be extracted and still retain its activity.

Scott's widow and Romanian friends of Paulesco claimed in the 1970's that credit had not been given to those who had really done the work. Israel Kleiner, who in 1919 was closer to success than any of them, made no claim at all.

The ball of insulin's discovery rolled on the chess board on both sides of the Atlantic, but ultimately came to a halt at Toronto, where it attained the final fruitful feather of success and eternal glory.

Unquestionably, it was the "Toronto - Four" (Banting, Best, Collip and Macleod) who first shattered the veneer of invincibility that made diabetes such a terrifying affliction in those days. The discovery of insulin at the University of Toronto in 1921 - 1922 was one of the most sensational of all therapies in its impact, and it symbolized and stimulated the 20th century's commitment to medical research.

### **The Economics of Insulin**

In accordance with the Lilly - University of Toronto Agreement, American insulin had been distributed free of charge throughout the experimental period. "ILETIN" - the Lilly's brand of insulin was first sold wholesale for five cents per new unit - 40 cents to 1 dollar a day the diabetic patient was paying for insulin - in 1923 and it was an expensive treatment.

Macleod offered the patent of insulin to the Medical Research Council (MRC) of Great Britain for the British market. Henry Hallett Dale (1875 - 1968 ), Nobel Laureate in Physiology or Medicine in 1936, Director of the Biochemistry and Pharmacology Department of the Council, visited Toronto in September/early October, 1922, and was convinced about the efficacy of "the anti- diabetic miracle". On his recommendation, the MRC accepted the patent to regulate the commercial production of insulin in the British Empire. Schack August Steenbergen Krogh (1874-1949) of the University of Copenhagen, Nobel Laureate in Physiology or Medicine in 1920,



visited Macleod's laboratory in November, 1922, and being convinced, took the insulin trail to Scandinavia.

The German chapter started with Banting and Best's presentation of "Insulin vial" to Prof. Oskar Minkowski of Breslau (Germany ) in the Spring Quarter of 1923. The insulin situation in France was less satisfactory than in Germany. It may be of interest that Paulesco's works on "Pancreine" were all published in French journals. Paulesco himself was also trained in Paris. There seemed to be an element of rivalry in the insulin saga. There was a small trial of pancreatic extracts on a diabetic patient which took place in Spain in early 1923.

### **The Epilogue**

Insulin research claimed two Nobel Prizes during the last century (Banting and Macleod, 1923; Sanger, 1958). It was symbolic of intense global interest in pancreatic research. It was not a miracle perceived in a day- dream or dropped from the blue. Insulin was the brain- child not of a single person but of many scientific minds nourishing the idea of the existence of a sugar - manipulating internal secretion in the pancreas - Langerhans Von Mehring, Minkowski, Paulesco, Klein, Banting, Best, Collip, Macleod, Joslin (Elliot P. Joslin of Joslin Diabetic Foundation, U.S.A.), Sanger and others. The hero of the whole drama was the first patient treated with Toronto's first pancreatic insulin extract for juvenile diabetes - the 14 year old Canadian boy, Leonard Thompson. Insulin was undoubtedly one of the most significant discoveries in medical science in the twentieth century. During the 20's of the 20th century, insulin roamed vividly over the latitude and longitude of medical imagination of the day and to the first group of diabetics treated with it, insulin was an echo of eternity.

## **APPENDIX - I**

### **A Century of Research: A Century of Innovation :**

- |      |  |
|------|--|
| 1869 | Paul Langerhans - a German medical student - describes 'islet like' tissues in the pancreas and also acinal cells secreting digesting enzymes. |
| 1889 | Joseph Von Mehring and Oscar Minkowski discover that removing the pancreas causes diabetes mellitus.   |

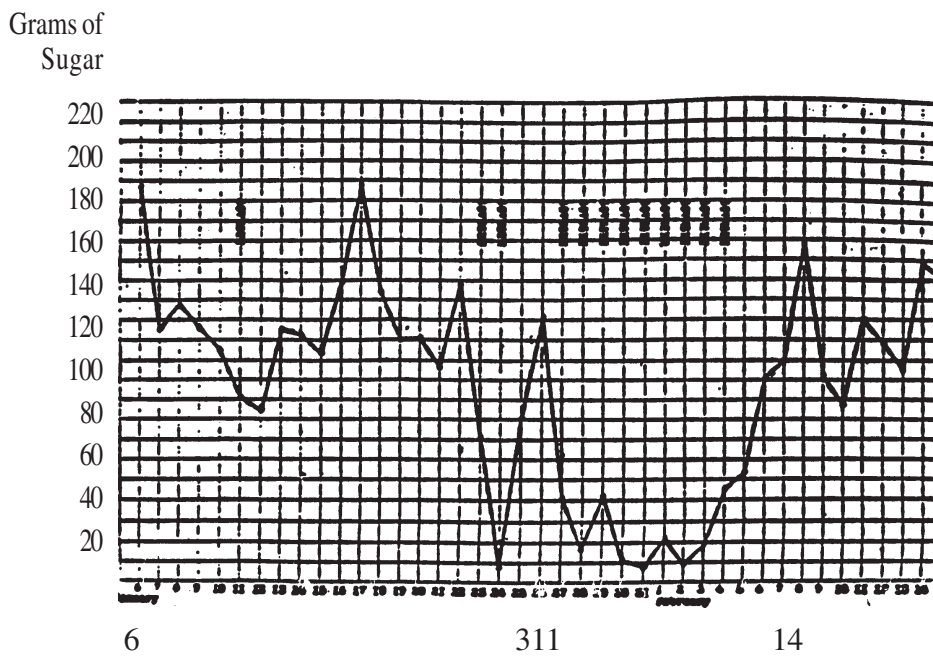
- 1893 Laquesse suggests that a substance to reduce glucose in the blood may be produced by 'Islets of Langerhans'.
- 1898 Blumenthal reduces blood glucose using pancreatic extracts.
- Early  
1900's Gurg Ludwig Zuelzer, an internist in Berlin - Treating a diabetic patient with extracts of pancreas - Temporary improvement - Sank into coma - Died when supply of extract was exhausted.
- 1900 Schultze demonstrates that ligation of the pancreatic duct leads to atrophy of the gland and to diabetes.
- 1907 Zeulzer uses extracts of pancreas to reduce glucose and ketone bodies in urine.
- 1910 Hoechst, Germany, begins to study new ways of treating diabetes.
- 1911 E.L. Scott, Chicago University student: Treated several diabetic dogs with pancreatic extracts.
- 1912 Hoechst starts to use improved methods to manufacture pancreatic enzymes.
- 1916/  
1920 Nicolas Paulesco, Romanian Physiologist: Injection of pancreatic extracts reduces urinary sugar and ketones in diabetic dogs. Results published, but their significance not appreciated at the time.
- 1921 Hoechst isolates extract that reduces blood glucose from cattle pancreas.
- 1921 Frederick G. Banting and Charles H. Best succeed in reducing blood glucose in a diabetic pancreatectomised dog.
- 1922 Leonard Thompson, Aged 14, becomes the world's first human insulin patient (Toronto General Hospital).
- 1922 Banting, Best and J.B. Collip donate patent for insulin extraction process to the University of Toronto.
- 1923 Frederick G. Banting, a young Canadian surgeon, and J.J.R. Macleod are awarded the Nobel Prize in Physiology or Medicine.

- 1923       Hoechst makes insulin available to doctors in Germany.
- 1926       Abel produces the world's first insulin crystals.
- 1930       Hoechst sets the standard for slow-release insulin preparation.
- 1934       Hoechst develops a procedure to produce insulin crystalised with zinc.
- 1936       Hoechst becomes the first manufacturer to switch production to crystalline insulin.
- 1936       Hagedorn demonstrates that the effect of insulin can be extended if bound to protamine, a protein found in fish sperm.
- 1950       Hoechst increases production from 352 to 955 million units per annum.
- 1955       Frederick Sanger identifies the chemical structure of insulin after 14 years of dedicated work.
- 1967       Hoechst decides to restrict production to single species insulins only.
- 1976       Hoechst carries out the first semi-synthesis of human insulin.
- 1977       Hoechst introduces a novel enzymatic method for large- scale production of insulin.
- 1981       Hoechst develops genetically modified bacteria for use in insulin production.
- 1984       Hoechst develops the world's smallest insulin pump.
- 1989       Hoechst introduces the first Opti Pen for facilitated insulin injection.
- 1990       Hoechst develops the world's first programmable insulin pump.
- 1993       Hoechst commences work on biosynthetic human insulin production.
- 1994       Hoechst receives authorisation to manufacture human insulin.
- 1998       Hoechst starts production of insulin using an environmentally friendly process.
- 2000       Aventis announces the dawn of a new era in diabetes management.

**NOBEL PRIZE WINNERS IN PHYSIOLOGY OR MEDICINE, 2000**

YEAR	NATIONALITY	WINNERS	CONTRIBUTION
2000	SWEDISH	ARVID CARLSSON (1923- )	Discoveries: concerning signal transduction in the nervous system - Crucial for an understanding of the normal function of the brain and how disturbances in signal transduction (slow synaptic transmission) give rise to neurological and psychiatric diseases.
	AMERICAN	PAUL GREENGARD (1925- )	Role of dopamine as an important neuro - transmitter (work in 1950's)
	AMERICAN	ERIC KANDEL (1929- )	Role of protein phosphorylation in determining neuronal excitability.
			Role of protein phosphorylation in neuronal signalling - molecular basis of short - term and long-term memory.

**APPENDIX - II**



**Chart 5: The effect of extract on the sugar in Leonard Thompson's urine taken from the 1922 published report**

(SOURCE: Michael Bliss: The Discover of Insulin  
Faber and Faber, London/Boston, p.121, 1982)

## सारांश

### इन्सुलिन के इतिहास की झलकियाँ

- सिसिर के मजुमदार

इस आधुनिक युग में इन्सुलिन एक महत्वपूर्ण खोज है। चिकित्सा विज्ञान के क्षेत्र में उत्तर अमेरिका का एक और प्रथम योगदान है। इन्सुलिन के आविष्कार केनडा के टोरंटो शहर में सन 1921-22 में हुआ था, इस योगदान के लिए प्रो: जान जेम्स रिचर्ड मेकलियोड और फ्रेडेरिक ग्रांट बांटिंग की जोड़ी को सन 1923 में नोबेल पुरस्कार भी प्राप्त हुआ। फ्रेडेरिक सांगर जो जीवनरसायन शास्त्र के विशेषज्ञ थे उनको भी इन्सुलिन की बनावट जानने के लिए सन 1958 में नोबेल पुरस्कार प्राप्त हुआ।

यूनानी भाषा में डयाबेटिस का अर्थ एक नल, और लेटिन में मेल्लिटस का अर्थ शहद है। प्राचीन भारतीय चिकित्सा शास्त्र, आयुर्वेद में इस बीमारी को मधुमेह कहते हैं। मिस्री और यूनान भी इस के बारे में जानते थे। यूनान के एक चिकित्सक अरेटियस केपाडोसिया ने पहलीबार डयाबेटिस का पद उपयोग में लाया और उसकी पूरी जानकारी दी।

यह संदेह नहीं है की 80 साल पहले जानने के पश्चात इन्सुलिन पर अनुसंधान के उत्तेजन अभीभी जारी हैं। इस प्रकार यह लेख में प्रथम रोगी जिन पर इन्सुलिन का प्रयोग किया गया था उनका पूरी जानकारी के साथ पैंक्रियास और इन्सुलिन पर हुई सारे अनुसंधान के विवरण भी प्रस्तुत हैं।