

# The History of Diabetes From 1500 BC To Now

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## RACHMIEL LEVINE

- This presentation is dedicated to Dr. Rachmiel Levine, my first mentor in diabetes mellitus at Michael Reese Hospital in Chicago, Illinois, and a student of the history of diabetes.

## QUESTION

- Protamine in NPH Insulin and PZI insulin is derived from
- 1. Beef Heart
- 2. Cow Liver
- 3. Goat Milk
- 4. Fish Sperm

## QUESTION

- Globin in Globin Insulin is derived from
- 1. Beef Heart
- 2. Cow Liver
- 3. Goat Milk
- 4. Fish Sperm

## Ebers Papyrus, 1500 BC

- Mention of a disease with increased urinary output.
- Specific plans for treatment were advanced.
- Translated by Egyptologist George Ebers

## Hesy Ra



## EBERS PAPYRUS 1500 BC

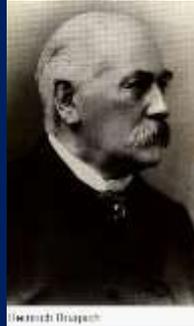


## HESY RAH

- 1552 BC – Written on a 3rd Dynasty Egyptian papyrus, physician Hesy-Ra mentions frequent urination as a symptom. This is the earliest known record of diabetes. 1500 BC – Ancient Hindu writings note that ants are attracted to the urine of people with a mysterious emaciating disease. 500 BC – The first descriptions of sugar in the urine and its occurrence in obese individuals. 250 BC – Apollonius of Memphis is credited with coining the term “diabetes”, meaning to go through, or siphon, for a disease that drains patients of more fluid than they can consume.

## Papyrus of Brugsch, 1350BC-1250BC)

- Recipes are found for treating polyuria



The Papyrus was translated into German

## Old Sanscrit Texts

- Indian Doctors of the 6<sup>th</sup> century A.D. found that the urine of people with diabetes tasted sweet, and was sticky to the touch.
- The Indian name for diabetes is Madhumeha and means urine of honey.
- Susruta, a great Indian Doctor of 5<sup>th</sup> century A.D., gave a good clinical description of diabetes

## SUSRUTA



## Aretaeus, Greek physician, 2<sup>nd</sup> Century A.D.

- Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water, but the flow is incessant, as if the opening of aqueducts. Life is short, disgusting and painful; thirst unquenchable. Their mouth parched and their body dry. Many contemporary writers described diabetes mellitus after injury, moral shock, and after acute disease (influenza).

## ARETAEUS

After his death he was entirely forgotten until 1554, when two of his manuscripts, *On the Causes and Indications of Acute and Chronic Diseases* (4 vol.) and *On the Treatment of Acute and Chronic Diseases* (4 vol.), both written in the Ionic Greek dialect, were discovered. These works not only include model descriptions of pleurisy, diphtheria, tetanus, pneumonia, asthma, and epilepsy but also show that he was the first to distinguish between spinal and cerebral paralyses. He gave diabetes its name (from the Greek word for “siphon,” indicative of the diabetic’s intense thirst and excessive emission of fluids) and rendered the earliest clear account of that disease now known.

## Pancreas

- Pancreas is derived from the Greek
- Pan-all
- Creas-flesh
- The word pancreas first appeared in the Oxford dictionary at the end of the 16<sup>th</sup> century

**PARACELUSUS**

- 16th Century – Paracelsus identifies diabetes as a serious general disorder. For thousands of years, no one knows how to live with diabetes, let alone treat or cure it. Children with diabetes often die within days of onset and older people deal with devastating complications. Remedies range from herbs to bleeding.

**THOMAS WILLIS(1621-1675)**

In 1674, Thomas Willis (Of the Circle of Willis) discussed the Sweetness of urine in diabetes, And for the first time we heard About DIABETES MELLITUS



## MATTHEW DOBSON (1735-1784)

- Matthew Dobson was a Liverpool physician who was recognized for his numerous and varied publications. He investigated a patient with diabetes, which at the time was considered to be a kidney disorder, associated with excessive sweet tasting urine. His experiments showed that the sweet urine, on evaporation, contained white granular material indistinguishable from sugar. However, he also made the crucial observation that the blood serum was also sweet to taste. He concluded that the emaciation in diabetes was due to 'a large proportion of the alimentary matter being drawn off by the kidney before assimilation'

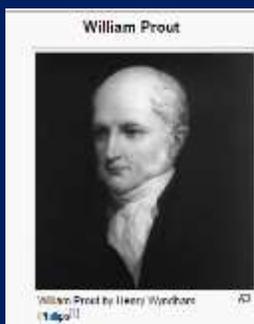
## MATTHEW DOBSON

- **1775 - Matthew Dobson discovered elevated sugar levels in the blood as well as the urine of diabetics. He concluded that the disease was metabolic and not just a defect of the urinary system. He discovered the white mass from the dried urine was cane sugar.**

## Thomas Cawley

Thomas Cawley in 1788 suggested a relationship between the pancreas and diabetes after observing stones and signs of tissue damage at the autopsy of a patient with diabetes,<sup>6</sup> but the significance of this clue was not appreciated for another hundred years.

### DIABETIC COMA



- Diabetic coma was first reported by W. Prout (1785-1850) of Guy's hospital Medical School of London England. He was a pioneer in applying chemistry to medicine and physiology.

## JOHN ROLLO

In 1797 Rollo printed at Deptford *Notes of a Diabetic Case*, which described the improvement of an officer with diabetes who was placed on a meat diet. He was the first to take Matthew Dobson's discovery of glycosuria in diabetes mellitus and apply it to managing metabolism. By means of Dobson's testing procedure (for glucose in the urine) Rollo worked out a diet that had success for what is now called type 2 diabetes. The addition of the term "mellitus", distinguishing the condition from diabetes insipidus, has been attributed to Rollo

## ROYAL ARTILLERY ENGRAVING



Royal Artillery Hospital, engraving  
inscribed to John Rollo

## DIABETIC COMA



- Adolph Kussmaul (1822-1902) of Freiburg described the abnormal breathing in diabetic coma. The breathing abnormality still bears his name.

## THE GRAVE OF ADOLPH KUSSMAUL



His grave in Heidelberg

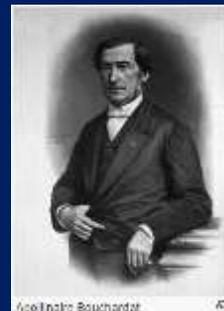
**PAUL LANGERHANS (1847-1888)**



- 1868
- Discovered the islet cells and thought that they were nerve cells but had no idea about their real function.
- Died at a young age from military tuberculosis and renal failure

## **APOLLINAIRE BOUCHARDAT (1809-1886)**

Bouchardat is often credited as the founder of diabetology, and was a major figure involving dietetic therapy for treatment of diabetes prior to the advent of insulin therapy. He recognized that fasting was a method to reduce glycosuria, and speculated that the principal cause of diabetes was located in the pancreas. In the treatment of the disease, he stressed the importance of exercise, and developed a procedure for self-testing urine to determine the presence of glucose.



Apollinaire Bouchardat

## Oscar Minkowski (1858-1931)

1889 – Minkowski and von Mering, at the University of Strasbourg, France, remove the pancreas from a dog to determine the effect on digestion and discover that diabetes develops. Did he taste the urine or analyze it?



## Joseph von Mering (1849-1908)



## BERNHARD NAUNYN (1839-1925)



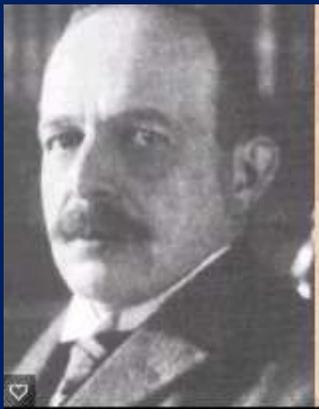
### Bernhard Naunyn

Another century passed before further advances were made at the end of the 19th century. In an institute in Strasbourg headed by an authority on diabetes, Bernhard Naunyn, Oscar Minkowski and Joseph Freiherr von Mering produced diabetes by removing the pancreas of a dog.<sup>3</sup> Serendipity is said to have played a role in this discovery. The urine of a polyuric depancreatized dog had been left uncleaned on the floor of the laboratory by a lazy attendant, and Minkowski checked it for glycosuria. This led to unsuccessful attempts to treat patients by feeding them pancreas in addition to the fat-rich, protein-poor, almost carbohydrate-free diet recommended by Naunyn

## Pancreatic Islets

- Pancreatic Islets were first noticed by Paul Langerhans, a medical student, (1849-1888) on a cut of the pancreas in 1869.
- Eugene Lindsay Opie of Johns Hopkins University in 1902 reported severe hyaline degeneration of the islets in individuals who died of diabetes.

George Ludwig Zuelzer  
(1870.1949)



1908 - Zuelzer, a German physician, extracts a pancreatic "substance" (Acomotrol) and injects it into five diabetes patients. Although sugar in the urine is reduced or disappears, the side effects of treatment are extreme and unacceptable. He also tries to save the life of a patient in diabetes coma but fails.

**Carl Harko von  
Noorden (1858-  
1944)**

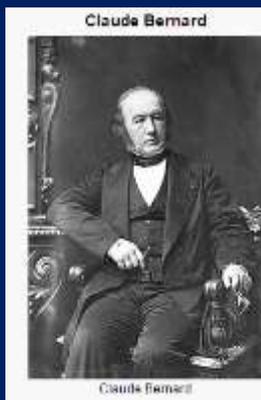


- "Metabolism and practical medicine", (3 volumes, 1907).

"Clinical treatises on the pathology and therapy of disorders of metabolism and nutrition" (8 volumes, 1903-09); with Karl Franz Dapper; Hugo Salomon; Hermann Strauss.

"New aspects of diabetes: pathology and treatment", 1912

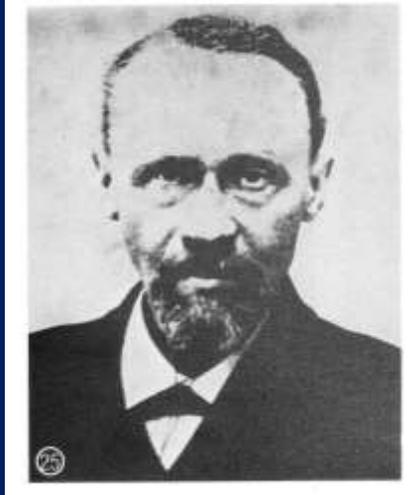
**CLAUDE BERNARD  
(1813-1878)-  
PHYSIOLOGIST**



- Claude Bernard's aim, as he said, He dismissed many previous misconceptions, took nothing for granted, and relied on experimentation. Unlike most of his contemporaries, he insisted that all living creatures were bound by the same laws as inanimate matter.
- Claude Bernard's first important work was on the functions of the pancreas gland, the juice of which he proved to be of great significance in the process of digestion; this achievement won him the prize for experimental physiology from the French Academy of Science
- A second investigation - perhaps his most famous - was on the glycogenic function of the liver; in the course of his study he was led to the conclusion, which throws light on the causation of diabetes mellitus, that the liver, in addition to secreting bile, is the seat of an internal secretion, by which it prepares sugar at the expense of the elements of the blood passing through it.

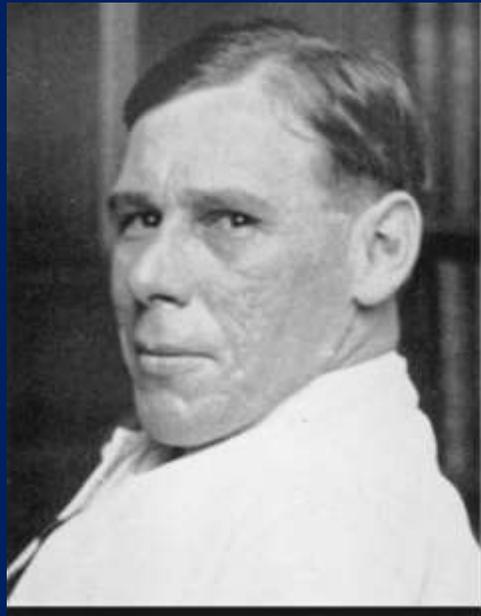
**Gustave-Eduard  
Laguesse (1861-  
1927)**

Named the  
Islets the Islets  
of Langerhans  
and thought  
that they had a  
digestive  
function ( a  
secretory one).



**STANLEY  
BENEDICT  
(1884-1936)**

Developed  
Benedict's  
Solution for  
the detection  
of glucose in  
the urine in  
1911  
(American  
Chemist)[n](#)



## EDOUARD HEDON (1863-1933)

In 1893 a very important contribution was made by French investigator Edouard Hedon in Montpellier, who showed that the total pancreatectomy was necessary for the development of diabetes. After removing the pancreas, he grafted a small piece of it under the skin. No evidence of diabetes in experimental animals was present at this stage. However, removal of the graft caused the symptoms of diabetes to develop immediately. Similar results were independently obtained by Minkowski. It was becoming clear that the internal secretion of the pancreas was pivotal to the pathogenesis of diabetes mellitus

## THERAPEUTIC ADVANCES

- 1900-1915 – Diabetes treatment includes: the “oat-cure” (daily allowance is approximately eight ounces of oatmeal mixed with eight ounces of butter, eaten every two hours), the milk diet, the rice cure, “potato therapy”, opium, and overfeeding to compensate for the loss of fluids and weight

## JEAN DE MEYER (1878-1934)



Jean De Meyer (1878-1934) was a Belgian clinician and physiologist mainly known to diabetologists for coining the term "insulin" thirteen years before this was finally isolated. Jean-Egide-Camille-Philippe-Hubert De Meyer entered the Free University of Brussels in 1897 and qualified with honours in 1905 in addition to taking degrees in botany and physiology. He joined the physiology laboratory at the University of Brussels as an Assistant in 1907 and rose through the ranks to become Professor of Pathology in 1924. Poor health forced his retirement in 1932. His work on the pancreas was conducted over the period 1904-10, and he was awarded a thesis for work on the internal secretion of the pancreas in 1910. The remainder of his career was mainly devoted to cardiovascular physiology, including work on the recently developed technique of electrocardiography

## Notable Events 1908-1911

- **1908** – Zuelzer extracts a pancreatic "substance" and injects it into five diabetes patients. Although sugar in the urine is reduced or disappears, the side effects of treatment are extreme and unacceptable.
- **1909** – de Meyer of Belgium proposes the name "insulin" (Latin: insula, island) for the unknown pancreatic substance.
- **1911** – Benedict devises a new method to measure urine sugar (Benedict's Solution)

## ERNEST SCOTT (1877-1966)

Meanwhile in Chicago, Ernest Scott (1877–1966) experimenting on dogs who had had their pancreas removed or tied off, was also searching for an effective pancreatic extract (Scott 1912). After his laboratory assistant had left him because of the constant presence of flies attracted to sticky puddles of urine in the laboratory, Scott realized that the dogs from whom the pancreas had been removed or destroyed had high levels of sugar in their urine. Further experiments showed that they also had high levels of glucose in the blood.

## ERNEST SCOTT CHICAGO

- Injection of isolated aqueous extracts made from excised pancreases temporarily reduced blood sugar levels and urinary output in the pancreatectomized dogs (alcoholic extracts were ineffective). Scott subsequently left the laboratory, and the head of the laboratory, Anton Carlson, published his thesis for him. The thesis appeared in the *American Journal of Physiology* in 1912, apparently edited to largely discount Scott's discoveries (Scott 1912). Ten years later, Banting came upon Scott's little-known article and repeated his experiments more fully

## Frederick Grant Banting (1891-1941) & Herbert Charlse Best and the dog Marjorie about 1920



## THE NOBEL PRIZE 1923

In 1923, the award of the Nobel Prize for Medicine and Physiology was given jointly to Banting and Macleod. This led to criticism that the Nobel Award Committee had not included Best in the award, but it has been suggested that it was not technically possible to do so because no one had nominated him. Banting, who resented the inclusion of Macleod, expressed his dissatisfaction by sharing one half of his prize with Best. Macleod thereupon shared his prize with Collip.

## THE NOBEL PRIZE 1923

It was extremely unusual for a medical discovery to be honoured in this way so soon after it had been made, and this reflected the significance of this medical treatment. It should be noted that the nomination was followed by protests from both Georg Zuelzer and Nicholas Paulesco, who claimed priority. Paulesco made representations to the French Academy of Medicine, but it was too late since, according to the rules of the Nobel Award Committee, an award once made cannot be reviewed. On a more positive note, had it not been for the discovery of insulin, George Minot would almost certainly not have survived to do the research on pernicious anaemia which led him and William Murphy to be the first American recipients of the Nobel Prize

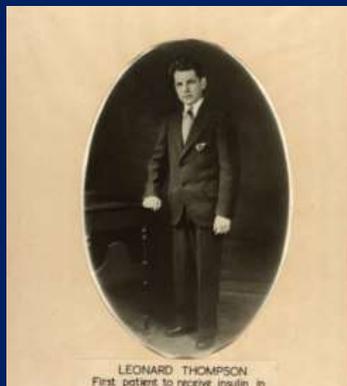
## TWO TONS OF PIG PARTS 1920s



## SORTING INSULIN AT LILLY 1923



Leonard Thompson (1908-1935)  
RECEIVED THE FIRST DOSE OF INSULIN  
7/11/1922  
(1908-1935)



LEONARD THOMPSON  
First patient to receive insulin in

## Elizabeth Hughes, ca. 1923

- Elizabeth Hughes, ca. 1923

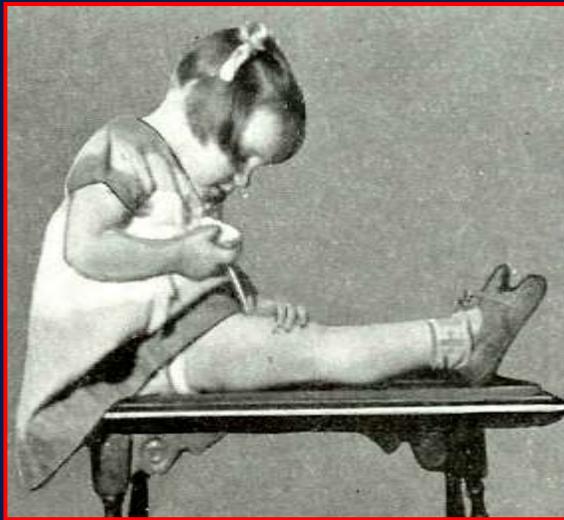


## ELIZABETH HUGHES

- Elizabeth was born on August 19, 1907. Just a few days shy of her 15th birthday, she became one of the first recipients of insulin. Her life was transformed.
- Elizabeth arrived in Toronto from America a frail child, fighting to stay alive just one more day, armed with a hopeful spirit that refused to diminish despite her dire condition.
- It was the discovery of insulin that allowed her to live a long life. She died in 1981 at the age of 73, having had children and grandchildren of her own. Over the course of 58 years, Elizabeth received some 42,000 insulin injections. Insulin made those 58 years possible.

## Before and After

One of the first patients to ever receive insulin therapy



# AUGUST KROGH



# AUGUST AND MARIE KROGH



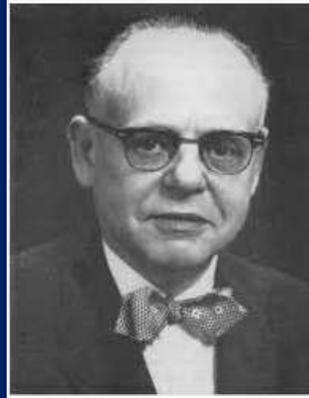
In 1922, August Krogh of Denmark, winner of the Nobel Prize for his studies of capillaries, was lecturing in the United States, accompanied by his wife Marie, who had recently been diagnosed with diabetes. Krogh and his wife were informed by the famous diabetologist of the time Eliot P. Joslin about a new diabetes treatment developed in Toronto by Banting's group. Marie and August Krogh decided to visit Toronto and stayed as John McLeod's guests. After return to Denmark, Krogh, with H.C. Hagedorn, founded Nordisk Insulin Company, a not-for-profit concern that, together with Novo Company, was responsible for making Denmark the main insulin-producing country outside of the United States. We now have Novo Nordisk.

## HANS CHRISTIAN HAGEDORN



Landmark article Jan 18, 1936:  
Protamine insulinate. By H.C.  
Hagedorn, B.N. Jensen, N.B. Krarup,  
and I. Wodstrup

## PAUL HERBERT KIMMELSTIEL



## PAUL HERBERT KIMMELSTIEL (1900-1970)

- **Biography of Paul Herbert Kimmelstiel**
- **Paul Herbert Kimmelstiel** was born to a Jewish merchant family in Hamburg. He studied medicine at the universities of Hamburg, Kiel, Munich, Bonn, and Tübingen. He received his medical doctorate in 1923, and in 1930 he was promoted associate professor at the department of pathology at Hamburg-Eppendorf. However, in 1933 he fled Nazi Germany and immigrated to the USA with his wife and two small children.
- Kimmelstiel obtained a position at the Harvard Institute of Pathology under George Kenneth Mallory (born 1900). Here he met Clifford Wilson, then a prominent visiting professor, and together they described the intercapillary changes of the glomerulus in diabetes mellitus.
- Kimmelstiel was professor of pathology in Milwaukee 1958-1966, and for the last four years of his life he held the same tenure at the University of Oklahoma

## RT Woodyat Chicago

In the USA, RT Woodyat had introduced fasting management of diabetes, a method much followed over succeeding years, and in 1917, Frederick Allen published an important clinical study entitled: "Total dietary regulation in the treatment of diabetes". He suggested ruthless starvation until glycosuria disappeared, followed by very gradual reintroduction of food until the limits of tolerance were reached. Prolongation of life was at the expense of great suffering by the malnourished patients. Elliot Joslin, who contributed greatly to the practical management of people with diabetes, adopted many of Allen's calorific and dietary restrictions (Joslin 1917)

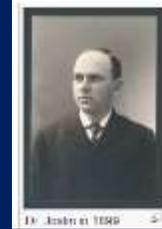
### Frederick Madison Allen (1879.1964)



1916 - Allen promotes a strict diet regimen, which is soon widely adopted. Allen believes that the diabetic's body cannot use food, so he limits the amount of food allowed patients. Patients were admitted to the hospital and given only whiskey mixed with black coffee (or clear soup for teetotalers) every two hours from 7 am to 7 pm. This diet is followed until there is no sign of sugar in the urine - usually 5 days or less. A strict diet follows. Outcomes are better than ever seen before for those with Type 2 diabetes. Unfortunately, those patients with Type 1 commonly die during the treatment, likely from starvation. A few young people do survive and become the first insulin users.

## DR. ELLIOTT JOSLIN (1869-1962)

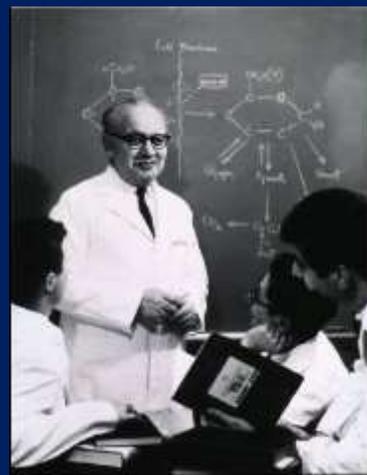
Walter Proctor Joslin, M.D. (6 June 1869 – January 1962) was the first doctor in  
 Founder of the Joslin Diabetes Center, Dr. Joslin was involved for seven decades in most every aspect of diabetes investigation and treatment, save for the fact that he did not discover insulin. Following the Toronto group's blockbuster discovery of insulin in 1921, and the group's disbanding several years later, Joslin became effectively the Dean of diabetes mellitus. In the mid 1920s, Joslin, in his mid 50s, took the reigns as the world spokesman for the "cause of diabetes." He was the first to advocate for teaching patients to care for their own diabetes, an approach now commonly referred to as "DSME" or Diabetes Self-Management Education. He is also a recognized pioneer in glucose management, identifying that tight glucose control leads to fewer and less extreme complication



## RACHMIEL LEVINE (1911-1998)

Mechanism of Action of  
 Insulin

RACMIEL LEVINE 1949



## PROFESSOR HARRY KEEN (1925-2013)



## THE BEDFORD STUDY

- **The Bedford Study**
- This landmark study, undertaken by Harry Keen with his long-term colleague John Jarrett, set out to examine whether people with impaired glucose tolerance have a similar risk of cardiovascular disease as those with frank diabetes. Over a 10 year follow-up period it emerged that mortality in borderline diabetes was intermediate between that seen in controls and those with diabetes. Cardiovascular risk was more marked in women than men in the intermediate group, and blood pressure and smoking were confirmed as important additional risk determinants

## LORD JOHN BUTTERFIELD (1920-2000)



## LORD JOHN BUTTERFIELD

- In 1962, John's broad interest in human populations, combined with his scientific flair, gave birth to the Bedford diabetes survey. The department moved en masse to the Swan hotel, Bedford, where, with the assistance of the enterprising medical officer of health, the late Dr Clive Sharpe, the local Round Table, Boy Scouts, Women's Institute and moribund civil defence organisation, we screened the population for undiagnosed diabetes.
- During an unforgettable weekend, urine samples were collected from the front doors of more than 20,000 adult inhabitants and tested for sugar by a production line of doctors, nurses, technicians and students.

## LORD JOHN BUTTERFIELD

- We spent the next six weeks doing blood tests on all the positives, and, providentially, on a carefully constructed random sample of the population as a whole. History does not relate whether the health of Bedford took a turn for the better, or worse, but what was learnt from that operation had a decisive influence on the prevailing views of diabetes, and led to internationally-accepted diagnostic standards for the disease, which are still in use today.

## DR. ROBERT DANIEL LAWRENCE (1892-1968)

Dr. Lawrence was a British physician at King's College Hospital, London. He was diagnosed with diabetes in 1920 and became an early recipient of insulin injections in the UK in 1923. He devoted his professional life to the care of diabetic patients and is remembered as the founder of the British Diabetic Association. *I had the pleasure of meeting him in 1962.*



Robert Daniel Lawrence

## POST INSULIN DISCOVERY

- Over the years, insulin purification methods improved and new insulin formulations were developed. Protamine–zinc insulin, a long-acting insulin, was introduced in the 1930s; Neutral Protamine Hagedorn (NPH) was introduced in the 1940s; and Lente series of insulin in the 1950s. Globin Insulin was short-lived in the early 1940s.

## NOBEL PRIZES FOR DIABETES RELATED RESEARCH

**Table 1.** Nobel Prizes for Diabetes-Related Research.

Year	Category	Recipient	Contribution
1923	Medicine	F.G. Banting and J.J.R. Macleod	Discovery of insulin
1947	Medicine	C.F. Cori and G.T. Cori	Discovery of the course of the catalytic conversion of glycogen
1947	Medicine	B.A. Houssay	Discovery of the role of hormones released by the anterior pituitary lobe in the metabolism of sugar
1958	Chemistry	F. Sanger	Work on the structure of proteins, especially insulin
1971	Medicine	E.W. Sutherland	Discoveries concerning the mechanisms of action of hormones
1977	Medicine	R. Yalow	Development of radioimmunoassays for peptide hormones
1992	Medicine	E.H. Fischer and E.G. Krebs	Discoveries concerning reversible protein phosphorylation as a biologic regulatory mechanism

## Insulin Changes at a Glance - Decade Development in insulin therapy

- 1920s Regular insulin
- 1930s Long-acting (PZI)
- 1940s Intermediate-acting (NPH)
- 1950s Lente insulins
- 1960s Purified insulins
- 1970s Recombinant human insulins
- 1980s Insulin analogs
- 1990s... Nasal, oral insulins, and newer delivery devices; the search continues

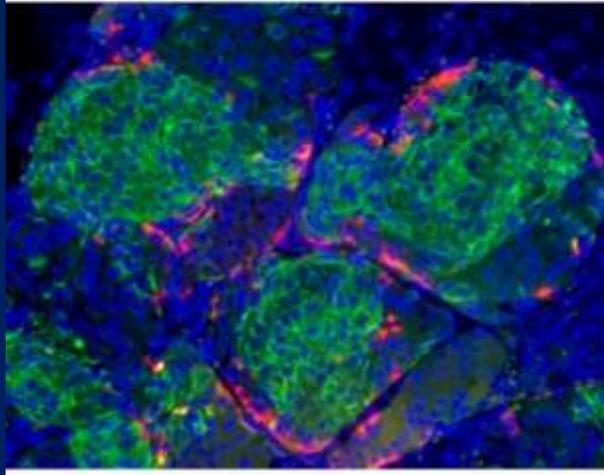
# THE PRESENT

## THERAPEUTIC ADVANCES

- 1922 Insulin
- 1946 Sulfonylureas
- 1995 Metformin
- 1996 Insulin Analogs
- 1997 Thiazolidinediones
- 2005 GLP Receptor Agonists
- 2006 DPP 4 Inhibitors
- 2013 SGLT 2 Inhibitors

## A LOOK INTO THE FUTURE

## STEM CELLS TO BETA CELLS



## COMMENT ON STEM CELLS TO BETA CELLS

- Richard A. Insel, MD, chief scientific officer of the JDRF, a funder of Melton's work, said the "JDRF is thrilled with this advancement toward large scale production of mature, functional human beta cells by Dr. Melton and his team. This significant accomplishment has the potential to serve as a cell source for islet replacement in people with type 1 diabetes and may provide a resource for discovery of beta cell therapies that promote survival or regeneration of beta cells and development of screening biomarkers to monitor beta cell health and survival to guide therapeutic strategies for all stages of the disease

## RECOMMENDED BOOKS

- 1. PAPASPYROS NS: The History of diabetes. Georg Theme Verlag. Stuttgart : 1964
- 2. ENGLEHARDT DV: Diabetes its medical and cultural history. Springer-Verlag. Berlin : 1989
- 3. BINDER C: Diabetes and Denmark. Gad. Denmark : 2007
- 4. BLISS M: The Discovery of Insulin. University of Chicago Press. Chicago : 1982