Diabetes Through the Ages

Dr. Michael Hall

Vice President, Diabetes UK and Honorary Consultant to the International Diabetes Federation – European Region

In antiquity

• Aretaeus of Cappadocia in the second century AD gave the most complete description of the condition and named it “diabetes” – the Greek word for “siphon”

• He described it as “a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine ... and the outpouring is profuse and without limit... the development of this disease is gradual, but short will be the life of the man in whom the disease is fully developed: Emaciation proceeds quickly and death occurs rapidly”

Searching for the cause

• Indian physicians described the sweetness of the urine of these patients but not until 1776 did an Englishman, Matthew Dobson, identify that the sweetness in the urine was due to sugar.
The islet cells in the pancreas
Paul Langerhans identifies the islets

But, what did they do?

Edouard Laguésse
• Edouard Laguésse & Paul Langerhans' son, Archibald:
  – Perhaps these cells help to regulate digestion
Oscar Minkoski and J. von Mering

- In 1889, two medical researchers in Europe, Mering & Minkoski, working on fatty acids, discovered that the removal of the pancreas of a dog resulted in it urinating a lot and subsequently a chance finding by their laboratory assistant noted sugar in the dog’s urine
- The dog had developed diabetes

Link between the pancreas and diabetes

- So the link between the pancreas and diabetes was now established
- Doctors and scientists began to focus on the pancreas, the islets and their secretions and the effect these had on carbohydrate metabolism and blood sugar

Sir Edward Albert Sharpey-Schafer

- 1916: Sharpey-Schafer - “insuline”
- BUT nobody had been able to prove its actual existence

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Linking the pancreas to diabetes

- With the link between the pancreas and diabetes established there was an expectation that the condition might be amenable to treatment.
- There were many attempts using various pancreatic preparations to treat patients in the terminal phase of the disease.
- Doctors were often under extreme pressure from desperate parents & all sorts of remedies were attempted to slow the inevitable deterioration of children dying of diabetes.
- In 1894, two Bristol doctors even transplanted a sheep’s pancreas into a young boy dying of diabetes; sadly the outcome was not altered.

In 1901 Eugene Opie
a young doctor at John Hopkins University, Baltimore, USA

- Confirmed the link between the Islets of Langerhans and diabetes.
- "Diabetes mellitus... is caused by destruction of the islets of Langerhans and occurs only when these bodies are in part or wholly destroyed.”

1906, George Ludwig Zuelzer

- Prepared pancreatic extracts which were partially successful in treating diabetic dogs; But, due to lack of support was unable to continue this work.
1911, Ernest Lyman Scott

- When preparing pancreatic extracts using alcohol and filtration and various other processes found an extract which when used on four diabetic dogs, diminished sugar excretion … he said

Ernest Lyman Scott

- “If one dared to say it, the dogs seemed even brighter for a time after the injection than before it”

Scott concluded:

- There is an internal secretion of the pancreas controlling the sugar metabolism
- By proper methods this secretion may be extracted and still retain its activity
- Sadly, his supervisor did not share these views and caused the conclusions to be rewritten in a much more cautious tone
- BUT: Scott did discuss his ideas with J.J.R. Macleod, then the Professor at Western Reserve
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Nicolae Paulescu

- 1911-13 research on the role of the liver and the pancreas
- He developed an aqueous pancreatic extract, when injected into a diabetic dog it had a normalising effect on blood sugar levels
- BUT this important work – interrupted by the 1st World War

Paulescu publishes his findings

- From April 24 to June 23, 1921, Paulescu published papers at the Romanian Section of the Society of Biology in Paris:
  - The effect of the pancreatic extract injected into a diabetic animal by way of the blood
  - The influence of the time elapsed from the intravenous pancreatic injection into a diabetic animal
  - The effect of the pancreatic extract injected into a normal animal by way of the blood
  - An extensive paper on this subject - Research on the role of the pancreas in food assimilation - was submitted by Paulescu to the Archives Internationales de Physiologie in Liège, Belgium, and was published in August 1921

The role of chance

- 1889 – Minkoski’s laboratory assistant
- 1901 – Opie, didn’t follow up the finding that the destruction of islet cells led to the development of diabetes
- 1906 – Zuelzer actually successfully treated diabetic dogs with an extract of the pancreas, but the work ceased through lack of support
- In 1911 – Scott drew very interesting conclusions from his research on similar extracts but his supervisor did not encourage further investigation
- AND finally, Paulescu’s promising work was curtailed by the 1st World War
Macleod & chance

- Macleod was a distinguished physiologist interested in carbohydrate metabolism
- He had met Scott and listened to his ideas on the effects of pancreatic extracts on diabetic dogs
- He was renowned for encouraging young researchers and listening to their ideas
- He knew Sharpey-Schafer and his view that the islets probably produced an internal secretion and that he had even suggested it should be called insuline
- And finally, he was able to see the possibility in furthering these ideas through the research project suggested by Frederick Banting

Treatments before insulin

- Dr. Frederick Allen of New Jersey & Boston – strictly enforced starvation, calorie intake often less than 10% of the normal diet

Sam Davidson

- Aged 7 when diabetes diagnosed
- Diet of ground up cabbage & moss
- Tincture of opium to suppress diet
- After two years, insulin became available and he went on to train to become a doctor, a surgeon
- And retired in his 80s
- … A lucky man!!!
Treatments before insulin (2)

- Dr. Elliott P. Joslin — one of the first U.S. doctors to specialise in diabetes
- Valued dietary restriction and exercise but also the importance of educating patients and their families
- He introduced nurses in the education process
- The Joslin Diabetes Center, Harvard, Boston

The two key players in 1920 in Canada

J.J.R. Macleod
&
Frederick Banting

J.J.R. Macleod

- J.J.R. Macleod took his medical degree with honours in 1898
- His career quickly progressed and only 5 years after qualifying he was appointed Professor of Physiology at Western Reserve University
- He was much sought after and admired
Frederick Banting

- Frederick Banting qualified in medicine during WWI
- After the war he wanted to become a surgeon and developed a special interest in orthopaedics
- He set up a general practice in London, Ontario
- He helped Professor Miller from Western Reserve University in his laboratory

The start of Banting’s research adventure

- Banting was preparing a lecture on CBH metabolism
- Not a subject he knew much about
- He had never treated a patient with diabetes
- He chanced upon an article about a case in which the formation of a pancreatic stone had obstructed the pancreatic duct and caused the digestive juice producing cells to die but left the islet cells intact …

Banting’s great idea

- He wrote: I was disturbed and could not sleep. I thought about the lecture and the article and I thought about my miseries and how I would like to get out of debt … about two in the morning, after the lecture and the article had been chasing each other thro’ my mind … the idea occurred to me, that by the experimental ligation of the duct and the subsequent degeneration of the pancreas, that one might obtain the internal secretion free of the external secretion… I got up and wrote down the idea…
In summary – Banting’s idea

- Try to isolate the internal secretion of the pancreas by de-activating that part of the gland which produces the external secretion
- Then use this internal secretion to try and relieve glycoeuria/diabetes*

*The newer notion of relieving hyperglycaemia did not come to him at the time

He was excited by his idea!

- Professor F.R. Miller at Western Reserve
- The wedding in Toronto next weekend
- The meeting with Macleod was set up for the Monday after the wedding: 7th November 1920

What was “decided” at the meeting

- Macleod: “Dr. Banting had only a superficial textbook knowledge of … what had been done on the effects of pancreatic extracts on diabetes...”
- Banting: “…Macleod sat back … closed his eyes …began to talk. He thought this might be the means of getting rid of the external secretion … never tried before … it was worth trying … even negative results would be of great physiological value…”
How did the meeting really go?

- In spite of what appears to be a disconnect between the two men; Macleod did offer to help - he would provide laboratory space and an assistant
- SO, in retrospect, the meeting must have gone better than either thought

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To do or not to do…

- Banting returned to London, Ontario
- He couldn't stop thinking of his "idea" and he set about winding up his general practice and moving to Toronto
- He arrived in the Spring of 1921

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Charles Best

- Two medical students, Charlie Best and Clark Noble
- Best and Noble tossed a coin to see which would assist Banting first; Best won
The research plan involved using two batches of experimental animals - dogs

The first batch of dogs:
• Would have their pancreatic ducts tied, thus causing the cells producing the external secretion to atrophy, leaving the precious islet cells active and secreting the “internal secretion”
• The dogs would then be killed and pancreas removed
• The “internal secretion” would be harvested, that is, extracted and purified from these pancreas

The second batch of dogs:
• Would have pancreas removed, thus making them diabetic
• The samples of the “internal secretion” obtained from the first batch of dogs would then be tested on these second animals, who would be monitored, their blood glucose measured and observed – to see if their diabetes could be controlled

Difficulties

• Unfortunately, the first dog died from an anesthesia overdose on the very first day of the experiment
• Dogs died from infection and surgical error – pancreatic surgery is not easy and especially difficult in relatively small animals
• Dogs were expensive & difficult to obtain

But optimism ruled…

a glimmer of success...

• Banting reported to Macleod:
  – The extract invariably causes a decrease in the percentage of blood sugar and in the excretion of sugar in diabetic dogs
  – It is active at least for four days if kept cold
  – It is destroyed by boiling
  – Extracts of spleen and liver at least, prepared under similar conditions, have no such action
  – The clinical aspects of the animals are improved by the extract
But in fact

- Banting and Best were still having difficulties, ligating pancreatic ducts was difficult, the dogs often died due to infection or surgical error and dogs were difficult to come by.
- They began to look for other options which might reduce the need for dogs:
  - Were there other sources of pancreas where there was little or no external secretion?
  - What about the pancreas of the foetus, no active digestive process and hence perhaps little or no external secretion.

And another idea...

- Banting, remembering his parents and the farm
- Cattle were often sent to slaughter when in calf
- In November 1921, he and Best visited a nearby slaughter yard and quickly acquired calf foetal pancreatic material
- They set about preparing extracts of these and using them on diabetic dogs
- The results seemed excellent, they no longer needed to carry out the difficult duct ligation technique.

Progress...

- Matters quickly moved forwards
- Banting even tried a small dose of extract on himself, without harmful effect
- They persuaded Macleod that their extract should be tried on a human diabetic sufferer
- Macleod wanted to see a purer extract prepared and he brought Collip in to do this.
James B. Collip

- From Edmonton
- On sabbatical working on tissue extracts in the Physiology Department in Toronto
- Refining the pancreatic extract
- This immediately upset Banting who felt he and Best alone should handle “their” extract

Publication!

- Macleod also wanted news of the findings published:
  - “The Beneficial Influences of Certain Pancreatic Extracts on Pancreatic Diabetes”
  - Was presented to the American Physiological Society at a meeting at Yale University on 30th December 1921
  - Authors: Banting, Best, Collip, Macleod & Noble,
    Journal of the American Society of Physiology

Banting pushes for a clinical trial

- At the same time, Banting had been pushing for a clinical trial
- A pancreatised dog, Marjorie, had survived many weeks on injections of their extract
- He and Best had already tested extracts on themselves without harmful effect
- And just before Christmas they had given a dose of the extract by mouth to Banting’s classmate, Jo Gilchrist, who had been diabetic since 1917 and survived on the Allen Starvation regime; it had had no untoward nor beneficial effect
- Macleod agrees to speak with his colleague, the Professor of Medicine

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A clinical trial?

- Duncan Graham, Professor of Medicine, although agreeing with Macleod to allow a clinical trial, would not allow Dr. Banting into the hospital ward as “he was not currently in practice” and had “no experience to experiment on my patients”
- He said to Banting: “What right have you to treat diabetics? How many have you ever treated?”

Leonard Thompson
The first person to receive insulin

- Thompson admitted 2nd December 1921 under the care of Dr. Walter Campbell who ran a diabetic clinic under the supervision of Professor Graham
- Thompson had been on the Allen Starvation regime for over 2 years and was now in the terminal phase
- His father agreed to let the hospital try Banting and Best's new pancreatic extract for the first time

Collip worked furiously to prepare a purer extract
- Ten days later it was ready
- Thompson was given it
- His blood sugars gradually returned to normal and his diabetic symptoms began to disappear
- The news spread rapidly, inspiring people with diabetes and their families to write letters to Banting asking for urgent treatment
- Thompson lived another 13 years using insulin, dying of pneumonia aged 27 – thought to be a complication of his diabetes
Quarrels and rewards

- Disagreements in the "team"
- Dr. Banting treats his own patients
- Professor Macleod refers to him as my "clinical colleague"
- Further publications

The University of Toronto set up the Connaught Laboratory to manufacture insulin

A famous case

- It was to Dr. Allen that the eminent United States politician and lawyer, Charles Evans Hughes, turned when his daughter Elizabeth was diagnosed with diabetes in 1919, at age 11
- Elizabeth was an intelligent, cheerful little girl; She had a great interest in bird watching
- On Dr. Allen's diet her weight fell to 65 pounds, then 52 pounds, and then, after an severe episode of diarrhoea in early 1922, to 45 pounds
- By then she had survived three years, far longer than expected
- And then her mother heard the news: insulin had finally been isolated in Canada
Elizabeth Hughes

“My dear Dr. Banting: I am very anxious to know more of your discovery,” wrote Antoinette Hughes, going on to describe Elizabeth’s condition: “She is pitifully depleted and reduced.”

“Unspeakably wonderful”

• Charles Evans Hughes had by that time temporarily left the Supreme Court, and was serving as secretary of state to the United States President
• Dr. Banting, unimpressed, replied “no, sorry, no insulin available”
• In fact, the team was having difficulty making enough for more than a handful of patients
• A few weeks later, Dr. Banting changed his mind
• Elizabeth traveled to Toronto and the lifesaving injections were started
• She described the results of the treatment as “unspeakably wonderful”
• For many children around the world, without her connections, the anxious waiting continued whilst all those involved in Canada fought to try and distribute the limited amounts of insulin as fairly as possible

Manufacturing

• The Connaught Laboratories had difficulty in developing a reliable process and Macleod was able to persuade Eli Lilly to become involved
• Eli J. Lilly and Company, then of Indianapolis, won the right to mass-produce insulin; A partnership negotiated among academia, individual physicians and the pharmaceutical industry
Insulin around the world

- Generous terms from Toronto allowed the manufacture of insulin to be quickly and reliably produced in Canada, the USA, Great Britain and Denmark

Dr. R. D. Lawrence

- In Florence, Italy, a young British doctor was approaching the final stages of diabetes
- A message from a friend in King’s College Hospital, London “come back at once, I think we’ve got something”
- He came back, was treated with insulin and became one of the leading doctors to treat people with diabetes
- The Line Ration Diet
- The Carbohydrate Content of Food (1929)
- He and one of his patients, H. G. Wells, later founded the British Diabetic Association

Dr. Ernesto Roma

- In Portugal, in 1926 Dr. Roma founded the APDP – the Diabetes Association of Portugal
- It aimed to provide insulin to those who could not afford it
- APDP is now the oldest diabetes association in the world
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1923
The Nobel prize for physiology or medicine

Honours

• Paul Langerhans
• Oscar Minkowski’s & von Mering’s laboratory assistant
• Eugene Opie
• George Zuelzer
• Ernest Scott
• Nicolae Paulescu
• Drs. Allen & Joslin

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C. H. Best (Left) and F. G. Banting ca. 1924

Laboratory 221 in 1929, much as it was when Frederick Banting and his assistant Charles Best conducted their research and ultimately discovered insulin

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Insulin was recognised and described in ancient times.

Only in the 18th century it was confirmed that the urine is loaded with sugar.

Another 100 years were to pass before the link was made to the pancreas and the islet cells.

Another 50 years before this "unspeakably wonderful" life-changing hormone was isolated and purified.

All around the world people with diabetes, especially children and their parents, now had hope.

It is now over 90 years since insulin was available to the first patient.