Is Insulin a Specialty Medication?

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- I have no conflict of interest relating in the material covered today
- I do not serve on any speaker bureau
- I do not have any personal grants concerning the area of discussion today
- Some lame jokes included
- Lots of brand names mentioned, but no financial interest in any of them
- Promise: no Kaplan-Meier Mortality curves

Objectives

- Discuss the history of insulin
- Discuss insulin development and how it laid the framework for drug delivery systems and specialty medications
- Discuss Banting and Best discovery of insulin and the intimate details of involving industry in the process
- Define a specialty medication

Is Insulin a Specialty Medication?





INSULIN THERAPY FLAME OF HOPE

A must read!!





ISBN: 987-0-312-64870-1

About Elizabeth Hughes and the Discovery of insulin

Flame of Hope



- A flame of hope was lit by Her Majesty the Queen Mother in 1989 as a tribute to Dr. Frederick Banting and all the people that have lost their lives to diabetes.
- The flame will remain lit until there is a cure for diabetes.
- When a cure is found, the flame will be extinguished by the researchers who discover the cure.
- The flame is located at Sir Fredrick Banting Square in London, Ontario, Canada beside the Banting House National Historic Site of Canada.

Flame of Hope 🐸





Dr. Frederick Banting



- He was more than a scientist
- He was committed to his country
- He fought in wars
- His life ended during WWII days as he boarded a plane to England on a secret mission to discuss use of chemical weapons
- The plane crashed, he was 49 years old

A Discovery Beyond Discoveries

- It was the first "cure" of a disease (type I DM)
- Diabetes connected the industry into academic medicine
- It's a lesson in compassion and persistence
- On the grave of Eli Lilly
 - "To the glory of God with thanksgiving for the wonder of life."

- Type I diabetes in early 20th century carried a diagnosis of poor prognosis
- After diagnosis, patients had an expected life span of a mere 11 months, filled with suffering and then death.
- The Egyptian papyrus in early 1550 BC describes a treatment of boiling an assortment of bones, wheat, grain and earth for 4 days – yummmm!

- The name "diabetes" was coined by a Greek physician (Aretaeus of Cappadocia) in the 2nd century – the word comes from the Greek word sieve because of the symptoms of thirst and urination
- Matthew Dobson of England in the 18th century determined that the sweet sticky substance in diabetic urine was sugar
- The Father of Physiology was Claude Bernard. He postulated that the problem was the pancreas. This lead to a number of experiments

- An unrecognized discovery in 1889 was a dog surgery by Oskar Minkowski and Joseph von Mering (Germans) – they removed the pancreas and the dog had all the symptoms of diabetes
- Paul Langerhans (German) found the clusters of cells in the pancreas but did not investigate the purpose
- Edouard Laguesse of France suggested that these cells lower blood glucose and he called them islets of Langerhans

- In the early 1900's Jean de Meyer of Belgium named the mysterious substance from the pancreas "insulin" after the Latin word island (islet) – but all this was speculation
- It would be years before the insulin was isolated and produced
- Until then the children were institutionalized and placed on a strict "starvation treatment"
 - Dr. Fredrick Allen
 - > 1914-1922 is known as the "Allen years"
 - His hope was to increase life span in hopes of a cure

Dr. Diabetes, as he was known

- The approach was to find the minimal amount of food to sustain life
- "The cure is worse than the disease" fits
- "To starve is to survive"
- "Less food, the more life"
- Dr.Allen tells a family that he can extend their time, the mothers comments, "at what cost to my daughter", "is a year of agony better than 2 happy months?"

Physiatric Institute







Dr. Allen

Before Insulin

After Insulin

"To starve is to survive"



Dr. Banting

He was in the Class of 1917, University of Toronto Medical School

- The class finished a year early to get the stue war (WWI) at the cry of England
- After the war he opened a practice in London, Ontario
- He made most of his money handing out prescriptions for alcohol to alcoholics during the prohibition. His first month income was \$4

It began with a boring article!

- It all start with reading an article that was suggested for him to read from a doctor (Dr. C.L. Starr) in the local hospital
- Banting was frustrated (does he marry or not?)
- It was I AM in the morning on Halloween 1921
- It was a long paper, I2 pages
 - "The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis"
 - November issue of Surgery, Gynecology, and Obstetrics

It persisted with an idea?

- He suffered through the article saying, "I pity the poor %*&*@ in that field" speaking of endocrinology!
- ▶ He dozed off only to open his eyes to an idea he wrote it down
- "Diabetes ligate pancreatic ducts of dogs. Keep dogs alive till acini degenerate leave Islets. Try to isolate the internal secretion of these to relieve glycosurea"
 - Not a new idea, been tried before, but few persisted
 - The idea lead to <u>persistence</u> that lead to the discovery

Write down ideas!







Persistence leads to reality!

- He ended up at University of Toronto with an idea, an opportunity to have a dusty old Frankenstein lab for the Summer and a graduate student Charley Best
- All under the direction of the department chair Dr. John Macleod (Banting's arch nemesis)
 - Dr. Macleod introduced Banting at a presentation. Macleod essentially presented the paper in his introduction and use the term "we" in the experiments. The real war began!
- They did many experiments on dogs and removed the pancreas and made an extract they called isletin
- They intentionally overdosed the dogs to see if the sugar would drop below normal – it did!

A cure was on the way!

- The original paper of the discovery was generated from the Summer work and was accepted for presentation at the 34th Annual Physiological Society in 1921
- It was the last presentation on a Friday
- At the presentation was Dr. Elliott Joslin, Dr. Fredrick Allen, Dr. Alec Clowes, research director of Eli Lilly

Eli Lilly Products of 1920

- Charcoal Lozenges for indigestion
- Cape Aloes for constipation
- Passolaria for insomnia and anxiety
- Liquid Blaud for anemia
- Elixir #63 (catnip and fennel) for colds, headaches, colic and fever
- Eli, the grandson John Lilly said that the future of pharmaceutical manufacturing was in the fundamentals of biologic research

Industry vs. Academia

- For years Dr. Clowes tried to get Dr. Banting and Macleod to let his company manufacture there pancreatic mixture
- They were very suspicious of the industry in that day besides University of Toronto had it's own manufacturer – Connaught Labs
- They were very concerned with a patent because they felt it was in direct violation of the Hippocratic oath.
- Best and Collip (chemist) got the patent because they had never taken the oath and then assigned the rights over to University of Toronto for \$1

Industry vs. Academia

- Separation of church and state
- Separation of earth and state
- Separation of university research and commercial enterprise
- The problem became a moral one the high ground of seperation would be at the expense of children dying – they needed mass production
- Eli Lilly and Company was ready Dr. Clowes fueled the collaboration
- All Mr. Lilly wanted was a brand name to ensure the public of the quality - he called it lletin after isletin, the original Banting formula

Boo!! Yea!!

Sorry, no picture – says a lot, huh!

The Real Hero

- Mr. Austin Brown of Lilly and Company
- He was the one put in charge of finding 2,000 pounds of beef or pork pancreas glands weekly ⁽²⁾
- He traveled all over America, talking to all farmers and meatpackers
- They got suspicious and had to change some of their procedures to get him the pancreas glands
- He had to tell them that for every pound Lilly got, a child's life would be saved! He became a salesman!

Dr. Elliott Joslin

- In America as Lilly scaled up production, Mr. Joe Lilly, Sr. allowed Dr. Elliott Joslin of Boston to be the first to administer Lilly insulin in the America
- Dr. Joslin called Ezekiel 37 the "Banting Chapter" of the Bible
 -and the valley of the bones came to life
 - p. 196 in book
- Joslin died at the age of 92 he keep a registry of the patients he treated with diabetes
 - 58,784 names in 80 volumes

The Arch Nemesis.....

Secret shhhhhhh

- Dr. Macleod secretly gave the insulin formula to Dr. August Krogh of Copenhagen – his wife had diabetes and he was a Nobel Prize winner for Physiology – he came over to investigate the discovery
- \blacktriangleright He is the founder of Nordisk labs in Denmark $\textcircled{\odot}$
- His partner was Dr. Hagedorn
 - Discovered protamine from fish sperm to slow the action of insulin
 - Cut the shots in half
 - Connaught labs added the zinc which further slowed the action

And the story continues.....

- It still took 2.5 tons of pancreas glands to produce 8 oz of insulin in 1948
- This paved the way to biotechnology and recombinant insulin in 1982 and the specialty drugs we have today
- Insulin took 2 years and \$2.5 million (in today's dollars) to get it to market
- Today it takes 10 to 15 years and \$1 billion to get a biologic to market



The Companies & The Drugs

Novo Nordisk

- Novolin
 - Novolin N (NPH)
 - Novolin R (regular)
 - Novolin 70/30
 - Novolog (aspart)
 - Novolog mix 70/30
 - Novolin L (lente)
 - Levemir (detemir)
 - Tresbia (degludec)
 - Ryzodeg 70/30
 - degludec/log

-Basaglar® (glargine)-

(Lilly/BI) 5-3 ml KwikPen

<u>Lilly</u>

Humulin

■Humulin N (NPH)

Humulin R (regular)

■Humulin 70/30, 50/50

Humalog (lispro)

Humulin L (lente)

■ Humalog Mix 75/25

Humulin U (ultralente)

Aventis

Lantus (glargine)

Toujeo (glargine, 300 units/ml)

□Apidra (glulusine)

<u>Wal-Mart</u>

ReliOn N (NPH)ReliOn R (regular)

Yikes-----

•ReliOn 70/30

Insulin Glargine (Toujeo®)

- Basically Lantus in a <u>300 unit/ml</u> formulation
- I:I conversion from other basal insulin
- Twice daily NPH use 80% of total daily NPH dose
- Insulin naïve 0.2 units/kg
- Titrate every 3-4 days
- SoloStar® 1.5 ml pen (3 for \$336) 450 units



*You will not see the plunger until you have injected a few doses

Degludec (Tresiba®)

Degludec

 Addition of hexadecanedioic acid to lysine at the B29 position allows for the formation of multi-hexamers in subcutaneous tissues and long activity

Ultra long-acting

- Last 40 hours while Lantus last up to 24 hours
- May need less dose can use once daily
- Can mix with short-acting insulins
 - Ryzodeg® 70/30
 - Not approved by FDA in 2013 awaiting additional cardiovascular data



Degludec (Tresiba®)

- Any time of day dosing
- Can last 8 weeks out of frig
- Flextouch, each 3 ml pen
- U-100 (5 pens, \$460)
 - I 500 units total
- U-200 (3 pens, \$550)
 - I 800 units total
- U-200 can deliver up to 160 units at a dose
- There is also a new Humalog 200 units/ml pen



Diabetes Care 2016;38(S1):52-9



more flexible

less flexible

Inhaled Insulin (Afrezza®)

- New inhaled insulin is FDA approved
- MannKind Corp is the maker and is seeking a potential partner to market the drug.
- It has been in development for more than 20 years
- FDA is still concerned about lung function and lung cancer so post-marketing research will be ongoing.
- It is not recommended in smokers, COPD, asthma patients.



Inhaled Insulin (Afrezza®)

- Human insulin
- Similar to "log" insulin
 - Onset 15 to 30 min
 - Peak I hour
 - Duration 2.5 hours
- Administer before a meal
- 4 unit (blue), 8 unit (green) cartridges
- NEW 12 unit cartridge (yellow)

\$226.06/90 4-unit cartridges plus 2 inhalers
\$252.33/60 4-unit cartridges plus 30 8-unit cartridges plus 2 inhalers
\$278.59/30 4-unit cartridges plus 60 8-unit cartridges plus 2 inhalers

Dosing

Injected Mealtime	AFREZZA® Dose	# of 4 unit (blue) cartridges needed	# of 8 unit (green) cartridges needed
up to 4 units	4 units		
5-8 units	8 units		
9-12 units	12 units	+	
13-16 units	16 units		
17-20 units	20 units	+	
21-24 units	24 units		



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