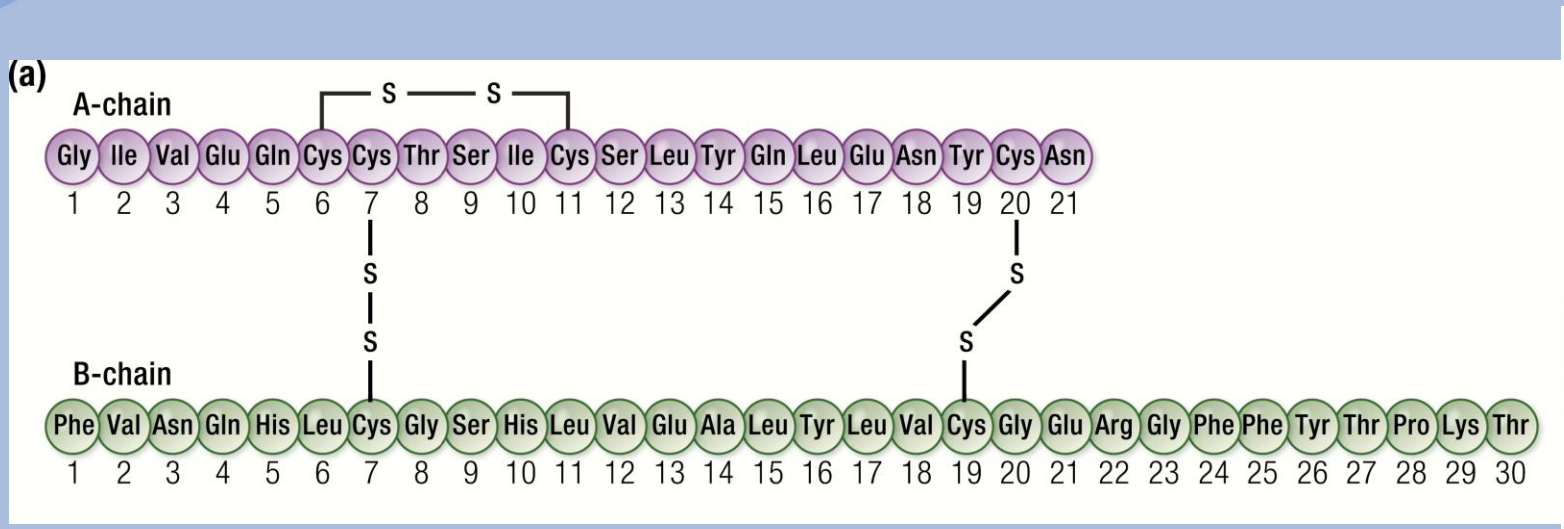
# One Hundred Years of Insulin Therapy: Why, When, and How?

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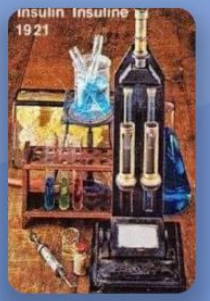
**Chief, Endocrinology, Diabetes and Metabolism Section**
**VA Caribbean Healthcare System**

Sociedad Puertorriqueña de Endocrinología y Diabetología 1976




100 Years of Insulin Therapy: A long Successful Path

Disclosure:

# No Conflicts of Interest to Disclose

This presentation is intended for educational purposes only and does not replace independent professional judgment.

I am expressing my own views based on my reading, analysis and interpretation of the scientific information.

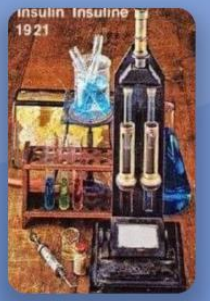
I am a member of SPED and a Federal Government employee
but I am **not** speaking in representation of or presenting the views of the
Veterans Administration,
Puerto Rican Society of Endocrinology and Diabetes,
State or Federal Government Agency or Department, other Professional Societies,
Public or Private Corporation, or Pharmaceutical Company.



# Learning Objectives

- At the end of this lecture, participants will be able to:
  - Voice the history on how was the insulin was discovered and evolved from a crude pancreatic extract to analogs into the purified products that we have these days.
  - Acknowledge new insulin products under investigation





# Diabetes Mellitus

- The earliest description of diabetes appears in medical texts in Egypt written around 1552 BC, the Ebers Papyrus.
  - Ants were attracted to the urine of certain patients whose other symptoms included emaciation, thirst, and exhaustion
  - Greeks diagnose it by tasting the urine

- Apollonius of Memphis coined the name "diabetes" meaning "to go through" or siphon. He understood that the disease drained more fluid than a person could consume. Later "mellitus" was added because it made the urine sweet.

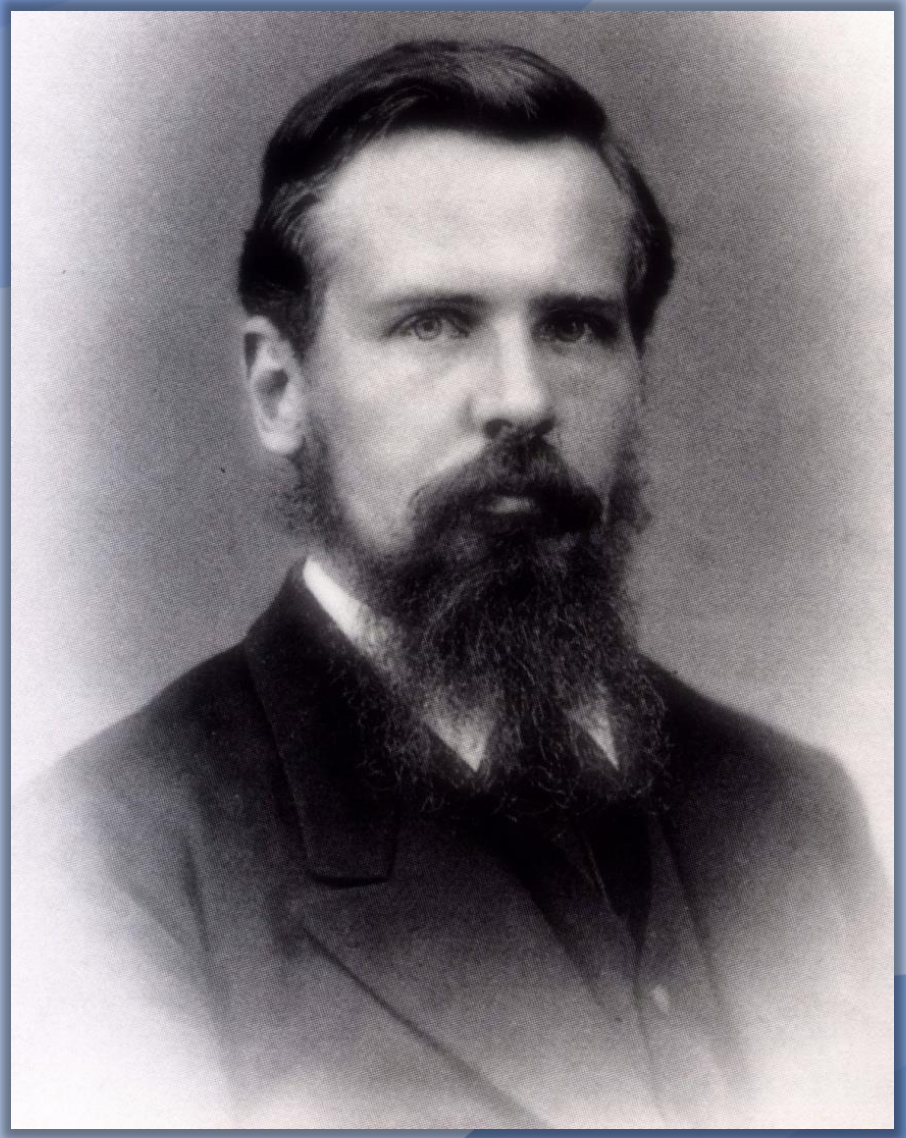
- During the early part of the 20th century, before insulin became available, physicians Frederick Allen and Elliot Joslin endorsed fasting and calorie-restricted diets for diabetes (starvation diet). This resulted in some improvement of glucosuria and acidosis, decreased coma, and delayed death among children with diabetes.

Sociedad Puertorriqueña de Endocrinología y Diabetología SPED 1976


Quianzon CC, Cheikh I. ***J Community Hosp Intern Med Perspect***. 2012;2:10.3402/jchimp.v2i2.18701.


Emaciating Disease
“Pissing Evil”
‘El demonio de orinar’”

# Paul Langerhans
(1847 to 1888)



- Paul Langerhans, pathologist in Berlin, in 1869, described tissue clumps scattered throughout the pancreas. He named them as the islets of Langerhans.
- Their function was unknown.

Quianzon CC, Cheikh I. J Community Hosp Intern Med Perspect. 2012;2:10.3402/jchimp.v2i2.18701.
Hirsch, IB. ***Endocrine Reviews*** *2020;* 41:733
ADA https://www.diabetes.org/blog/history-wonderful-thing-we-call-insulin

# Paul Langerhans' Thesis Face Page

- zur mikoskopischen anatomie der bauchspeicheldrilse
- On the microscopic anatomy of the pancreas

A

Beiträge

**zur mikroskopischen Anatomie der Bauchspeicheldrüse.**

INAUGURAL-DISSERTATION,

ZUR

ERLANGUNG DER DOCTORWÜRDE

IN DER

MEDICIN UND CHIRURGIE

VORGELEGT DER

MEDICINISCHEN FACULTÄT

DER FRIEDRICH-WILHELMS-UNIVERSITÄT

ZU BERLIN

UND ÖFFENTLICH ZU VERTHEIDIGEN

am 18. Februar 1869

VON

**Paul Langerhans**

aus Berlin.

**OPPONENTEN:**

G. Loeillot de Mars, Dd. med.
O. Soltmann, Dd. med.
Paul Ruge, Stud. med.

**BERLIN.**

BUCHDRUCKEREI VON GUSTAV LANGE.

B

# Oscar Minkowski (1858-1931)

- In 1889, Polish physician Oscar Minkowski in collaboration with German Joseph von Mering, removed the pancreas from a healthy dog to test its assumed role in digestion.
- On testing the urine, they found sugar in the dog's urine, establishing for the first time a relationship between the pancreas and diabetes.

Quianzon CC, Cheikh I. J Community Hosp Intern Med Perspect. 2012;2:10.3402/jchimp.v2i2.18701.
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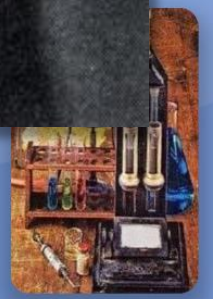
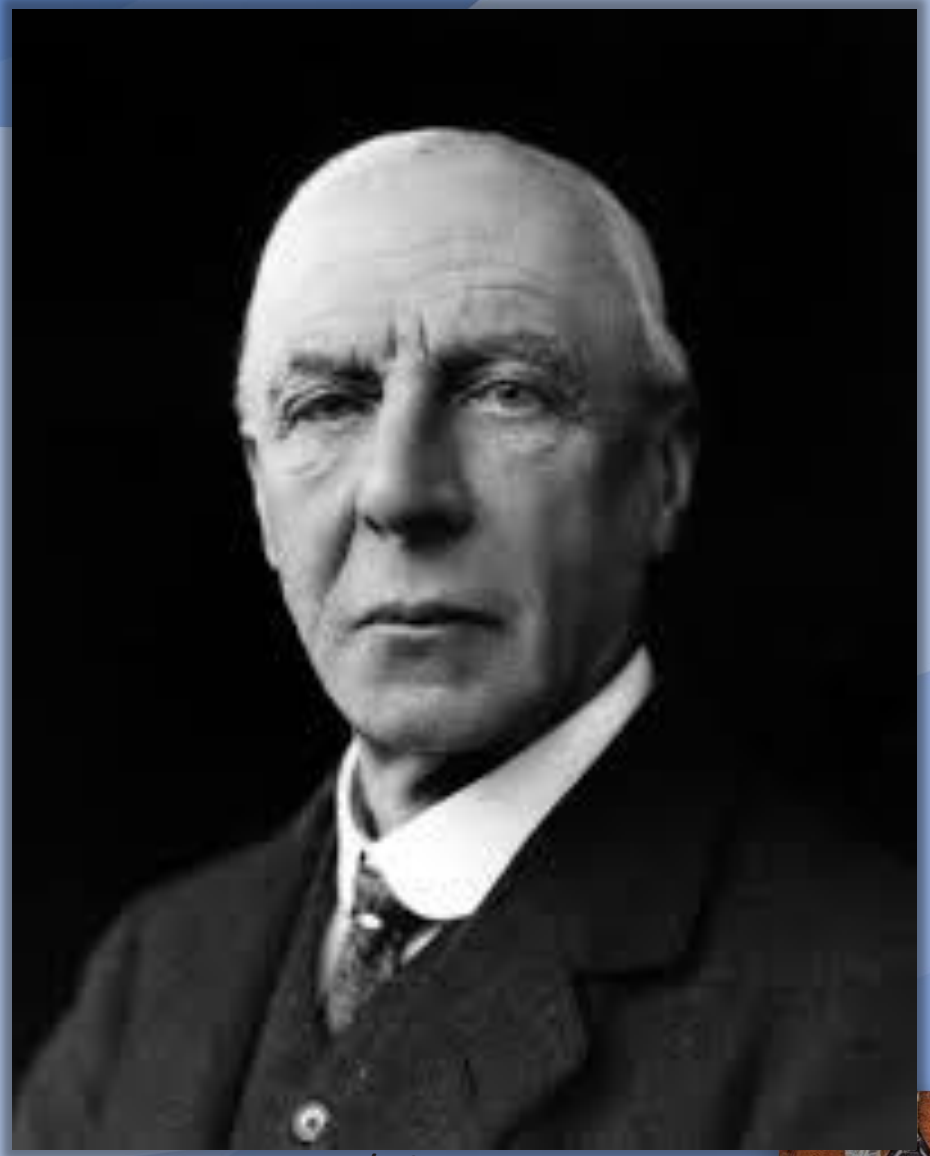


# Sir Edward Albert Sharpey-Schäfer (1850-1935)

- In 1894, Sir Edward Albert Sharpey-Schäfer suggested that the Islets of Langerhans drive the effects of the pancreas on blood glucose.
- In 1910-13, he used the term “insuline”, from the Latin word insula, meaning “island” but did not isolate it.



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**100 Years of Insulin Therapy: A long Successful Path**

# Banting's Research Started on May 17, 1920

- Pancreatic extract were shown to be toxic and caused severe side effects, including pain and fever, in animals.

- In 1920, John R. Macleod, professor of physiology, accepted a proposal by Frederick G. Banting, a 22-year-old orthopedic surgeon, to work at his laboratory at the University of Toronto.
  - Test if pancreatic extracts reduce blood glucose in dogs with diabetes.
  - Banting's plan was to tie up the pancreatic ducts of laboratory dogs until the cells that produce the enzymes degenerated, leaving the sturdy islet cells alive. He would then extract the residue.
    - The idea of isolating islets due to their slower degeneration was of keen interest to Macleod. Nobody had attempted to extract islets from a fully degenerated pancreas.

Quianzon CC, Cheikh I. ***J Community Hosp Intern Med Perspect.*** 2012;2:10.3402/jchimp.v2i2.18701.
Hirsch, IB. ***Endocrine Reviews*** *2020;* 41:733
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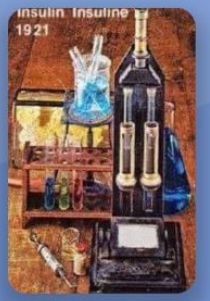
# Banting's Research

- On July 30, 1920 they injected the pancreatic extract into a dog with no pancreas.
  - Froze the degenerated pancreas from duct-tied dog
  - Ground it into a paste
  - Filtered it
  - Warm it to room temperature
  - Injected into the dog with no pancreas
- They observed a drop in blood glucose with the extract, but the dog died the next day of infection.
  - Initially 7 of 10 dogs die.
  - They had to resort buying black market dogs on the street of Canada.





# Banting's Research

- In July 1921, Frederick Banting and Charles Best kept a dog with severe diabetes alive for 70 days—the dog died only when there was no more extract. They named their pancreatic extract, **isletin**.
- Realizing that a supply of dogs for pancreas ligation was going to limit the progress of the research, Banting and Best moved on to using the pancreas of cows as source material.


Hirsch, IB. ***Endocrine Reviews*** *2020;* 41:733
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# Banting's Research

- J.B. Collip, a visiting biochemist, provided the expertise needed to purify the active glucose-lowering component from the extract.
- On January 11, 1922, Leonard Thompson, a 14-year-old boy dying from diabetes in a Toronto hospital, received an injection of the pancreatic extract **without** great success controlling the glucose and developing an abscess and some say he had a severe allergic reaction.
- The extract was further purified and upon injection on January 23, 1922, Leonard Thompson had a significant reduction in glucose and the ketones vanished from the urine.
- The trial leaders repeated these significant improvements across six more patients over the next month.

Hirsch, IB. ***Endocrine Reviews*** *2020;* 41:733

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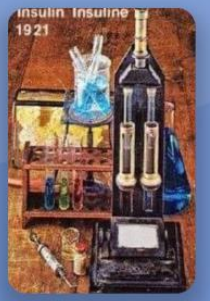
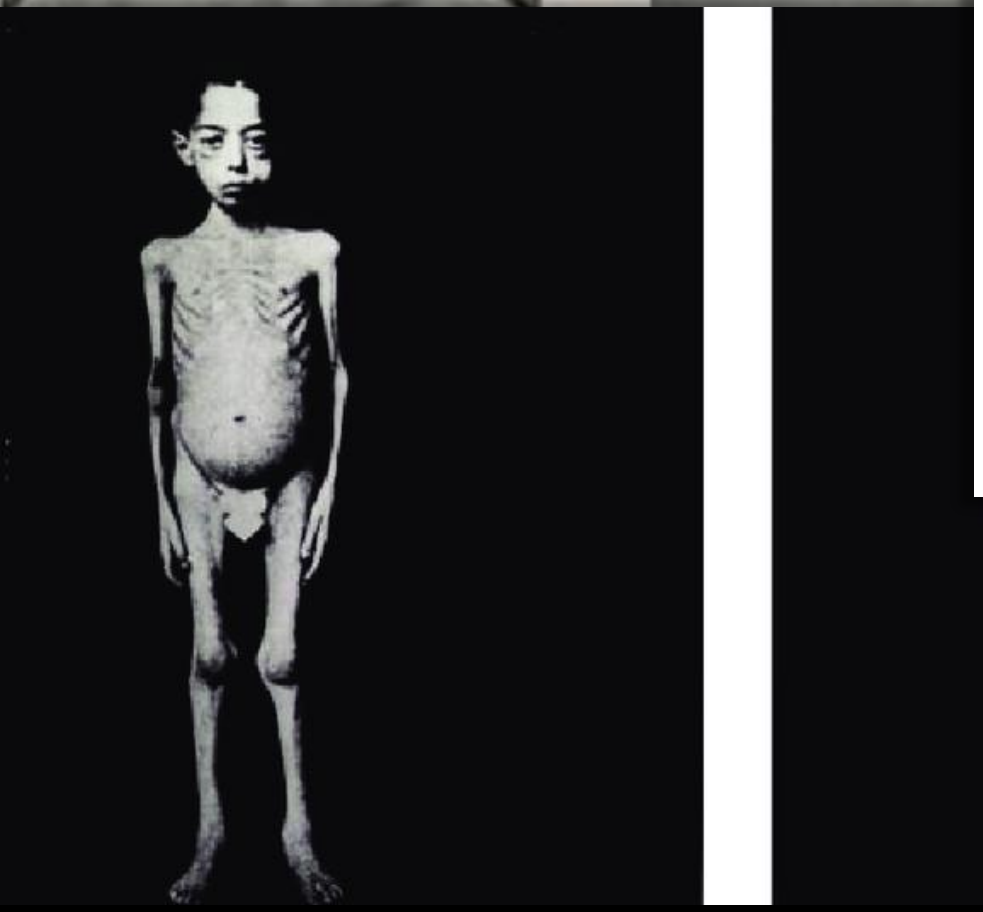
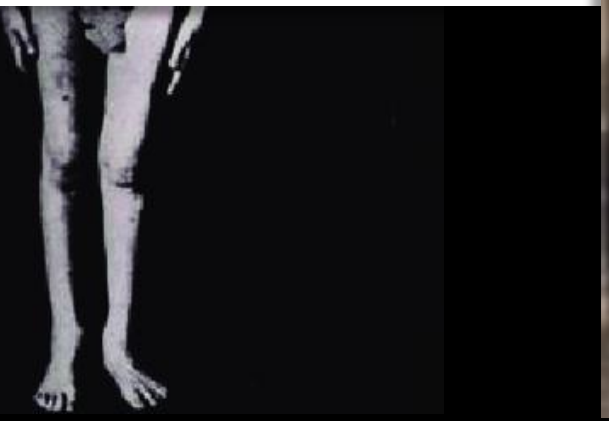




Patient JL, 15 pounds December 15, 1922



Elsie Needham

# Theodore Ryder

Born in 1916; diagnosed with diabetes mellitus in 1920
In 1921 he would only walk 3-4 steps before needing help
On July 10th, 1922, he received insulin.

DEAR DR. BANTING,

I WISH YOU COULD COME TO SEE ME. I AM A FAT BOY NOW AND I FEEL FINE. I CAN CLIMB A TREE. MARGARET WOULD LIKE TO SEE YOU.

LOTS OF LOVE FROM TEDDY RYDER

# In 1923, Banting and Macleod received the Nobel Prize in Medicine, which they shared with Best and Collip. F Banting is the youngest laureate.

Medicine | The Nobel Prize in Physiology or Medicine 1923 | Summary

The Nobel Prize in Physiology or Medicine 1923

Frederick G. Banting
John Macleod

Share this

## The Nobel Prize in Physiology or Medicine 1923

Photo from the Nobel Foundation archive.

Frederick Grant Banting

Prize share: 1/2

Photo from the Nobel Foundation archive.

John James Rickard Macleod

Prize share: 1/2

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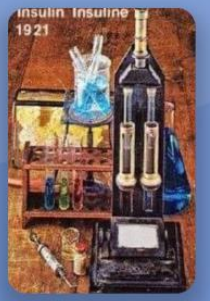
ssful Path



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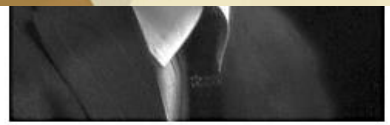

Photo from the Nobel Foundation archive.

Frederick Grant Banting

Prize share: 1/2

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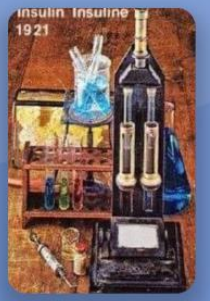
John James Rickard Macleod

Prize share: 1/2

ssful Path



# THE DISCOVERERS OF INSULIN

FREDERICK GRANT
**BANTING**
1891 - 1941

CONCEIVED THE IDEA FOR EXTRACTING INSULIN FROM THE PANCREAS — IN LONDON, ONTARIO OCTOBER 31, 1920

JOHN JAMES RICKARD
**MACLEOD**
1876 - 1935

OFFERED BANTING SPACE IN HIS TORONTO LABORATORY AND PROVIDED ADVICE ON METHODS FOR EXTRACTING INSULIN.

CHARLES HERBERT
**BEST**
1899 - 1978

ASSISTED BANTING DURING THE SUMMER OF 1921 IN PREPARING PANCREATIC EXTRACTS THAT PROLONGED THE LIVES OF DIABETIC DOGS.

JAMES BERTRAM
**COLLIP**
1892 - 1965

PURIFIED THE CRUDE INSULIN EXTRACT FOR USE IN HUMAN DIABETICS — FIRST SUCCESSFULLY TESTED IN JANUARY, 1922.

# Iletin Vial in 1920s


**The patent for insulin was sold for one half-dollar.**

**The scientists refused financial gain in order to serve science, research and humankind.**



# Insulin Pharmacokinetics and Pharmacodynamics

- Early insulin replacement therapy required multiple daily injections of one type of insulin only
- This situation was complicated by the lack of home blood glucose monitoring technology, not available until late 1970s.
- In 1930s protamine was introduced.
- n 1950, Novo Nordisk, Inc. introduced the first slow-acting insulin.



Hirsch, IB. ***Endocrine Reviews*** *2020;* 41:733

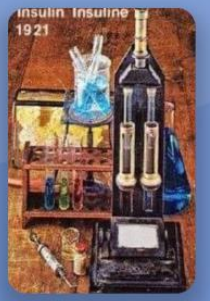
**100 Years of Insulin Therapy: A long Successful Path**

# Beef and Pork Insulins

- Initial insulins available in the market
- Similar pharmacokinetics and pharmacodynamics to human insulin
- Problems:
  - Formation of anti-insulin antibodies
  - '**Monocomponent**' (by Novo) or '**single peak**' (by Eli Lilly) insulin
    - In 1974, thru chromatographic processing techniques the insulin was purified from proinsulin and other immunogenic peptides

Hirsch, IB. ***Endocrine Reviews*** *2020;* 41:733





**10,000 lbs of pancreas to produce 1lb of insulin crystals**

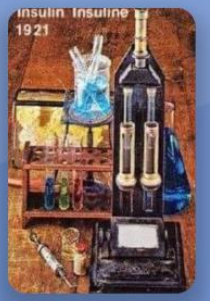

Ca. 1926. The above image illustrates the massive amount of pancreas glands it took to create a single pound of pure insulin crystals.  Photo courtesy of Eli Lilly and Company Archives.

# This Last Century Has Been A Time Of Change And Innovation In The Field Of Insulin Therapy

- Isolation of insulin
- Purification and concentration of animal pancreatic extracts
- Development of formulations with protracted duration of action
- **Progression to human insulin with recombinant DNA technology**
- **Modified insulin analogs made with recombinant DNA technology**

Hirsch, IB. ***Endocrine Reviews*** *2020;* 41:733

**100 Years of Insulin Therapy: A long Successful Path**



# Biosynthetic Human Insulin

## 1975: First synthetic insulin by Ciba-Geigy Labs. in Basel, Switzerland

- The discovery of the insulin gene and commercialization of recombinant DNA technology enabled the development and large-scale manufacturing of biosynthetic human insulin.
- The first genetically engineered, synthetic “human” insulin was produced in 1978 by **David Goeddel** and his colleagues (of Genentech) using E. coli bacteria to produce the insulin. Genentech and Lilly signed an agreement to commercialize rDNA insulin.
- The first biosynthetic human insulin product was approved in **1982**, marketed under the brand name Humulin® R and N (Eli Lilly and Company, Indianapolis, IN).
- Followed by Novolin® R (Novo Nordisk A/S, Bagsværd, Denmark) in **1991** and Insuman® R (Hoechst, Frankfurt, Germany) in 1997.

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# Human Insulins and A

The time course of action of insulin may vary in different individuals or within the same individual.

| Preparation | Trade Name | Timing of Action | | |
|---|---|---|---|---|
| | | Onset | Peak | Duration |
| **Rapid Acting** | | | | |
| Lispro | Humalog (100/200) | 5-15 mins | ~0.5-1.5 h | ~3-5 h |
| Aspart | Novolog | | | |
| Glulisine | Apidra | | | |
| **Short Acting** | | | | |
| Regular | Humulin R<br>Novolin R | 30-60 mins | ~1-3 h | 5 - 8 h |
| **Intermediate** | | | | |
| NPH | Humulin N<br>Novolin N | 1-4 h | 4-10 h | 12-18 h |
| **Long Acting** | | | | |
| Detemir | Levemir | ~2-4 h | No peak | 12-24 h |
| Glargine | Lantus, Toujeo | ~2-4 h | | 20-36 h |
| Degludec | Tresiba (100/200) | ~1 hr | | 3-4 days |
| **Mixtures** | | | | |
| 70/30, 50/50, 75/25 | | ~30 mins | ~7-12 h | ~16-18 h |
| Degludec/Aspart | Ryzodeg | <30 mins | | 3-4 days |

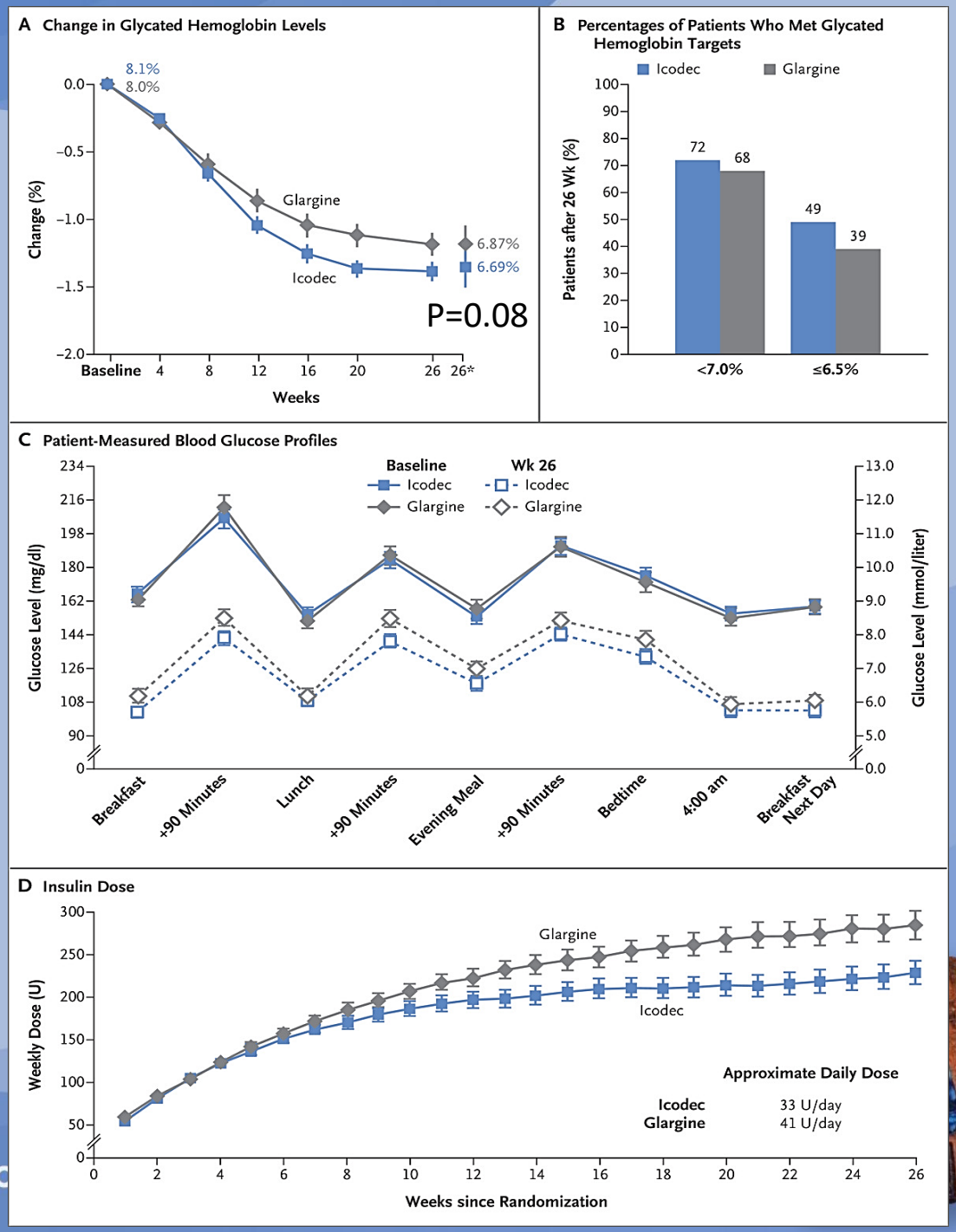
# New Products in the Pipeline



# Once-Weekly Insulin for Type 2 Diabetes

**NON FDA APPROVED NON FDA APPROVED**

- Randomized, double-blind, double-dummy, phase 2 trial, 26-week trial
  - Insulin Icodec® vs Glargine U100
- 247 patients with T2DM, naïve to insulin, A1c between 7.0 to 9.5% (~8%)
  - Patients were in metformin ± DPP-4 inhibitor
- Primary end-point: A1c change from baseline to week 26.
- The incidence of combined level 2 or level 3 hypoglycemia was 16.0% (I) vs. 9.8% (G).




Rosenstock J. ***N Engl J Med***. 2020;Sep 22

# Hepatic-Directed Vesicle Insulin for Prandial Use

UNDER INVESTIGATION. NON-FDA APPROVED

- Hepatic-directed vesicle insulin (HDV), a novel insulin delivery system, targets insulin to the liver, providing more normal insulin biodistribution by mimicking portal vein delivery.
  - By delivering a portion of the SC dose directly to the liver, ~30–60% of oral carbohydrate is expected to be sequestered as hepatic glycogen, reducing peripheral glucose exposure and demanding reduced peripheral insulin exposure.
- 26-week, phase 2b, multicenter, randomized, double-blind trial in T1DM in MDI
- 1ry goal: Noninferiority of HDV vs. Lispro
- Masked CGM (Dexcom G4) was used for 5–7 days at baseline and weeks 13 and 26.

Klonoff D. ***Diabetes Care***. 2019;42:2154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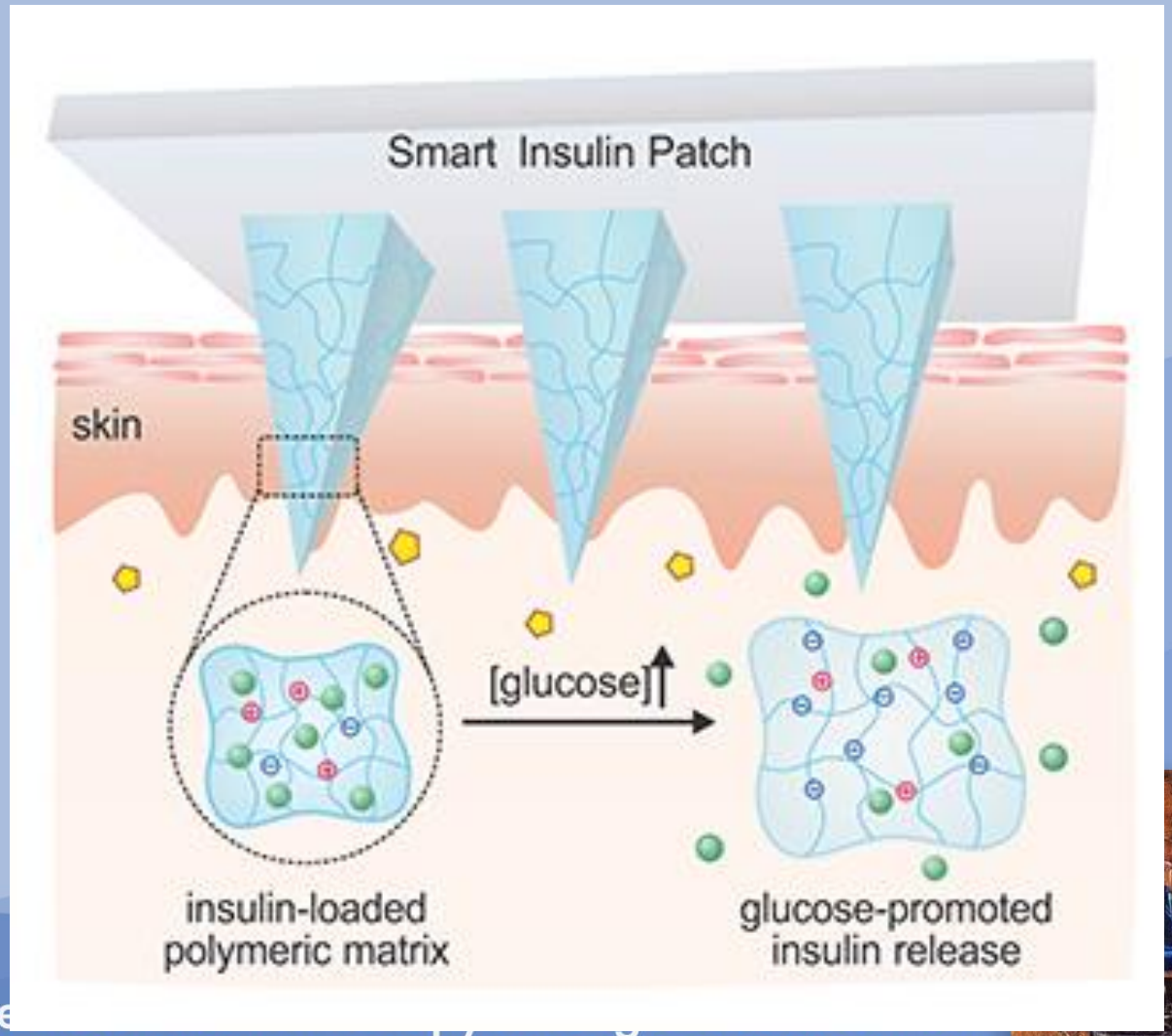
# Smart Insulin Patch

UNDER INVESTIGATION. NON-FDA APPROVED

- The smart patch monitors blood glucose. It has doses of insulin preloaded in very tiny microneedles, less than 1 millimeter in length, that deliver the medicine quickly when the blood sugar levels reach a certain threshold. When blood sugar returns to normal, its insulin delivery also slows down.

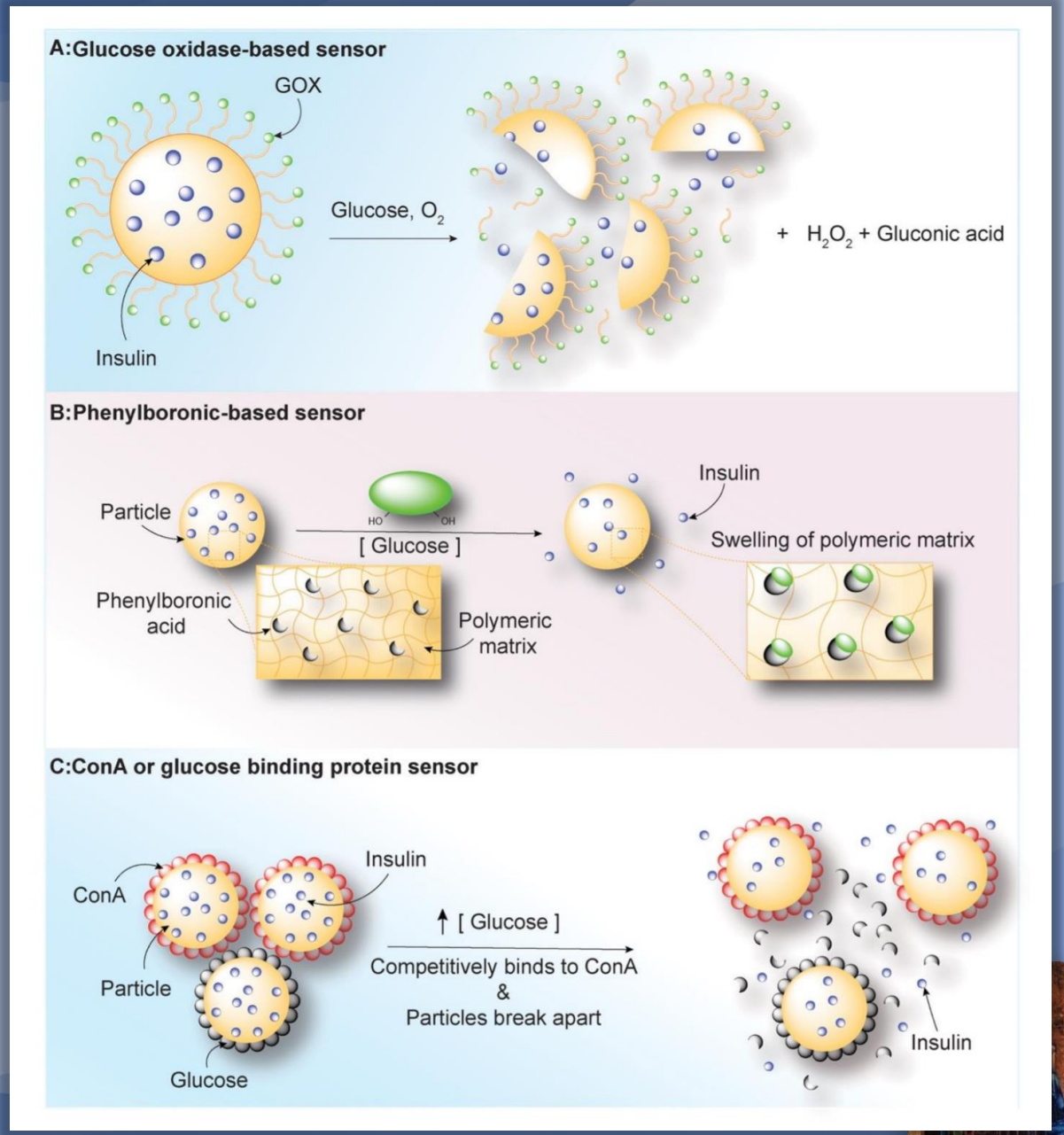
https://samueli.ucla.edu/smart-insulin-patch/



# Nanoimplant
# Particle-based glucose sensors.

- Polymer engineering and nanotechnology on insulin-delivering particles that carried glucose-responsive molecules, which can accurately mimic the physiological response to blood glucose changes.

UNDER INVESTIGATION. NON-FDA APPROVED

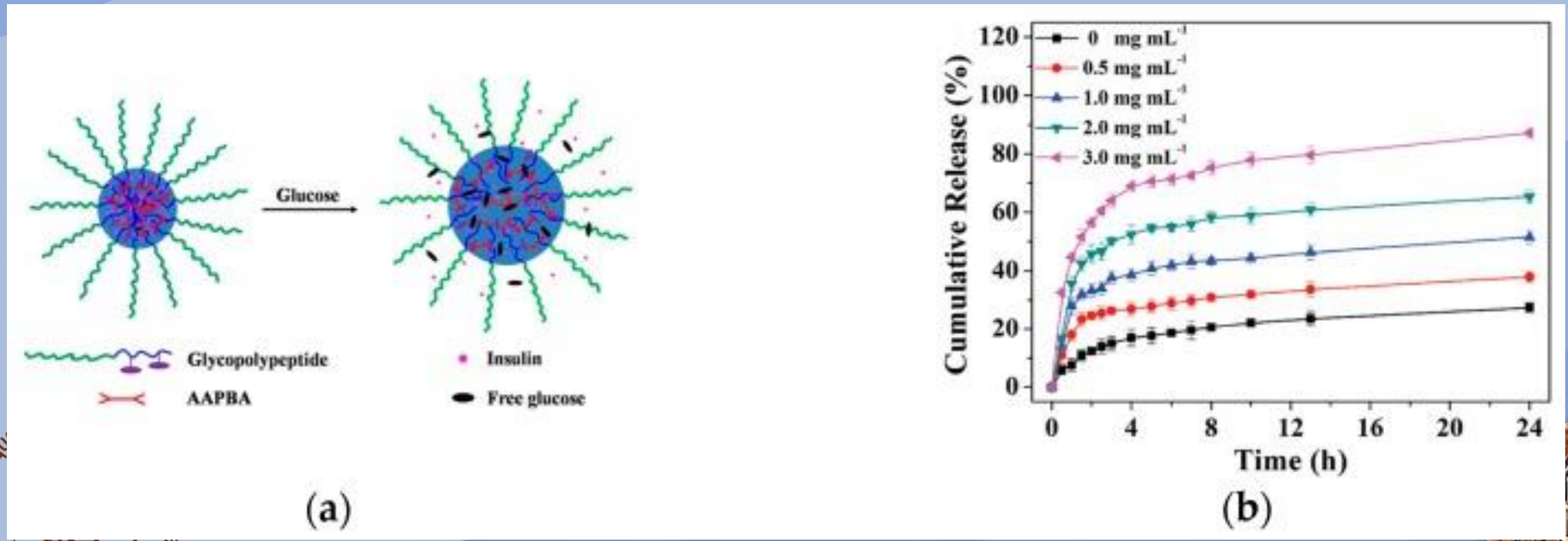



Primavera R ***Nanomaterials*** 2020, 10,789

# Hydrogels

UNDER INVESTIGATION. NON-FDA APPROVED

- Provide glucose-triggered drug release due to reversible swelling and shrinking induced by glucose.






Wang C. *Molecules*. 2019;24:1087

# Oral Insulin

**UNDER INVESTIGATION. NON-FDA APPROVED**

- ORMD-0801 produced by Oramed Pharmaceuticals
- Oral human insulin formulated to increase hepatic insulin exposure, and subsequently reduce hepatic glucose production and improve glycemic control
- Randomized, placebo-controlled, multicenter, phase 2b, 12-week study
- 354 subjects with T2DM uncontrolled by multiple oral antidiabetic drugs and with HbA1c levels ≥7.5%, received placebo or 8 mg, 16 mg or 32 mg ORMD-0801 capsules up to three times daily.

| | QD | | | | BID | | | TID |
|---|---|---|---|---|---|---|---|---|
| | Placebo | 8 mg | 16 mg | 32 mg | 8 mg | 16 mg | 32 mg | 32 mg |
| **HbA1c (%)** | | | | | | | | |
| N (Baseline/12wk) | 51/44 | 14/13 | 13/13 | 62/59 | 13/12 | 14/10 | 62/54 | 58/52 |
| Baseline | 9.5±0.5 | 10.1±0.6 | 9.6±0.6 | 9.2±0.5 | 9.2±0.6 | 9.4±0.6 | 9.5±0.5 | 9.8±0.5 |
| *12-weeks* | 9.2±0.5 | 8.8±0.6 | 9.4±0.6 | 8.5±0.5 | 8.1±0.6 | 8.9±0.6 | 8.8±0.5 | 8.9±0.5 |
| *change from baseline* | -0.1±0.4 | -1.0±0.5 | 0.1±0.5 | -0.6±0.4 | -1.0±0.5 | -0.5±0.5 | -0.6±0.4 | -0.5±0.4 |
| **Glucose AUC (mg*hr/dL)** | | | | | | | | |
| N (Baseline/12wk) | 43/41 | 13/12 | 13/12 | 58/48 | 11/13 | 11/12 | 54/51 | 48/50 |
| Baseline | 4529±373 | 4774±442 | 4497±443 | 4294±356 | 3873±438 | 4970±456 | 4672±340 | 4530±333 |
| *12-weeks* | 5305±423 | 5027±488 | 5514±498 | 4925±412 | 4235±456 | 5227±487 | 5182±381 | 5325±402 |
| *change from baseline* | 396±325 | 118±367 | 800±375 | 366±311 | 241±359 | 311±393 | 265±287 | 540±304 |
| **Body weight (kg)** | | | | | | | | |
| N (Baseline/12wk) | 51/44 | 14/13 | 14/13 | 62/59 | 13/12 | 14/10 | 62/55 | 58/52 |
| Baseline | 95.7±5.3 | 109.3±6.5 | 95.4±6.6 | 96.3±5.1 | 100.9±6.4 | 96.7±6.5 | 94.0±4.9 | 97.2±5.1 |
| *12-weeks* | 92.8±5.5 | 110.3±6.9 | 97.0±6.9 | 95.8±5.3 | 99.7±6.9 | 92.5±7.3 | 92.8±5.0 | 96.6±5.2 |
| *change from baseline* | -0.3±0.8 | -1.4±1.0 | 0.5±1.0 | 0.1±0.8 | -0.6±1.0 | 0.8±1.0 | -0.4±0.7 | -0.5±0.8 |
| **Safety** | | | | | | | | |
| Number of reported hypoglycemic events | 21 | 0 | 20 | 16 | 16 | 0 | 4 | 32 |
| Subjects with drug-related adverse event | 7 | 2 | 0 | 6 | 0 | 1 | 3 | 9 |
| Notes: Least Square Means ± Standard Error are presented for all summary statistics. | | | | | | | | |

Roy Eldor, G ***Diabetes*** 2020;69: (Suppl 1) 1015-LB: Evening Oral Insulin Glycemic Effects



# Therefore, Concerning Insulins:

## One Size does NOT Fill All

- Practice patient centered medicine.

There is no such things as the "best insulin".

Use the insulin correctly.

100 Years of Insulin Therapy: A long Successful Path