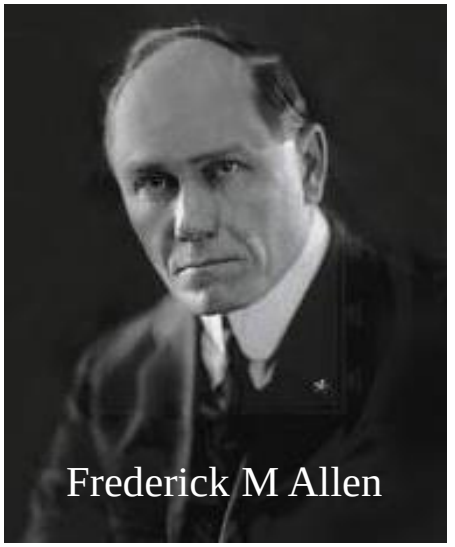
The story of insulin

- Early history
- Toronto 1920-23 – Nobel Prize
- Industry gets involved
- Insulin around the world
- Its clinical impact
- Recombinant insulins
- The economics of insulin

Diabetes – a fatal disease

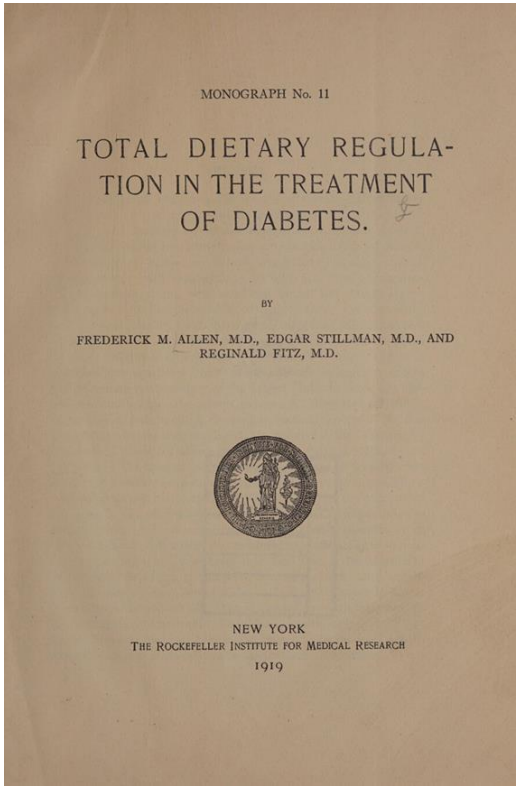


Diets as low as 400 calories/day were prescribed, with carbohydrates virtually eliminated from the diet.

Although successful in eliminating glycosuria, Allen's extreme diets were difficult to follow.

People who dropped out of treatment and returned to their former diets would die shortly afterwards.

Those who followed the diets faithfully would live longer but become undernourished and die of starvation.

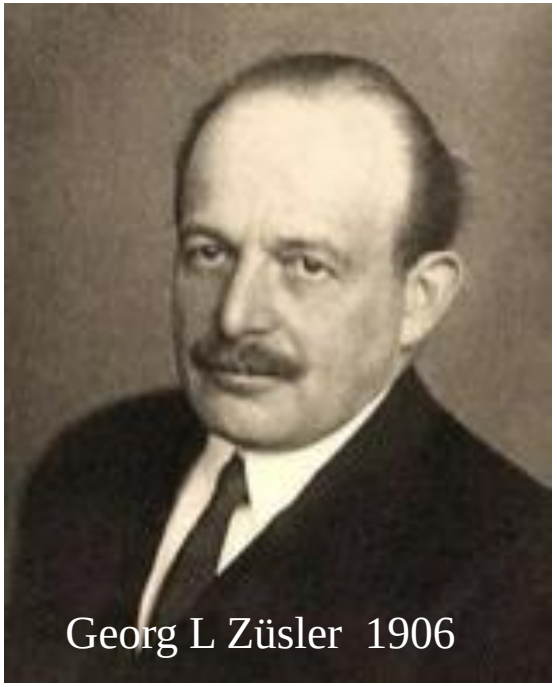

MONOGRAPH No. 11

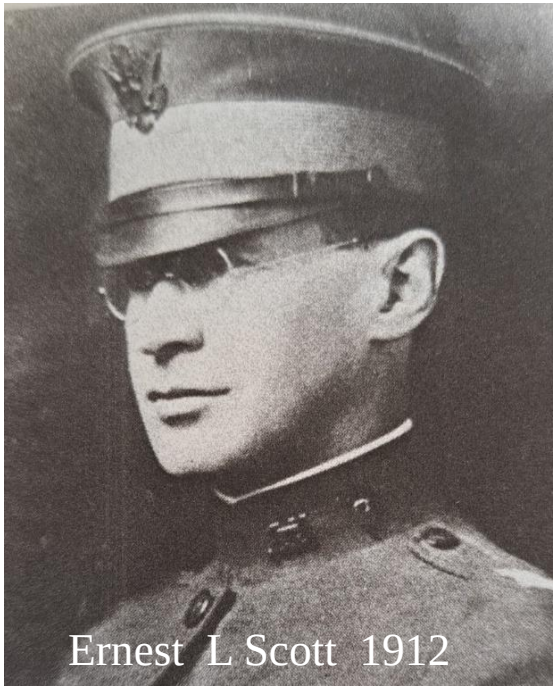
TOTAL DIETARY REGULATION IN THE TREATMENT OF DIABETES.

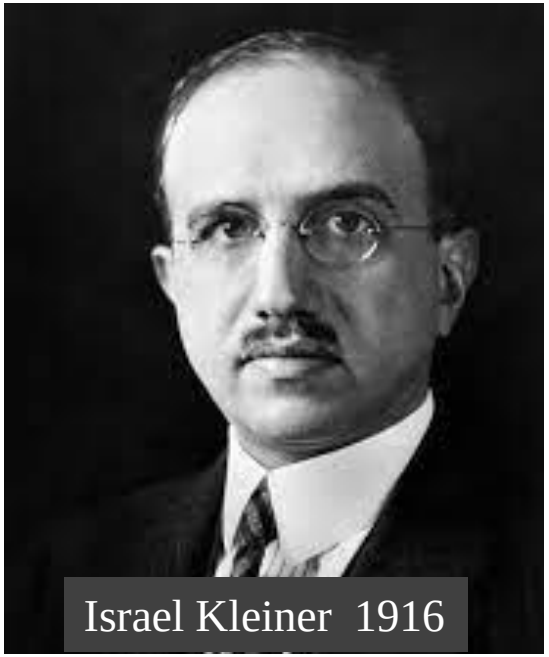
BY

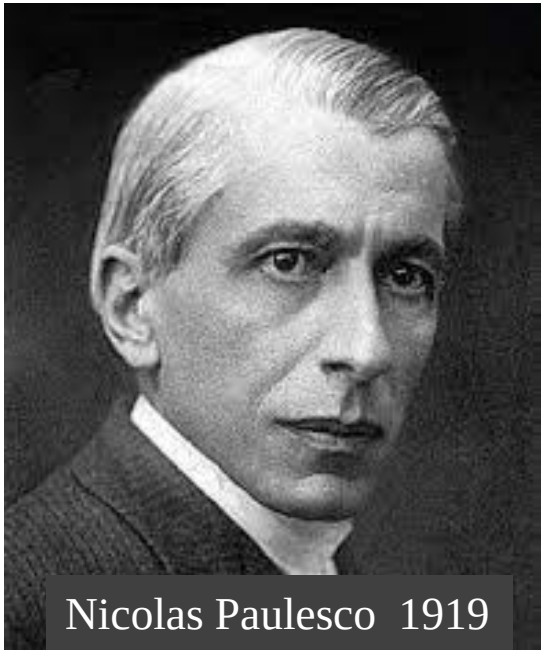
FREDERICK M. ALLEN, M.D., EDGAR STILLMAN, M.D., AND REGINALD FITZ, M.D.

NEW YORK
THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH
1919


Georg L Züsler 1906


Ernest L Scott 1912

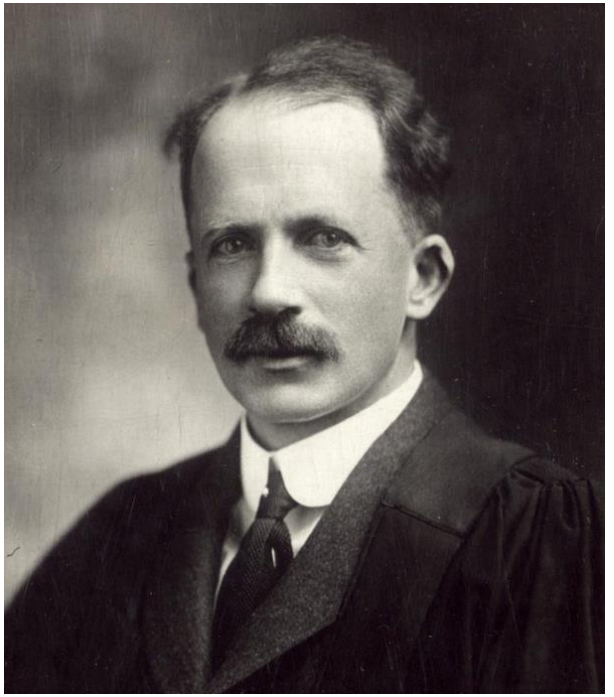

Israel Kleiner 1916


Nicolas Paulesco 1919

Early demonstrations of anti-diabetic effect of pancreatic extracts

Toronto
1921-22

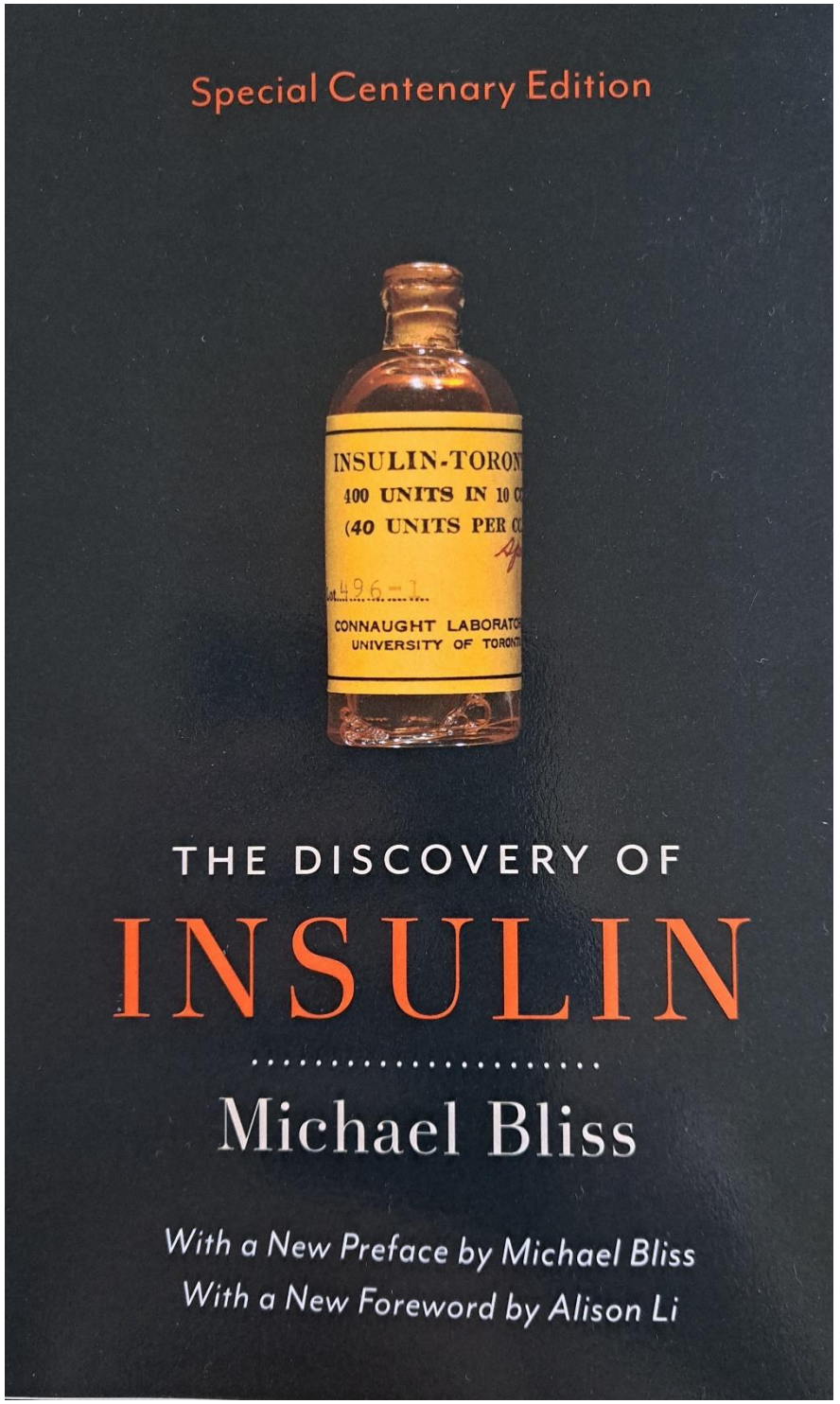
FG Banting



JJR Macleod

CW Best

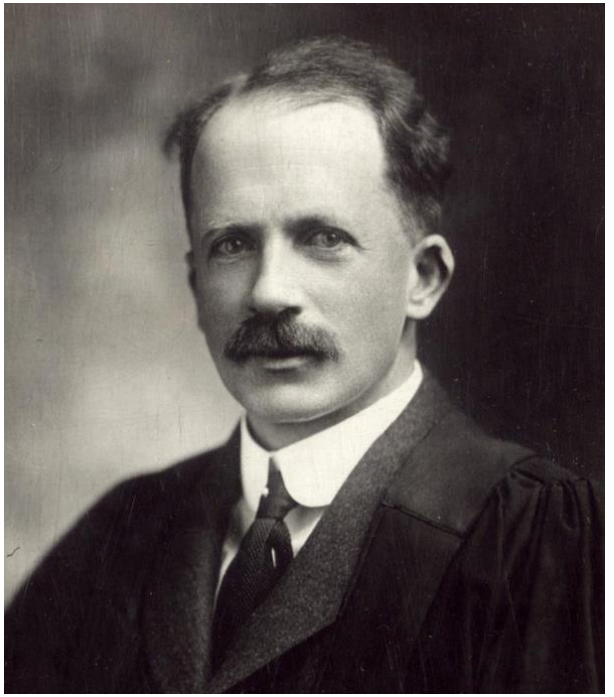
JB Collip



Improved ease and reliability of blood glucose measurement 1910 to 1920

Toronto
1921-22

Fred Banting

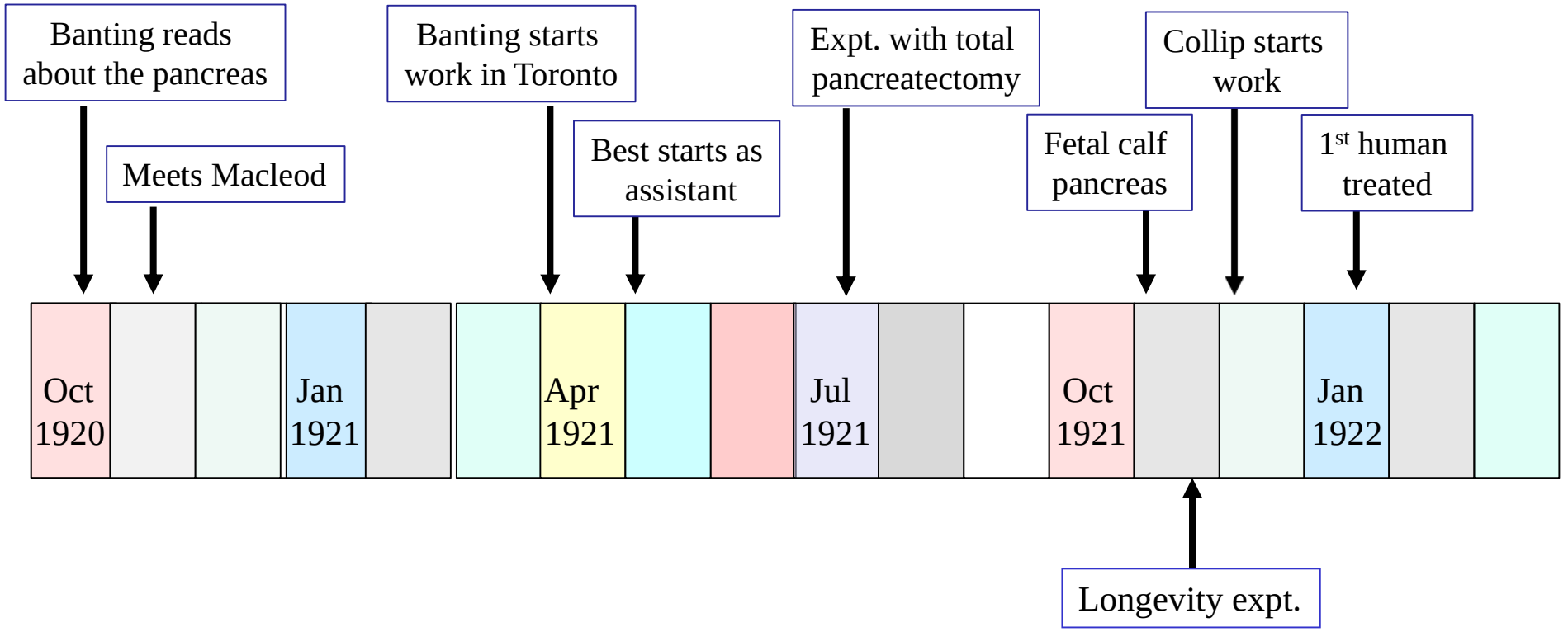


John Macleod

Charley Best

Bert Collip

Toronto timeline 1920-21



Toronto timeline 1921-23

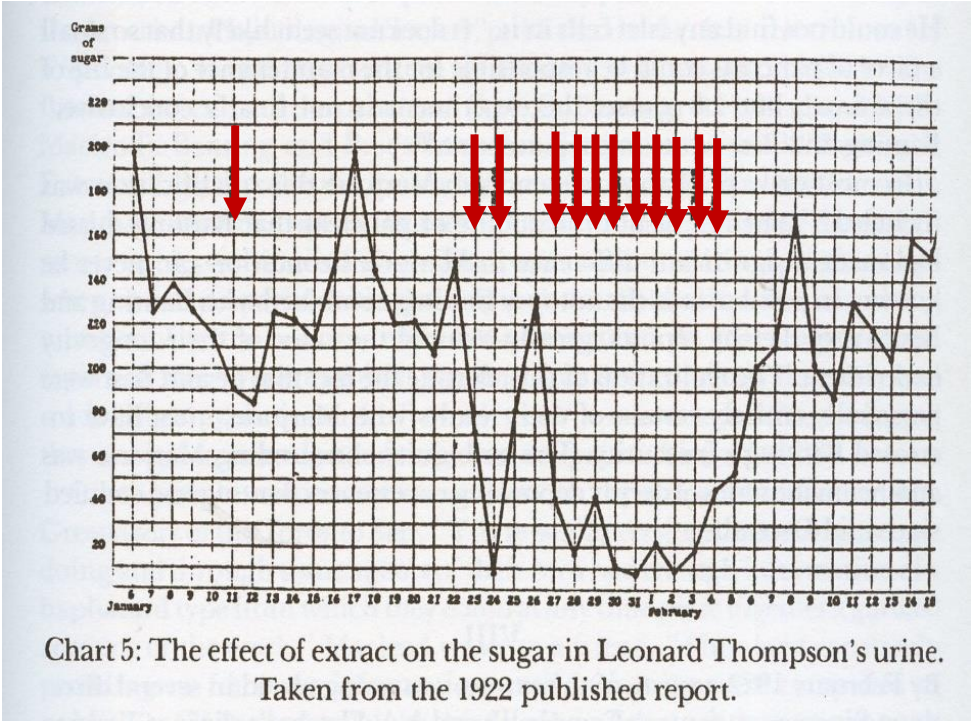
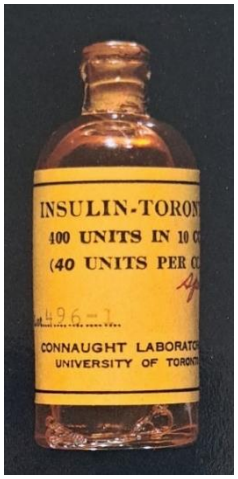


Chart 5: The effect of extract on the sugar in Leonard Thompson's urine.
Taken from the 1922 published report.

Leonard Thompson
1908-35



Insulin production begins at Connaught Laboratory, Toronto

January 1923 US patent awarded: sold for $1 to the University of Toronto.

"Insulin does not belong to me, it belongs to the world"

Nobel Prize 1923 - Banting & Macleod

Phyllis Adams

first person in Australia to receive insulin - 1922

In 1921, five-year-old Phyllis Adams developed diabetes. Her father contacted Banting who urged the family to keep Phyllis alive as they had begun testing their insulin discovery on dogs.

Surviving off a teaspoon of peanut butter, a lettuce leaf and a glass of junket a day for eight months, she weighed just 10kg when insulin arrived from Vancouver.

Phyllis's father met the P&O ship in the middle of Sydney Harbour; collected the insulin and rushed back to the wharf where the frail Phyllis was waiting at the pier.

"The minute she had the insulin at the wharf, they gave her half a Sao biscuit which she recalled as one of her greatest meals; she never forgot it."

Her parents were told even with insulin she might only live until she was nine. But she survived – dying in 1998 after 76-years using insulin.

Insulin arrives in New Zealand 1922-23

Napier

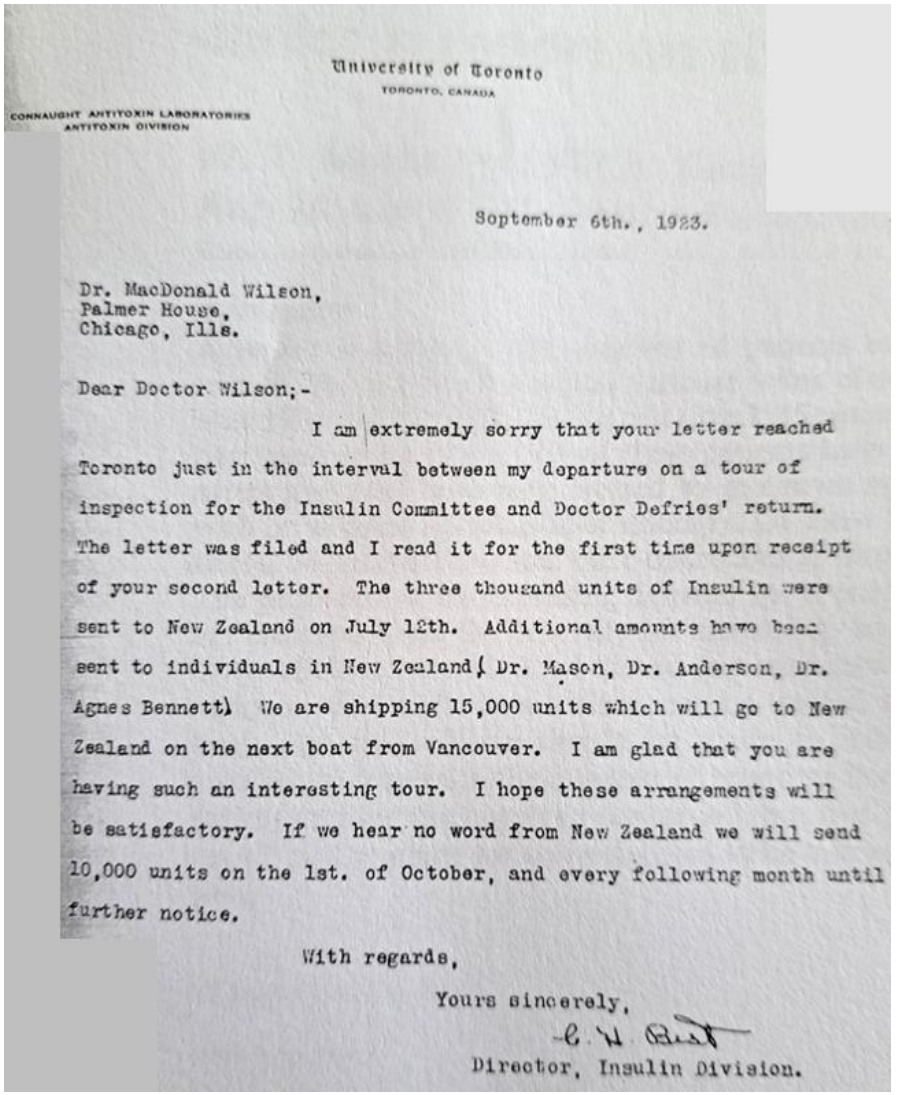

Thomas Johnson


Jake Caton

Dunedin


Charles Burns

Isabell Styche



University of Toronto
TORONTO, CANADA

CONNAUGHT ANTITOXIN LABORATORIES
ANTITOXIN DIVISION

September 6th., 1923.

Dr. MacDonald Wilson,
Palmer House,
Chicago, Ills.

Dear Doctor Wilson;-

I am extremely sorry that your letter reached Toronto just in the interval between my departure on a tour of inspection for the Insulin Committee and Doctor Defries' return. The letter was filed and I read it for the first time upon receipt of your second letter. The three thousand units of Insulin were sent to New Zealand on July 12th. Additional amounts have been sent to individuals in New Zealand (Dr. Mason, Dr. Anderson, Dr. Agnes Bennett) We are shipping 15,000 units which will go to New Zealand on the next boat from Vancouver. I am glad that you are having such an interesting tour. I hope these arrangements will be satisfactory. If we hear no word from New Zealand we will send 10,000 units on the 1st. of October, and every following month until further notice.

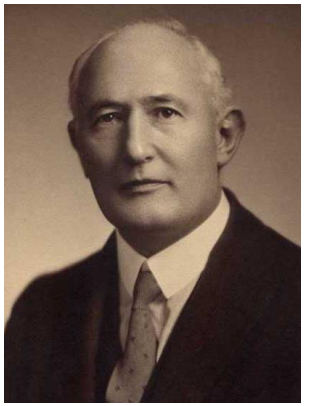
With regards,

Yours sincerely,

C. H. Best

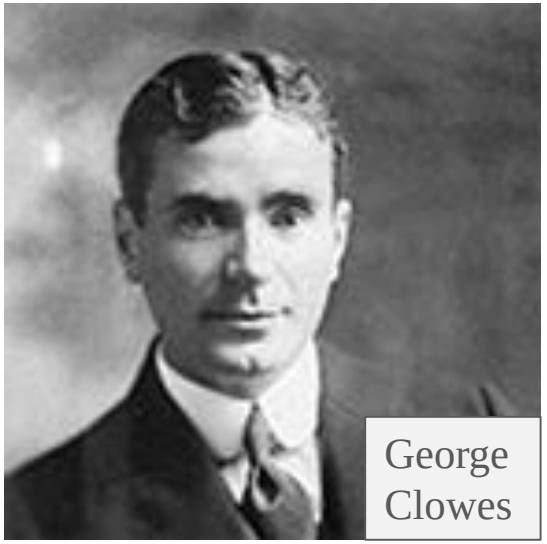
Director, Insulin Division.

Wellington


McDonald Wilson

HB Ewen

M H Watson NZMJ 1981 93: 347-50



George Clowes

Industry involvement

After hearing Banting present his research on insulin, Clowes became an enthusiastic supporter.

In 1922, Eli Lilly Co. negotiated an agreement with the University of Toronto for the rights to mass produce insulin for the U.S. market.

Lilly manufactured and marketed insulin in record time, despite logistical, technical and political obstacles.

A long-term supply contract for pig pancreases was negotiated with a Chicago meat-packing company.

In 1923, Lilly began selling the first commercially available insulin in the US, under the trade name *Iletin*.


HC Hagedorn


August Krogh


Marie Krogh

The Danish Connection

Hans Christian Hagedorn and August Krogh obtained the rights to produce insulin from Banting and Best.
In 1923 they formed *Nordisk Insulin Laboratorium*.

In 1924, after an argument, Hagedorn fired an important colleague - Torvald Petersen - a chemist at Nordisk.
His brother Harald resigned too - they founded the *Novo Terapeutisk Laboratorium* company to make insulin.

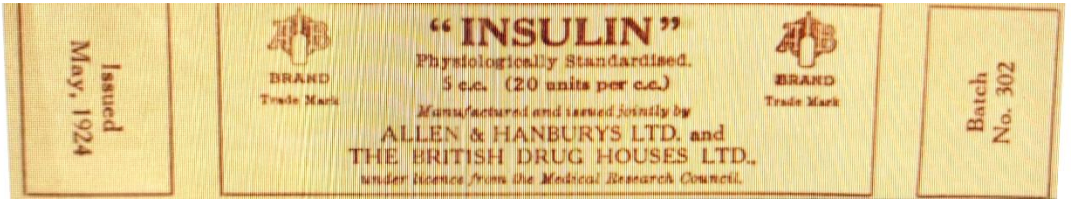
Hagedorn in 1936, discovered that adding protamine to insulin could prolong the action of insulin and later marketed crystals of protamine and insulin as Neutral Protamine Hagedorn (NPH or 'isophane') insulin.
This could be mixed with regular insulin.

Novo and Nordisk companies merged 1973

TERAPEUTISK LABORATORIUM
NOVO

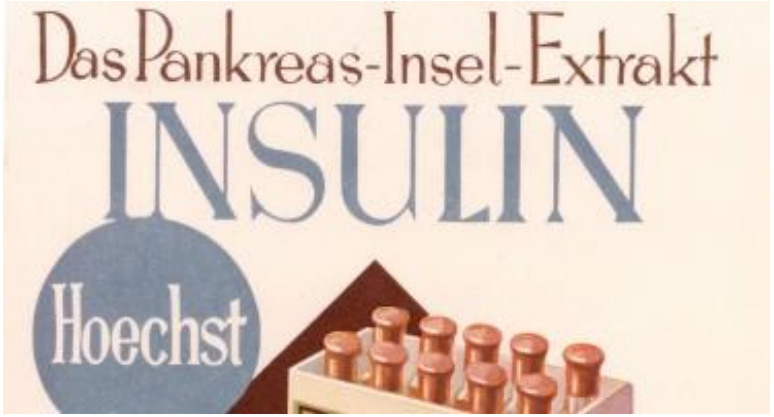
novo nordisk®

Insulin production takes off - 1923-24



By 1923, Allen & Hanburys were producing 95% of the UK's insulin

In Germany, Hoechst began bovine insulin production 1923



R D Lawrence diagnosed 1920 had first insulin injection May 1923

J P Bose introduced insulin in India 1924

In Australia, CSL produced insulin from 1923

In the UK, Burroughs Wellcome began production of bovine insulin 1924

Measuring insulin

The unit of insulin was first defined by the insulin committee at the University of Toronto (1922):
1 unit (U) of insulin was set as the amount of insulin required to reduce the blood glucose in a fasting rabbit to 2.5 mmol/L.
Of course, this depended on the size and nutrition of the rabbits.

Insulin was crystallised in 1926 (JJ Abel)
Became commercially available in 1934.
One international unit of insulin (1 U) is now defined as 34.7 µg pure crystalline insulin.

Until 1980s, insulin was sold in various strengths, including 40 U/ml and 80 U/ml formulations.

Standardizing the concentration to 100 u/ml reduced risk of dosage errors and eased doctors' prescribing of insulin.

Fred Sanger

Determined the chemical structure of insulin 1955

Nobel Prize in Chemistry 1958

Rosalyn Yalow & Solomon Berson

Radioimmunoassay of insulin 1960

Nobel Prize in Medicine 1977

Dorothy Hodgkin

Determined 3D structure of insulin 1969

Nobel Prize in Chemistry 1964

Emergence of ‘microvascular’ complications of diabetes

Definitive proof that these complications can be prevented or delayed by maintaining good glycaemic control:

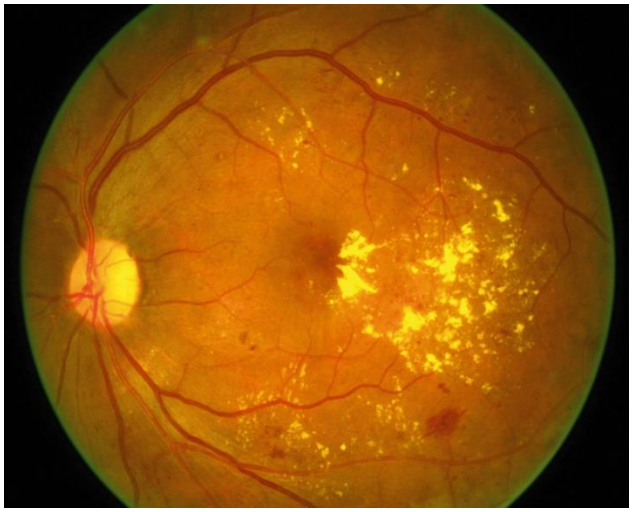
Type 1

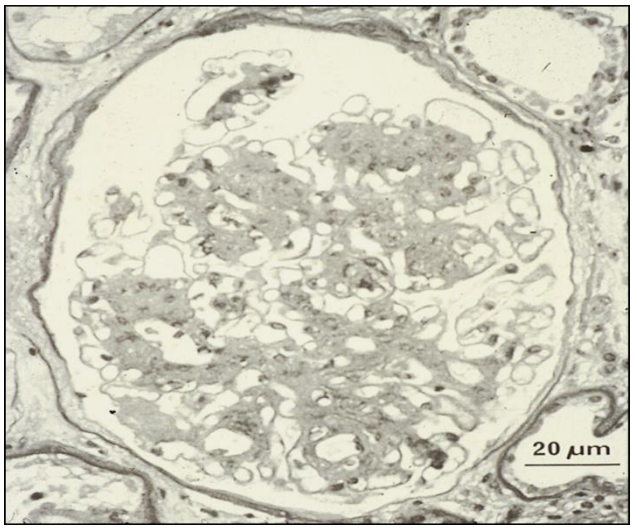
1993 - DCCT (USA)

Type 2

1995 - Kumamoto (Japan)

1998 - UKPDS (UK)





Life expectancy

Before the discovery of insulin:

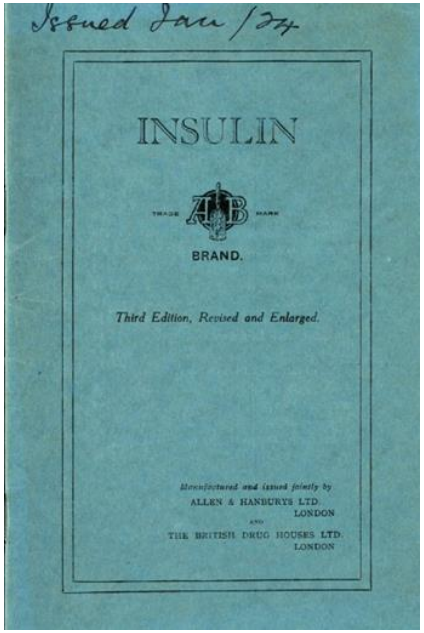
half died within 2 years; >90% within 5 years.

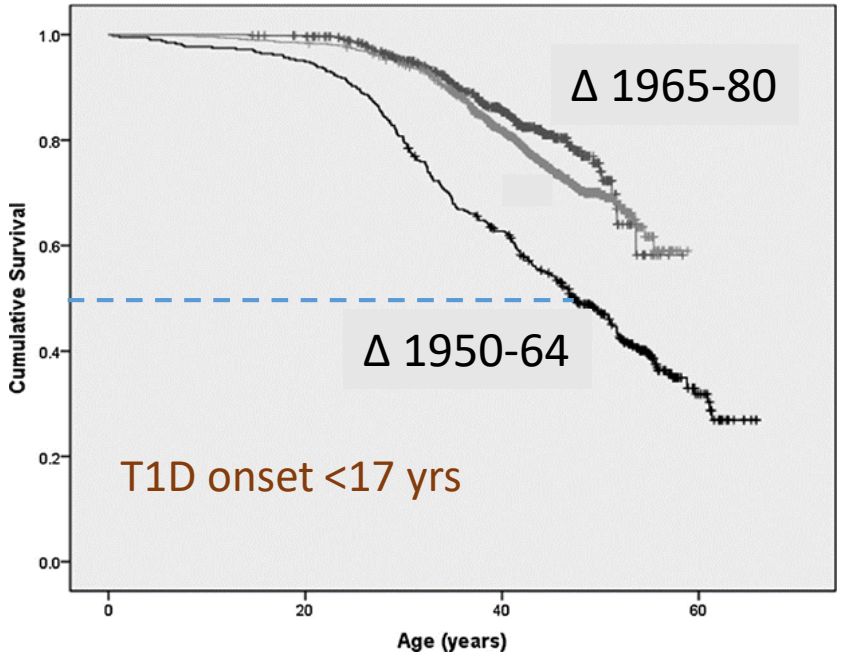
Early years after discovery:

average life expectancy extended by only 2 years

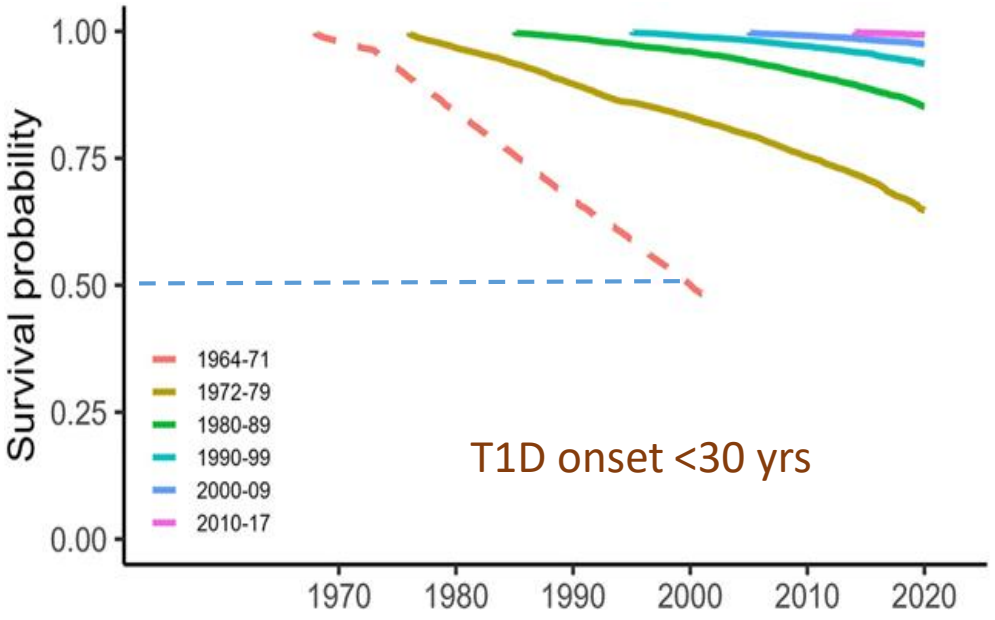
Recent times:

in 2017, life expectancy at age 20 for a person diagnosed with T1D was estimated to be 52 years (10 years less than the general Finnish population).



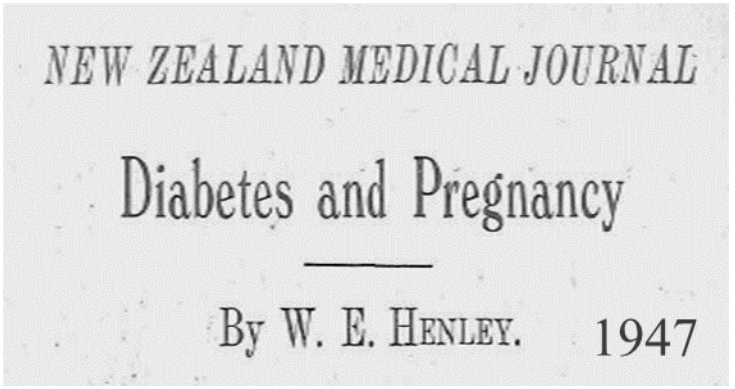


USA – *Diabetes* 2012



Finland – *DRCP* 2023

Pregnancy in women with diabetes



NEW ZEALAND MEDICAL JOURNAL

Diabetes and Pregnancy

By W. E. Henley. 1947

Nationwide survey 1938 - 1947
53 pregnancies in women with diabetes
Perinatal mortality 53%

Fetal mortality – 100%
Maternal mortality – 25%

Discovery of insulin

Fetal mortality – 40%
Maternal mortality -1%

Introduction of integrated care

Pregnancy losses were predominantly (~70%) due to intrauterine death and stillbirth after 28 weeks gestation*

1900 1920 1940 1960 1980 1990 2000

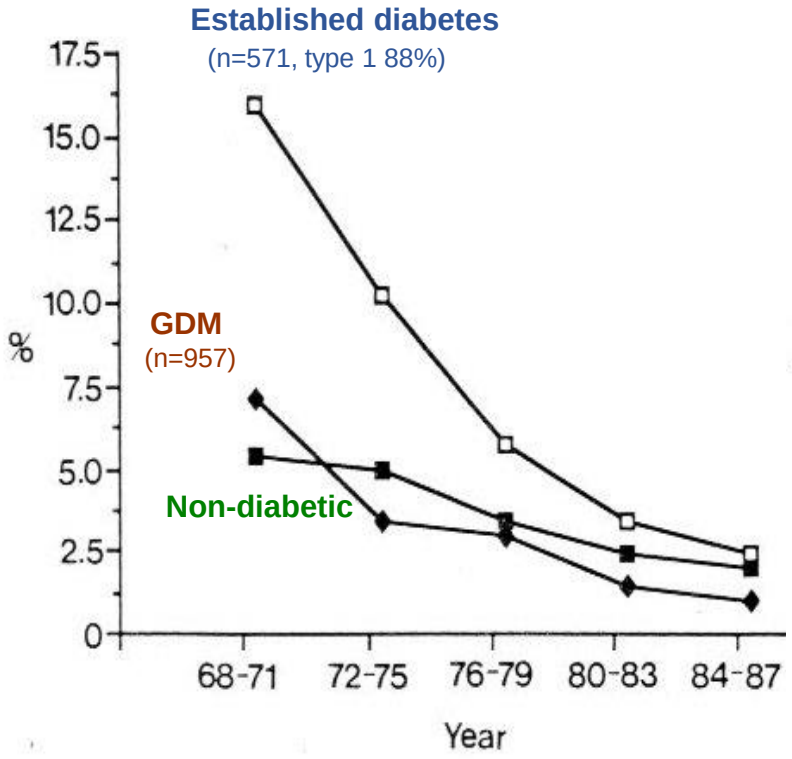
* J Peel, WG Oakley 1949
Transactions of the12th
Br Congress Obs Gynaecol 161

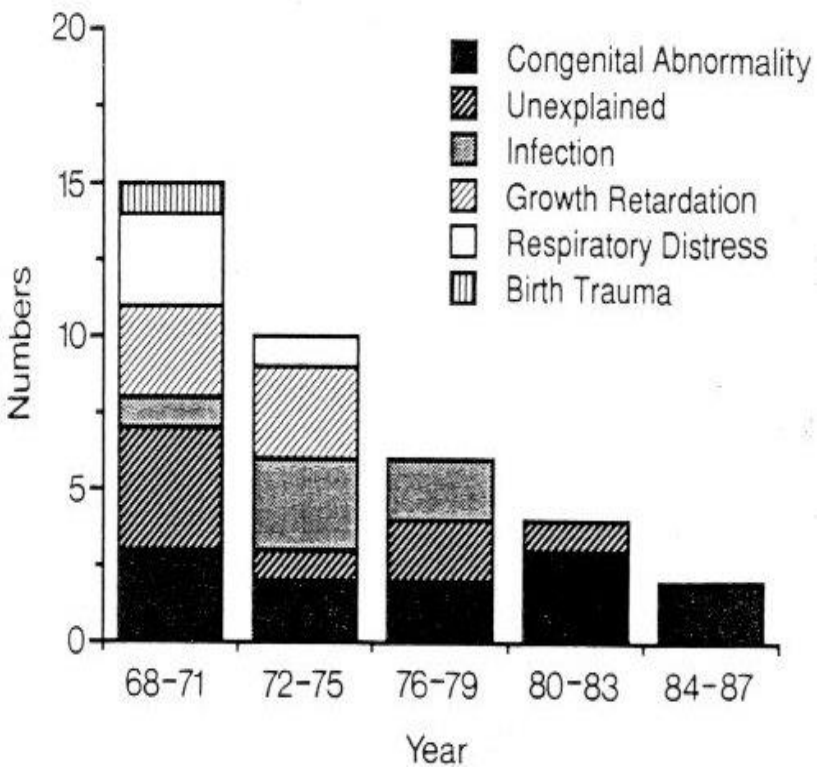
Perinatal mortality in women with diabetes

Specialization & teamwork

Tight glycaemic control
Early delivery
Better obstetric care
Better anaesthesia
Better neonatal care

National Women's Hospital 1968-87





AB Roberts & NS Pattison
NZMJ 1990 103: 211-3

Recombinant human insulin

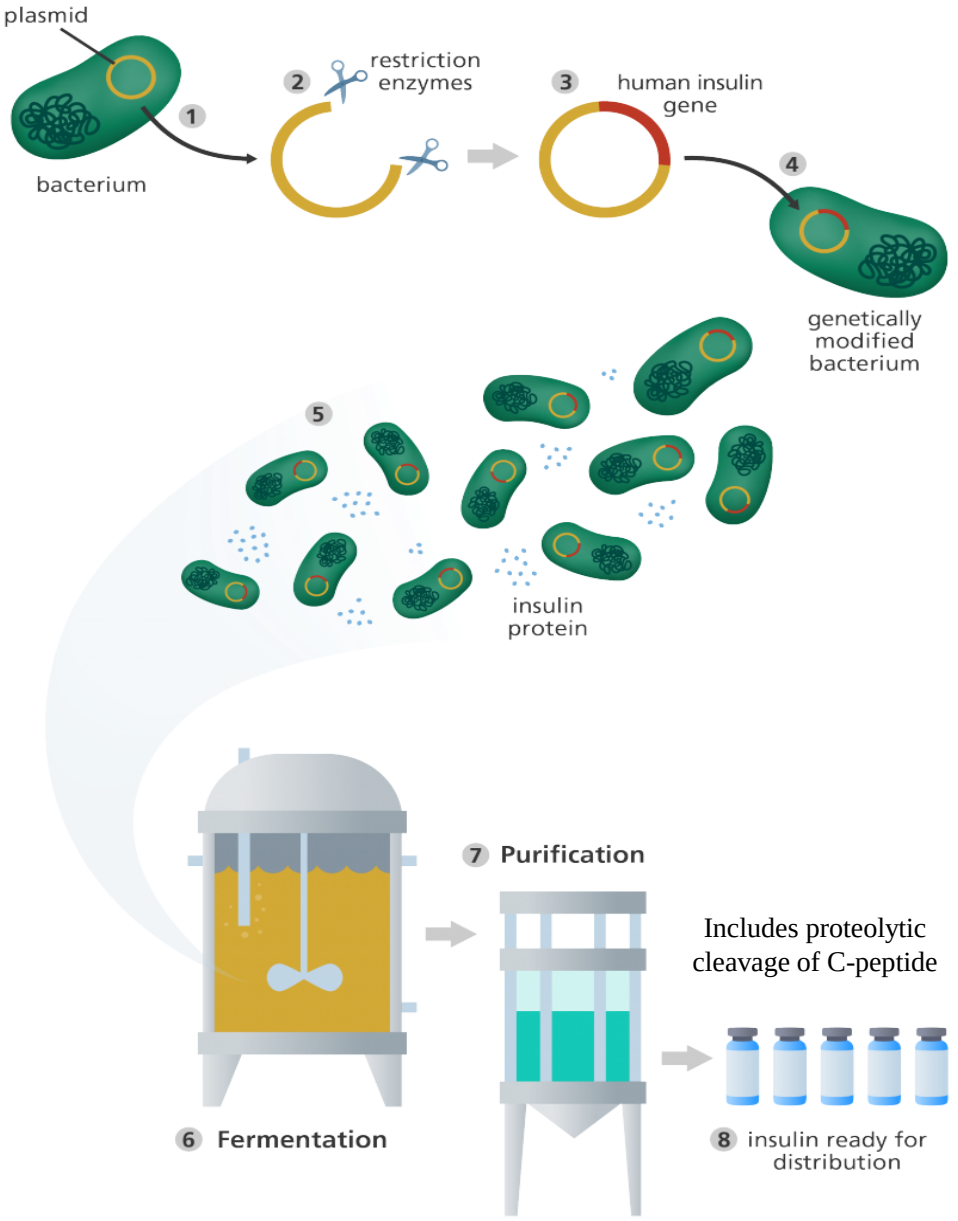
Insulin was for 60 years obtained from animal pancreas - but with increasing demand, supplies were constrained.

Recombinant human insulin first developed 1978; clinical trials in humans in 1980.

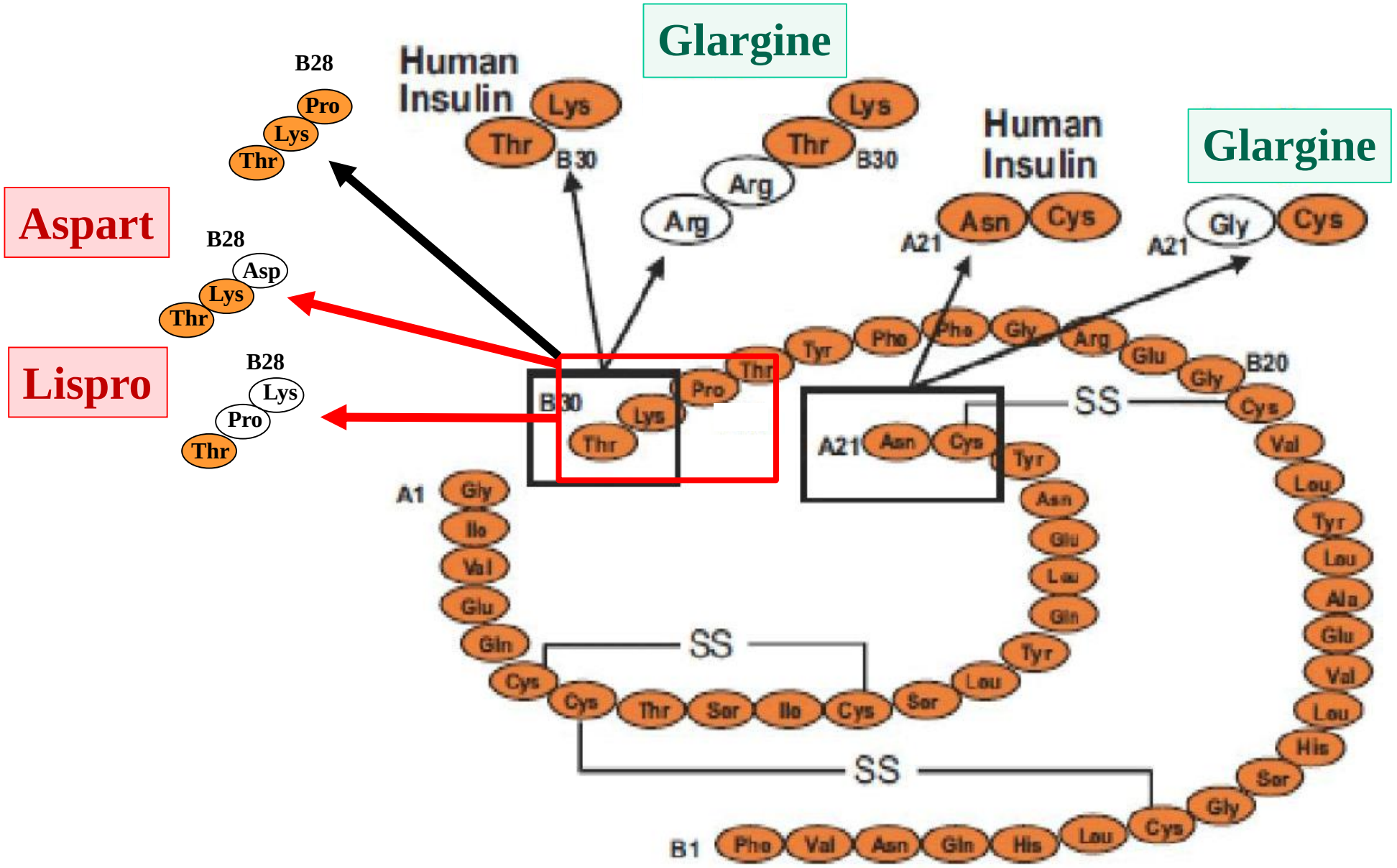
The human gene for proinsulin is inserted into *Escherichia coli* cells, or the yeast *Saccharomyces cerevisiae* which are then grown by fermentation to produce proinsulin.

The connecting peptide is cleaved enzymatically from proinsulin to produce human insulin

Manufacture of bovine insulin discontinued ~1998 and porcine insulin ~2006

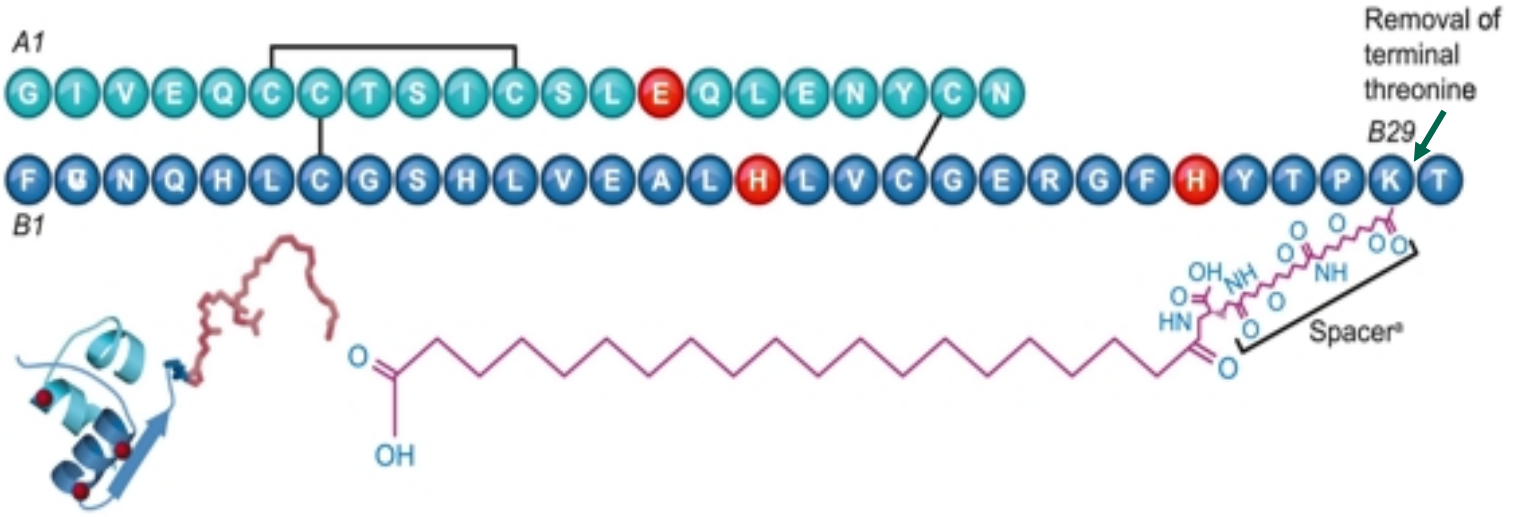


Insulin analogues



Isodec – once weekly insulin

Tightly albumin-bound
Ultra-long acting (t½ 196 hours)
Now in Phase III trials



Insulin icodec structure showing changes to the human insulin amino acid sequence and chemical modification attached to the lysine in position B29 of insulin. Insulin substitutions relative to human insulin are shown in red (TyrA14Glu, TyrB16His and PheB25His).

The cost of insulin in the USA

The same vial of insulin that cost $21 in 1996, cost ~$250 in 2022.
7 to 10 times more expensive than other countries.
Cost of production: $2 to $4 a vial.

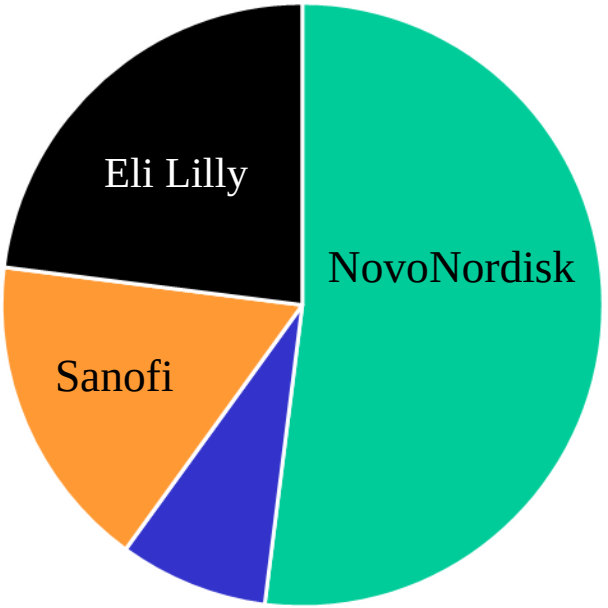
From when insulin is produced by the drug manufacturer to when it goes to a pharmacy, profit is extracted at every step of the way.

The insulin market dominated by three manufacturers
 - Eli Lilly, Sanofi, Novo Nordisk -
that have raised their list prices in lockstep.

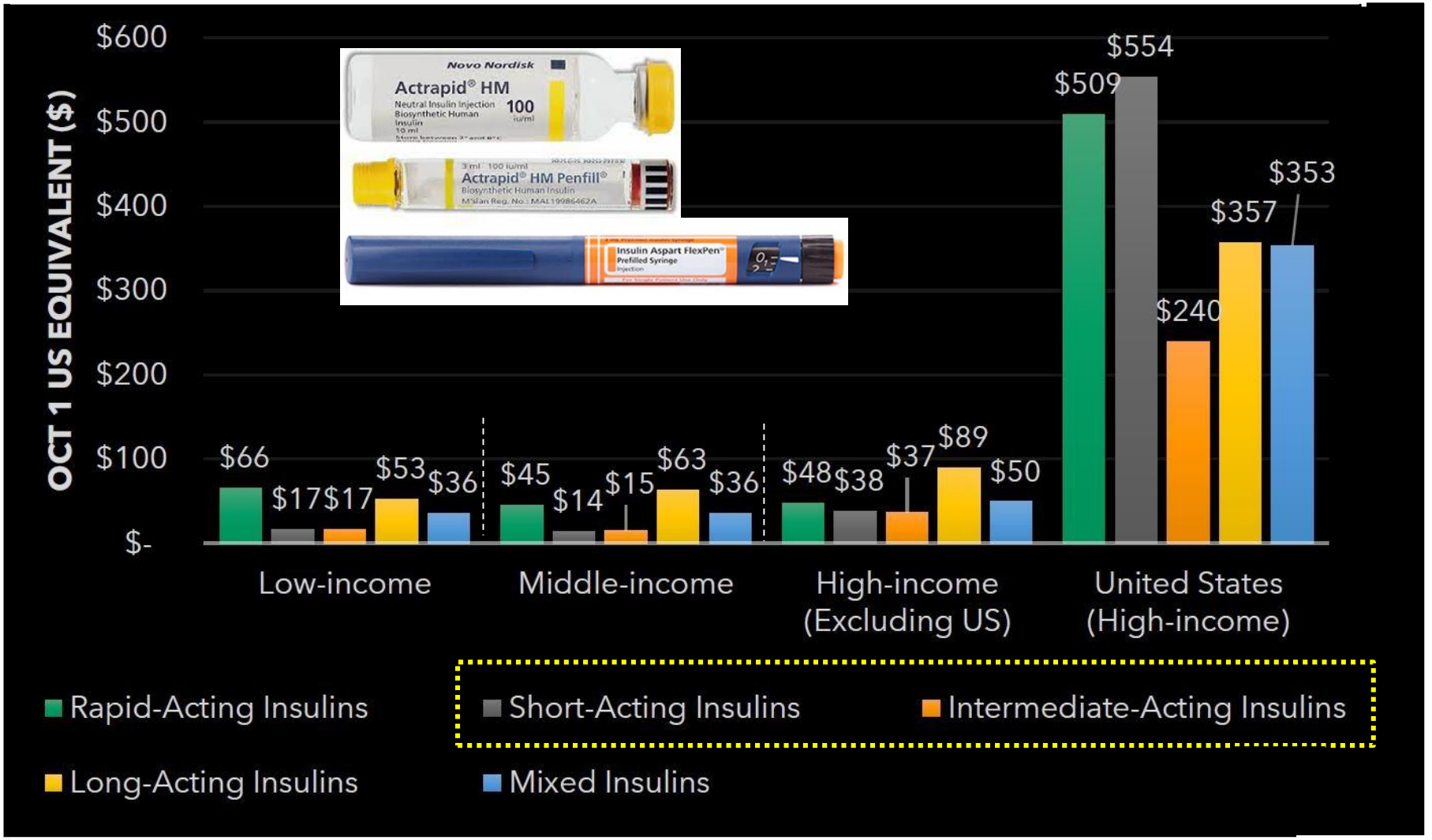
Insulin For All Act 2023
(Sen. Bernie Sanders)
fixed maximum price of a vial of insulin at $20.

Manufacturers reduced prices by 65-78%

Global insulin market ($55 billion) by volume



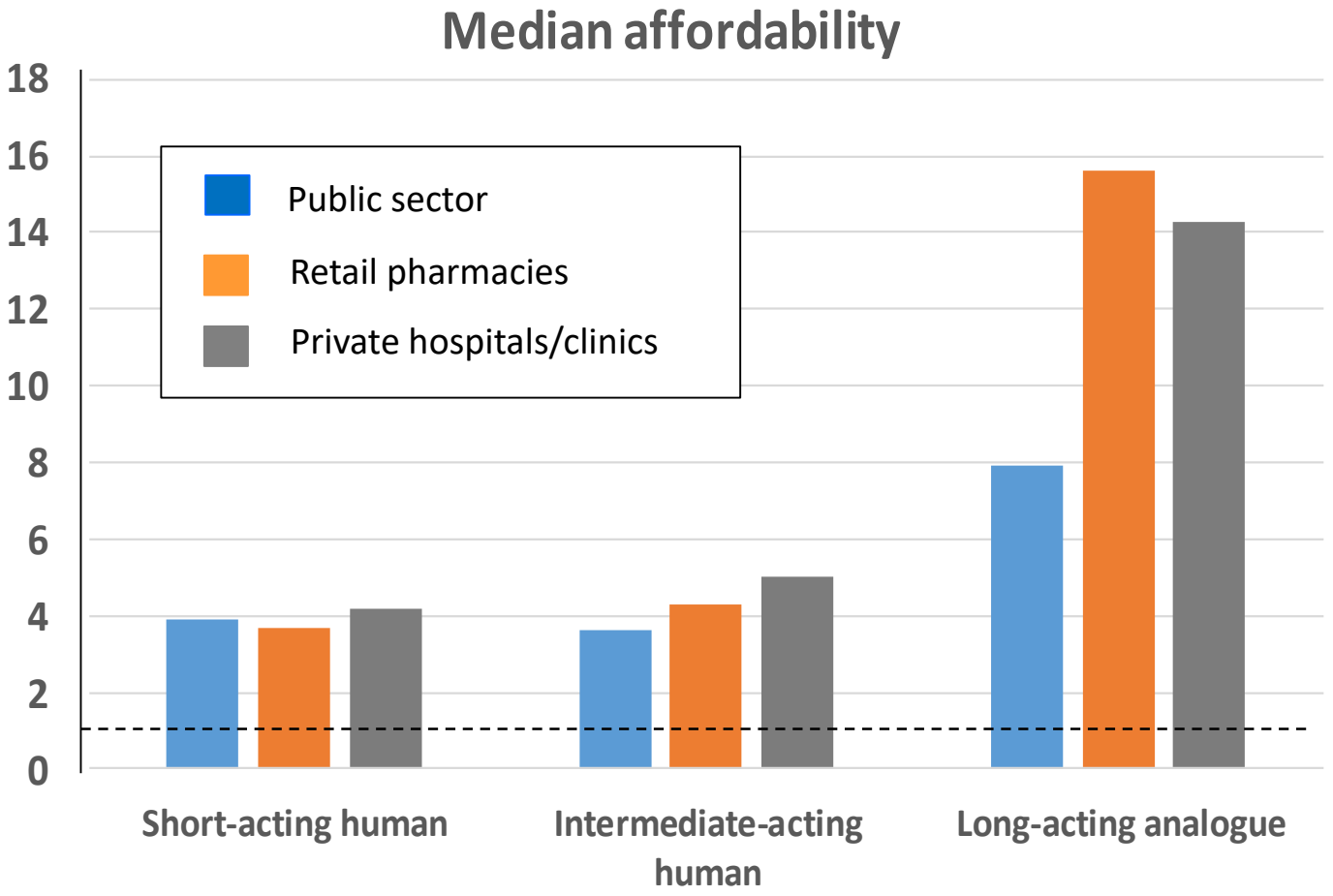
Average insulin product cost by economic status



- Insulin analogues are more expensive than ordinary insulins.
- Costs: vials < cartridges < prefilled pens
- **Insulins are largely unaffordable for those on low incomes**

Insulin prices, availability and affordability in 13 low-income and middle-income countries

Number of days a low-income person had to work to buy 10 mL insulin



Affordable: requiring no more than 1 day's wages of the lowest paid unskilled government worker to purchase 30 days' treatment

Margaret Ewen et al.
BMJ Glob Health 2019;4:e001410

The story of insulin

- Early history
- Toronto 1920-23
- Industry gets involved
- Insulin around the world
- Its clinical impact
- Recombinant insulins
- The economics of insulin

Thank you for listening….