



Making a Difference:
Milestones in Public Health &
Biotechnology: Canadian Connections

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Lecture #4 – From Insulin to Heparin (1920s-30s)

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& Adjunct Lecturer,

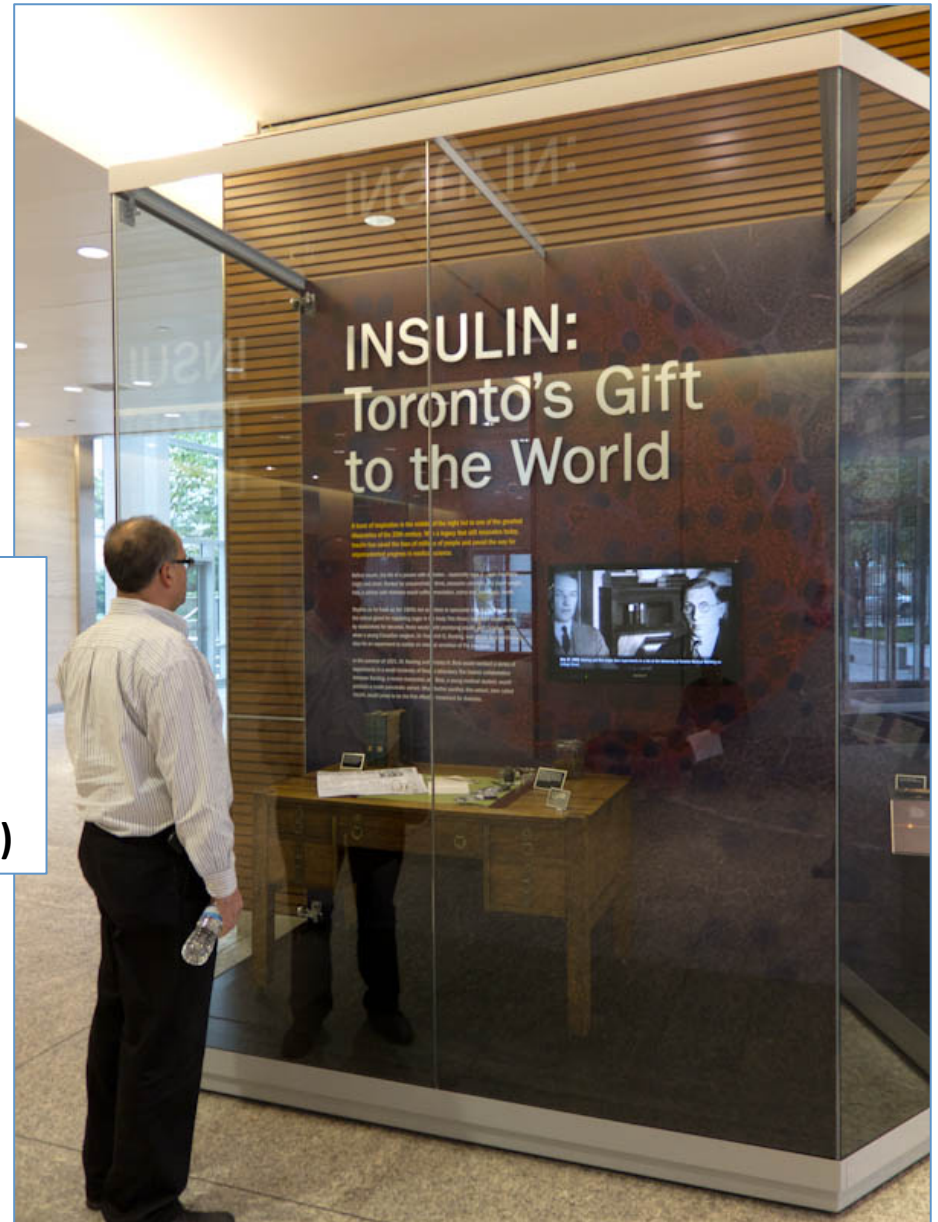
Dalla Lana School of Public Health,

University of Toronto

Living and Learning in Retirement, Course E

Class #2, October 6, 2017

Glendon College, York U., Room A002



Previous lecture slides available via:

<http://healthheritageresearch.com/clients/LLiR/>

Introduction

- The 1920s and 1930s saw two transformative advances in made-in-Canada biotechnology: one is well known – the discovery of insulin
- The other, less known, but more broadly significant, was the development of heparin at Connaught Labs
- Heparin, like insulin, is an extract of animal tissue and is used to control blood coagulation, making possible open-heart surgery, heart-lung machines and kidney dialysis.
- Indeed, heparin sparked a surgical revolution
- In today's class we'll recount the dramatic discovery of insulin story, and then trace its development and impact in Canada and beyond by the end of the 1930s, including on the development of Heparin

THIS IS PUBLIC HEALTH: A CANADIAN HISTORY Executive Summary

This is Public Health, A Canadian History explores the evolution of public health from its early foundation before Canada was a country until 1986, when the Ottawa Charter for Health Promotion launched what many considered to be a new era in public health. During this time span, numerous public health milestones were achieved through organized community efforts to promote health and to prevent disease and injury, which have always been at the core of public health.

Canada, despite the tensions of jurisdictional boundaries. The struggle to eliminate disparities—between geographic regions, urban and isolated communities, Aboriginal and non-Aboriginal people—was a longstanding concern that continues to this day. Since its beginnings, public health has faced changes and challenges and has too frequently been undervalued. However, a number of remarkable advances in Canada over the past 100-plus years can be attributed to public health.

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PATENT MEDICINES
FAKE CONCERNS
Note the Quality of our Advertisements
If ever product is worth while, advertise it well in your community.
'The Public Health Journal'

Public Health Journal, November 1917

This history has been compiled by the Canadian Public Health Association (CPHA), to mark its 2010 centenary. Like the field of public health, CPHA has much to celebrate in addressing ongoing challenges over 100 years as the national voice for a very diverse field. This narrative is dedicated to those public health advocates and activists who have “fought the good fight,” struggling to advance community health long before Canadian health systems were in place.

This history underlines the importance of federal leadership in the implementation of successful public health initiatives in

THE GOVERNMENT INSPECTOR'S OFFICE
Hours from 9 to 4

THE GOVERNMENT INSPECTOR'S OFFICE
The government inspector's office, 1850

Canadian Public Health Association 1

C.J. Ruty, *This is Public Health: A Canadian History* (Canadian Public Health Association eBook, 2010) - <https://www.cpha.ca/history-e-book>

Displaying the Insulin Story in Toronto

- I have curated two public exhibits on the Discovery & Development of Insulin:
- **2008** – 16 Posters @ Diabetes Clinic, Toronto General Hospital, Eaton Wing, 12th floor



<http://healthheritageresearch.com/Insulin/TGH-posters/TGHInsulinPosters.html>

Displaying the Insulin Story in Toronto

- I have curated two public exhibits on the Discovery & Development of Insulin:
- **2011** – Multimedia display @ MaRS Discovery District, East Tower, for Faculty of Medicine, University of Toronto



Deadly Diabetes, Before Insulin

- Before Insulin, the life of a person with diabetes, especially a child with type 1, was inevitably tragic and short, dominated by unquenchable thirst, starvation diets and a body that ultimately feeds on itself
- Beyond strict dietary control, very little could be done to prevent death, despite the claims of patent medicines and others offering dubious cures

3050 Walnut, Philadelphia, Pa.

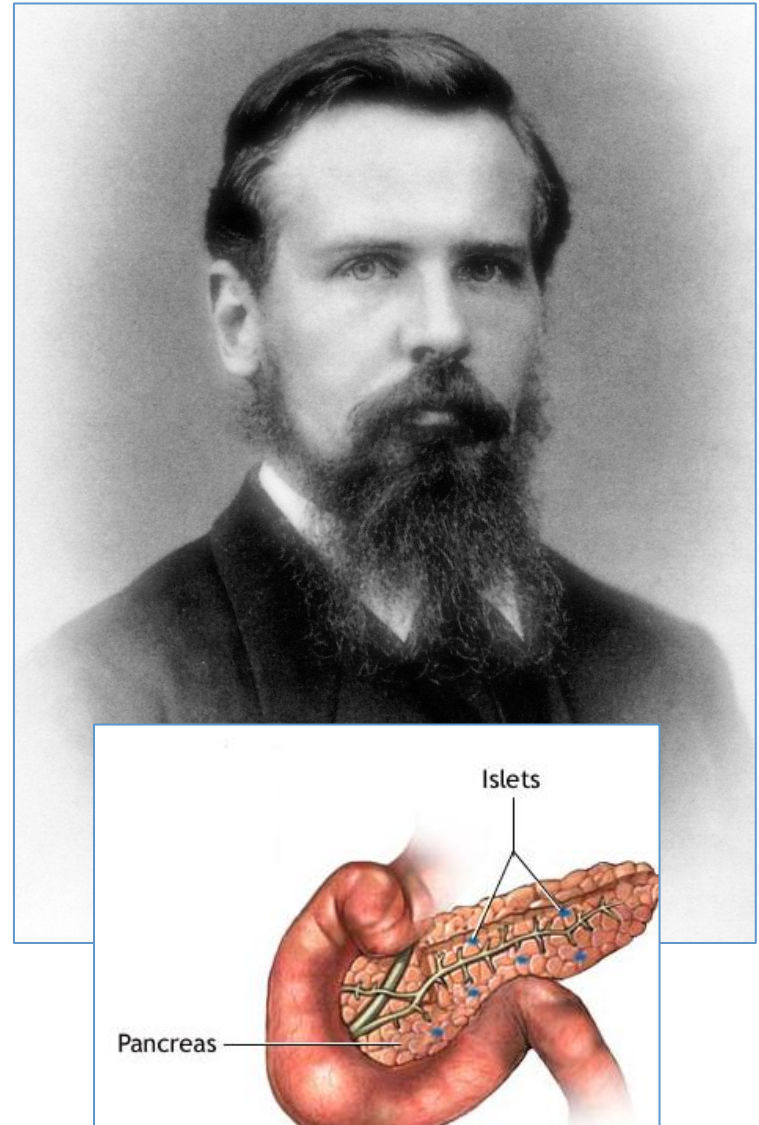
Diabetes Treated with greatest success without restricted diet. Physio-nutritive Sal-Sano removes all symptoms of the disease, produces gain in weight, muscle and nerve power and energy At leading druggists. Write for booklet.

SAL-SANO COMPANY
11½ WEST BROADWAY. NEW YORK



Deadly Diabetes, Before Insulin

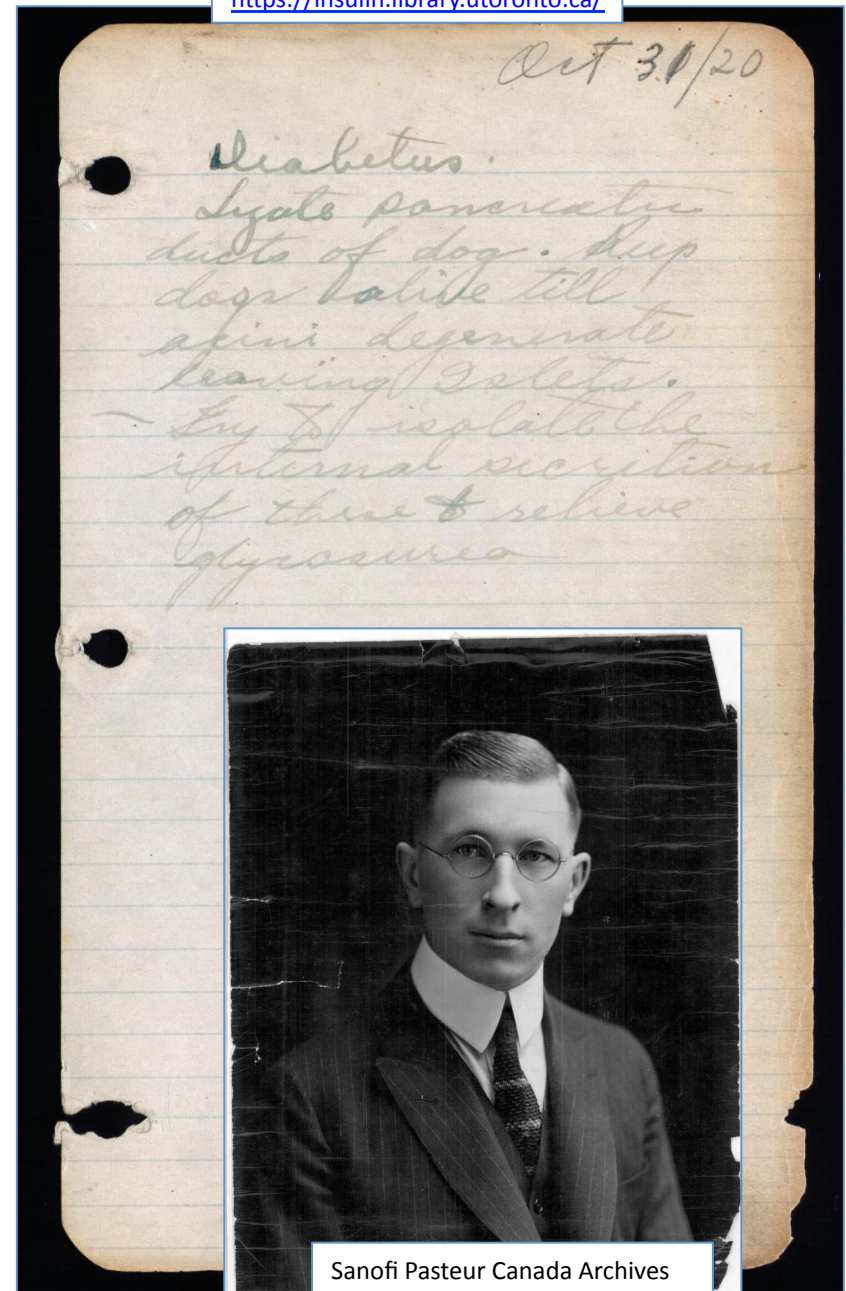
- **250 B.C.** – First use of “diabetes” (from the Greek “to pass through”)
- **1675** – “diabetes mellitus” term first used (“mellitus” Latin for honey or sweet)
- **1869** – Paul Langerhans (right) identifies “insulin”-producing “islets of Langerhans” in pancreas
- **1889** – Role of pancreas in diabetes discovered; diabetes developed in dogs when pancreas removed
- **1910** – Discovered that diabetes caused by the lack of “insulin” in the pancreas
- This work led researchers to conduct a variety of insulin extraction experiments, but with none yielding promising results until a young Canadian surgeon was struck by an compelling idea in October 1920



Banting's Idea

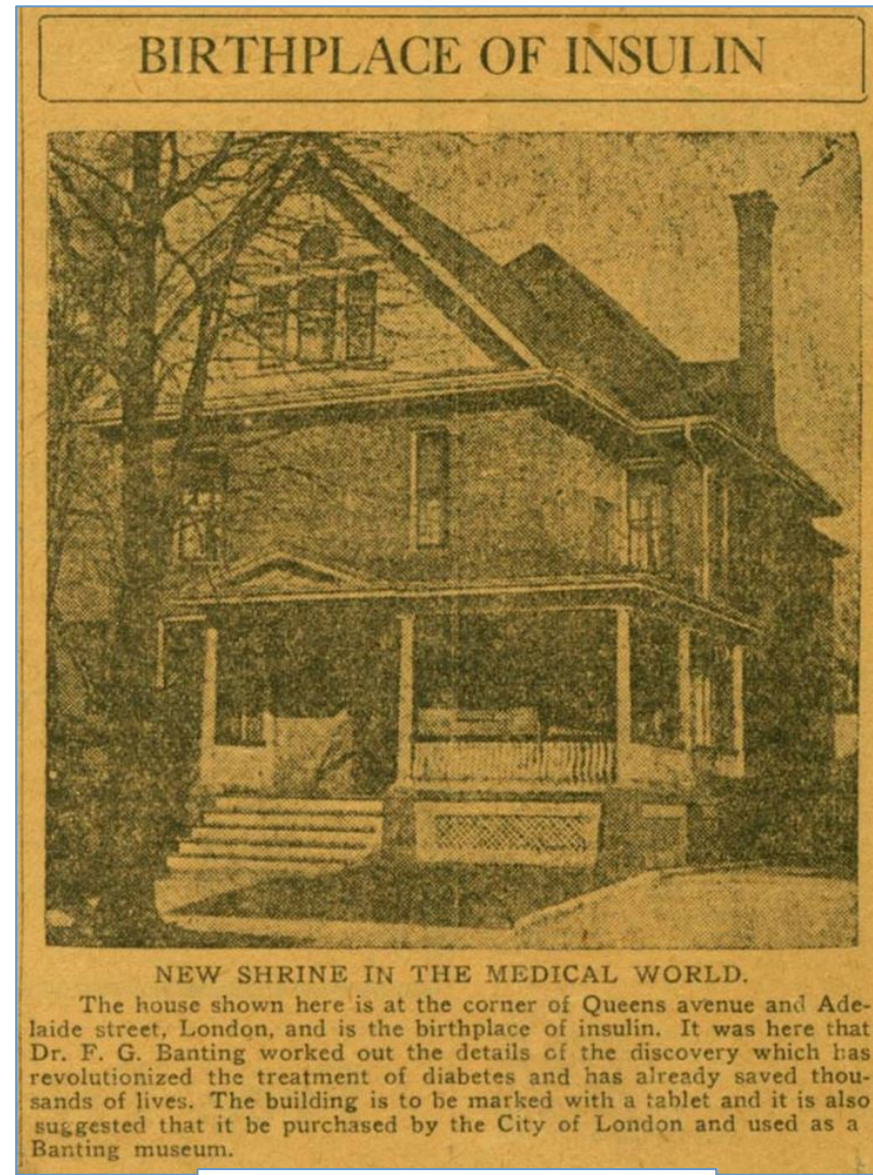
- **Oct. 31, 1920 (2:00 am)** - The Insulin story began in London, ON, when Dr. Frederick Banting awoke with a compelling idea
- Banting had read an article about the pancreas and diabetes for a lecture he was preparing and was struck with an idea for an experiment to isolate the internal secretion from the pancreas that might control diabetes
- He jotted down in a notebook,

- “Diabetes: Ligate pancreatic ducts of dog. Keep dogs alive till acini degenerate leaving Islets. Try to isolate the internal secretion of these and relieve glycosurea”



Banting's Idea

- Born on November 14, 1891 in Alliston, Ontario, Dr. Frederick G. Banting brought a surgeon's perspective to the problem of diabetes.
- **1912** - He had entered the University of Toronto and graduated with an expedited class because of WWI.
- After the war, he worked at the Christie Street Hospital for Veterans in Toronto and the Hospital for Sick Children before moving to London, Ontario.
- **1920** - Banting started his own practice in London, but lack of patients led him to work as a demonstrator in the University of Western Ontario medical school



<https://bantinghousehsc.wordpress.com/>

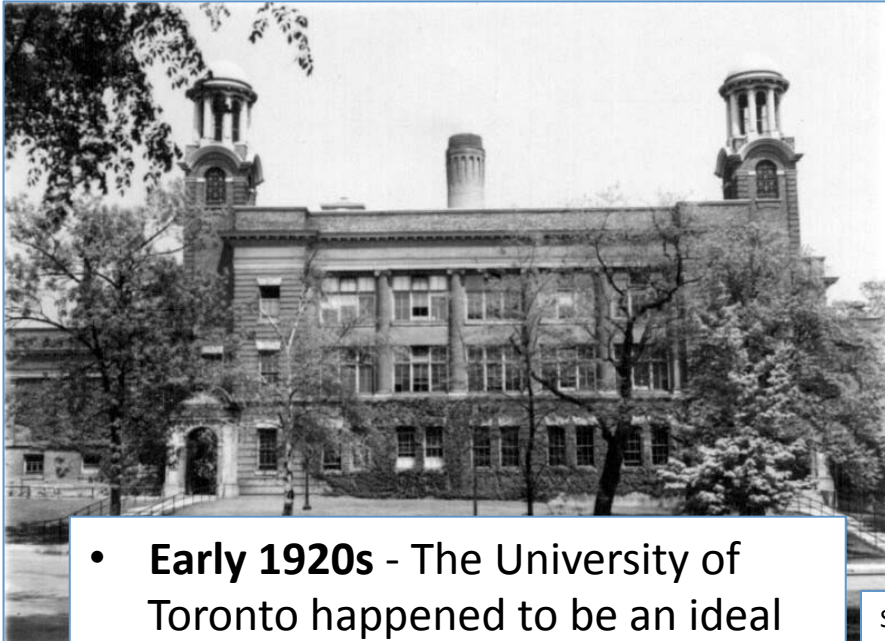
Banting's Idea



<https://bantinghousenpsc.wordpress.com/>

Banting's Idea

- **Nov. 6, 1920** – Banting took his idea to the University of Toronto and presented it to Dr. J.J.R. Macleod, Professor of Physiology and a specialist in the study of diabetes



- **Early 1920s** - The University of Toronto happened to be an ideal institution in which Banting could develop his idea



Banting's Idea

- U. of T. stood at the centre of a uniquely linked group of medical and scientific institutions - Toronto General Hospital (r), the Hospital for Sick Children (l), and, as discussed in recent classes, its singular public health biologicals producer, Connaught Antitoxin Laboratories - each ready to play key roles in the insulin story.

CONNAUGHT ANTITOXIN LABORATORIES
UNIVERSITY OF TORONTO
Established for research investigation in Preventive Medicine and for the production and distribution of all Public Health Biological Products at Minimum Prices..

SERVICE TO THE EMPIRE

VACCINES
For Prevention of
SMALLPOX
TYPHOID FEVER
WHOOPIING COUGH
HYDROPHOBIA

SERUMS
For Prevention or Cure of
DIPHTHERIA
LOCKJAW (TETANUS)
PNEUMONIA (CERTAIN CASES)
EPIDEMIC MENINGITIS

This map shows the success of the effort to prepare and distribute these life-saving products at minimum prices.

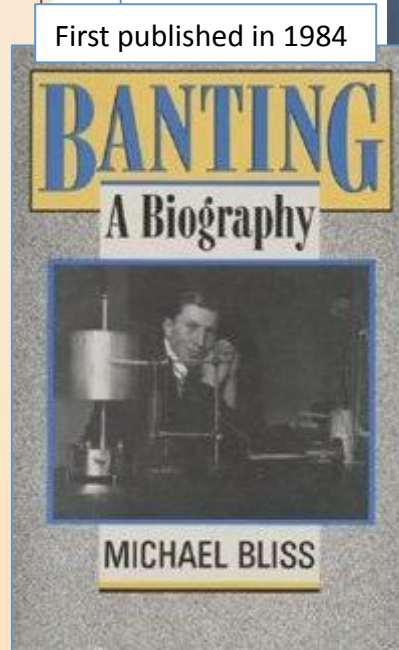
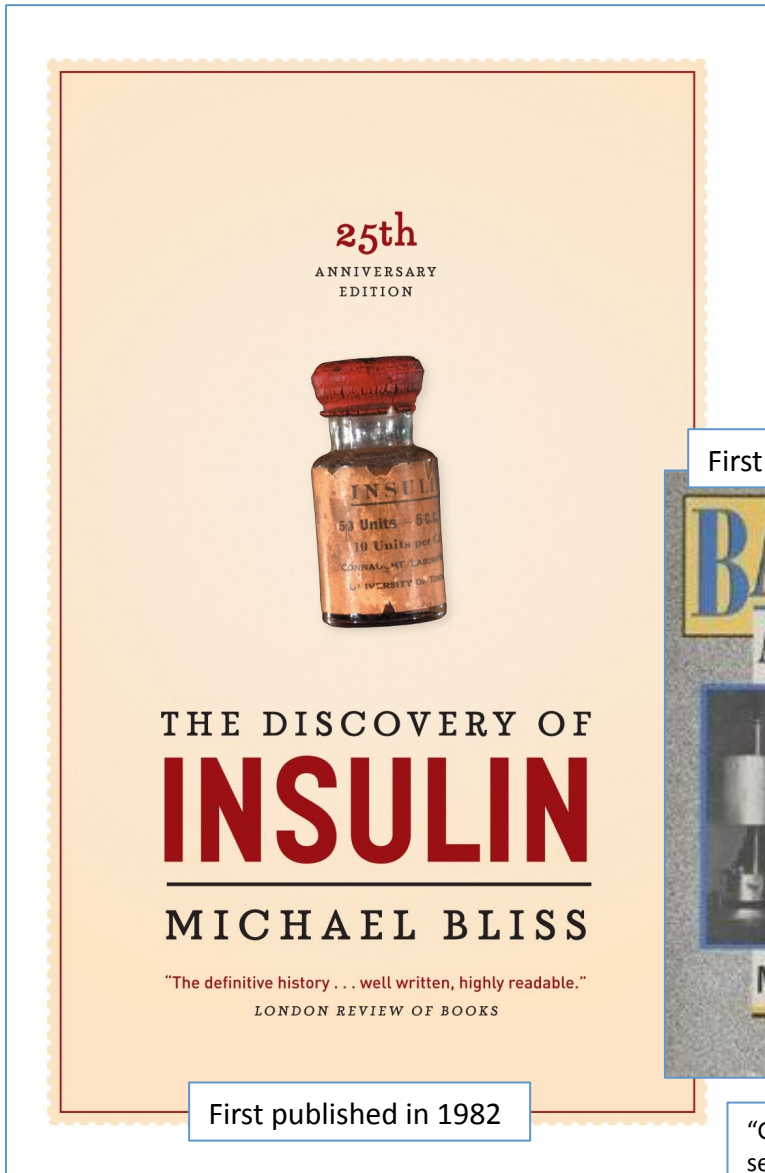
BY THE UNIVERSITY OF TORONTO.

Sanofi Pasteur Canada Archives



Discovering Insulin in Toronto

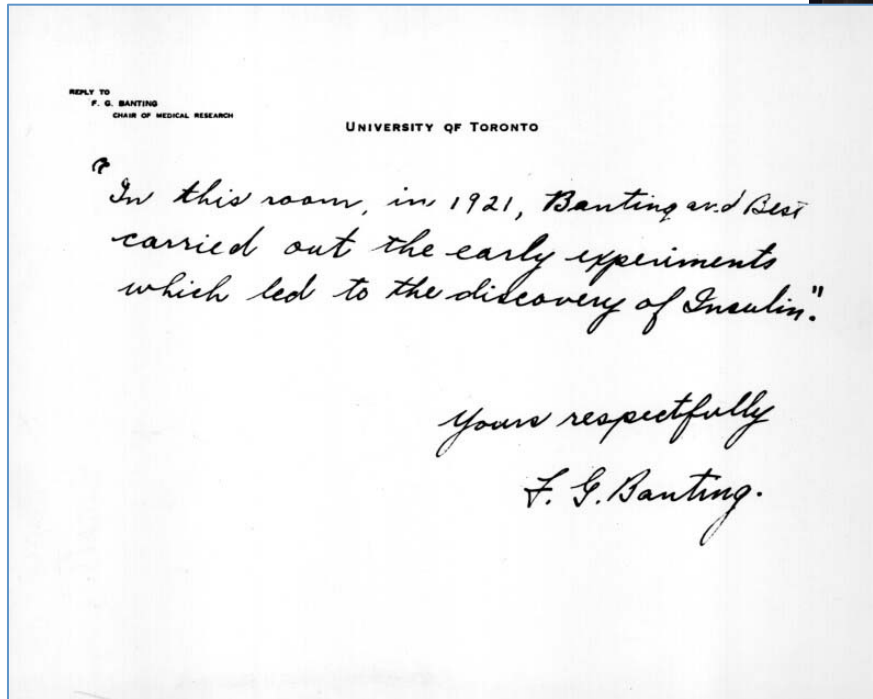
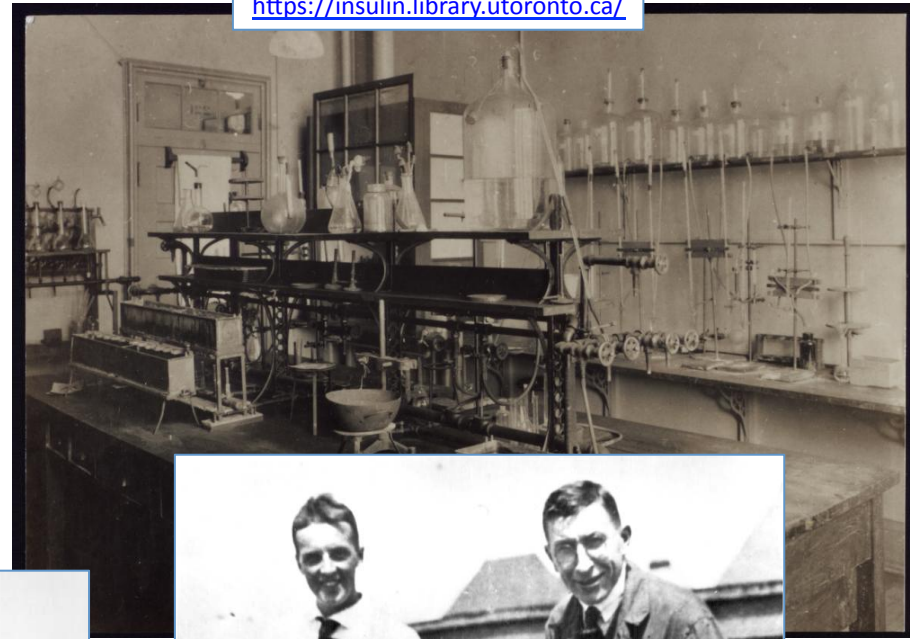
- Michael Bliss and the history of the history of the discovery of Insulin
- Ultimately, as Bliss concluded, there is glory enough for all...



<https://www.youtube.com/watch?v=brChPJ3AzkE>

Discovering Insulin in Toronto

- After meeting Macleod, who was intrigued, though skeptical, Banting was given a small lab, access to experimental dogs, a \$100 budget, and the assistance of Charles Best, a recent graduate in Physiology and Biochemistry

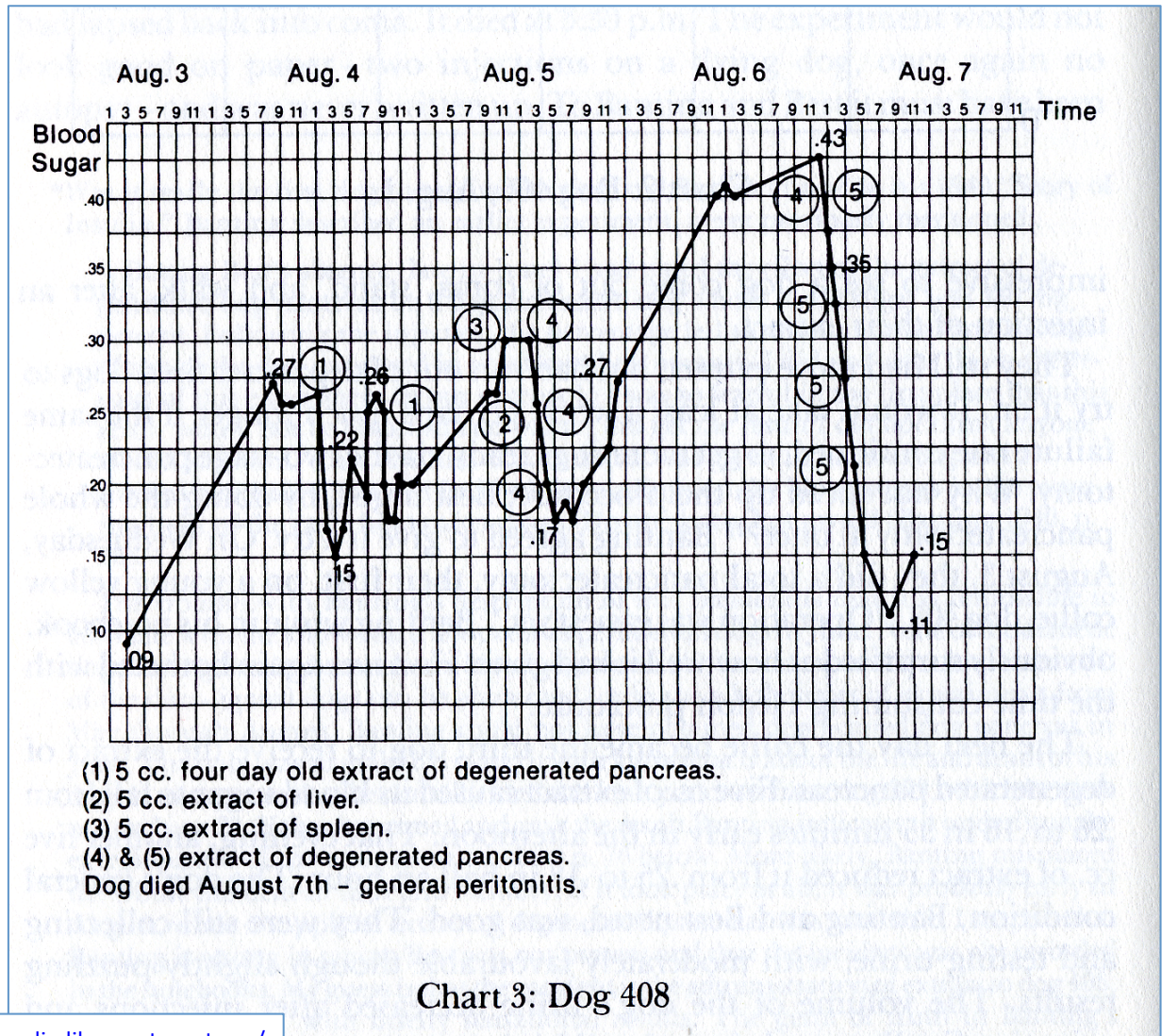


Discovering Insulin in Toronto

- **May-Aug 1921** – During an especially hot summer, Banting and Best reported encouraging results with a pancreatic extract controlling blood sugar levels in de-pancreatized dogs.

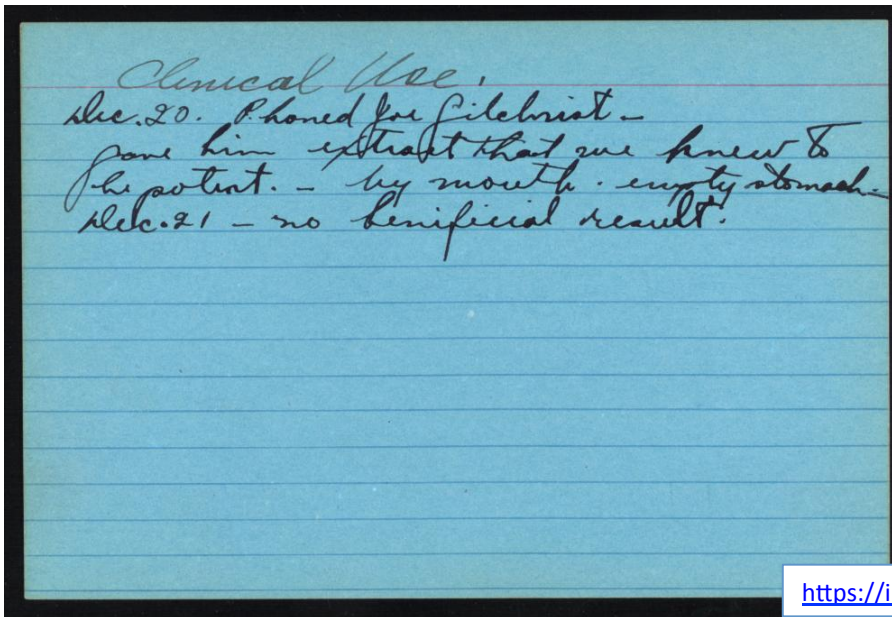


<https://insulin.library.utoronto.ca/>



Discovering Insulin in Toronto

- **Dec 1921** - Dr. James Bertram Collip, a biochemist from the University of Alberta on sabbatical in Toronto, joins Banting and Best to help purify the extract.
- Encouraging results with dog #33, “Marjorie,” lead to the extract’s first human use (administered orally), but it was unsuccessful



<https://insulin.library.utoronto.ca/>

Discovering Insulin in Toronto

<https://insulin.library.utoronto.ca/>

- **Jan 11, 1922** - 14-year-old Leonard Thompson is the first to receive an injection of the extract, but with no effect
- **Jan 23, 1922** – Leonard receives Collip’s more purified extract, with good results

The Journal of Laboratory and Clinical Medicine

VOL. VII

ST. LOUIS, FEBRUARY, 1922

No. 5

ORIGINAL ARTICLES

THE INTERNAL SECRETION OF THE PANCREAS*

BY F. G. BANTING, M.B., AND C. H. BEST, B.A.

THE hypothesis underlying this series of experiments was first formulated by one of us in November, 1920,† while reading an article dealing with the relation of the isles of Langerhans to diabetes.¹ From the passage in this article, which gives a résumé of degenerative changes in the acini of the pancreas following ligation of the ducts, the idea presented itself that since the acinous, but not the islet tissue, degenerates after this operation, advantage might be taken of this fact to prepare an active extract of islet tissue. The subsidiary hypothesis was that trypsinogen or its derivatives was antagonistic to the internal secretion of the gland. The failures of other investigators in this much-worked field were thus accounted for.

The feasibility of the hypothesis having been recognized by Professor J. J. R. Macleod, work was begun, under his direction, in May, 1921, in the Physiological Laboratory of the University of Toronto.

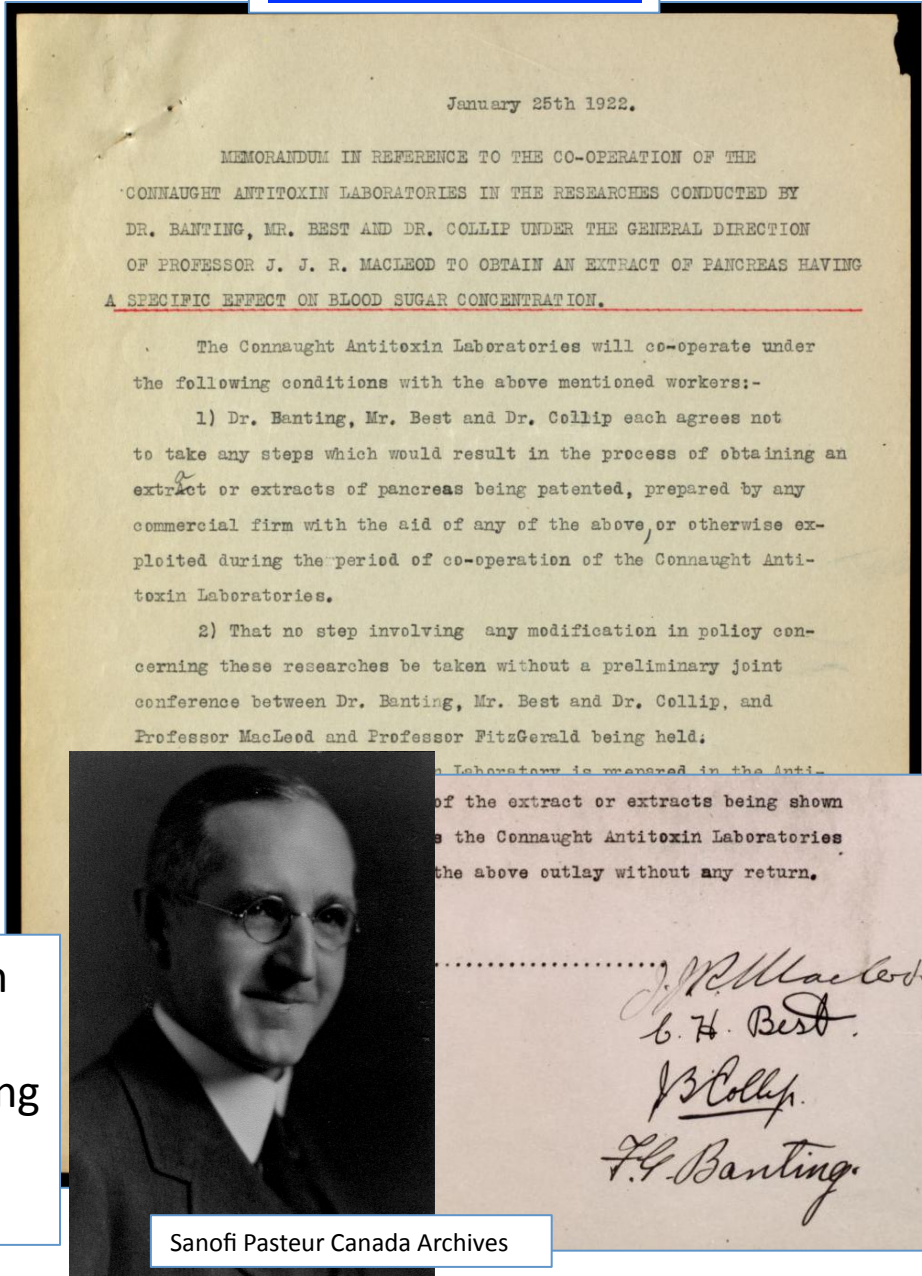


LEONARD THOMPSON
First patient to receive insulin in
Toronto.

Developing Insulin in Toronto

<https://insulin.library.utoronto.ca/>

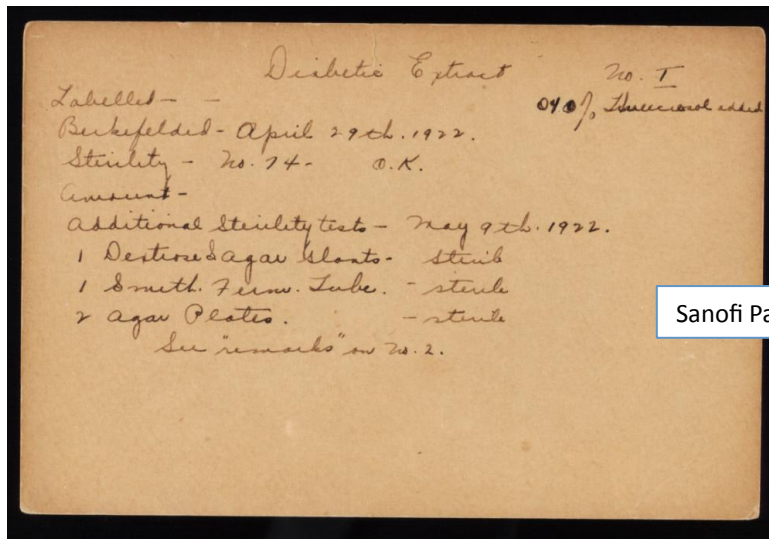
- **Jan 25, 1922** - Encouraged by Leonard Thompson's successful treatments, but concerned about the future control of the new extract's production, Connaught's Director, John FitzGerald (right), facilitated an agreement with Banting, Best, Collip and Macleod
- He offered them the Lab's facilities (in the basement of the Medical Building) to help develop methods to produce the extract for clinical trials
- Clinical trials of the extract soon began in several locations in Toronto (ie. Toronto General Hospital) and elsewhere, including in the U.S., through Banting and several diabetic specialists



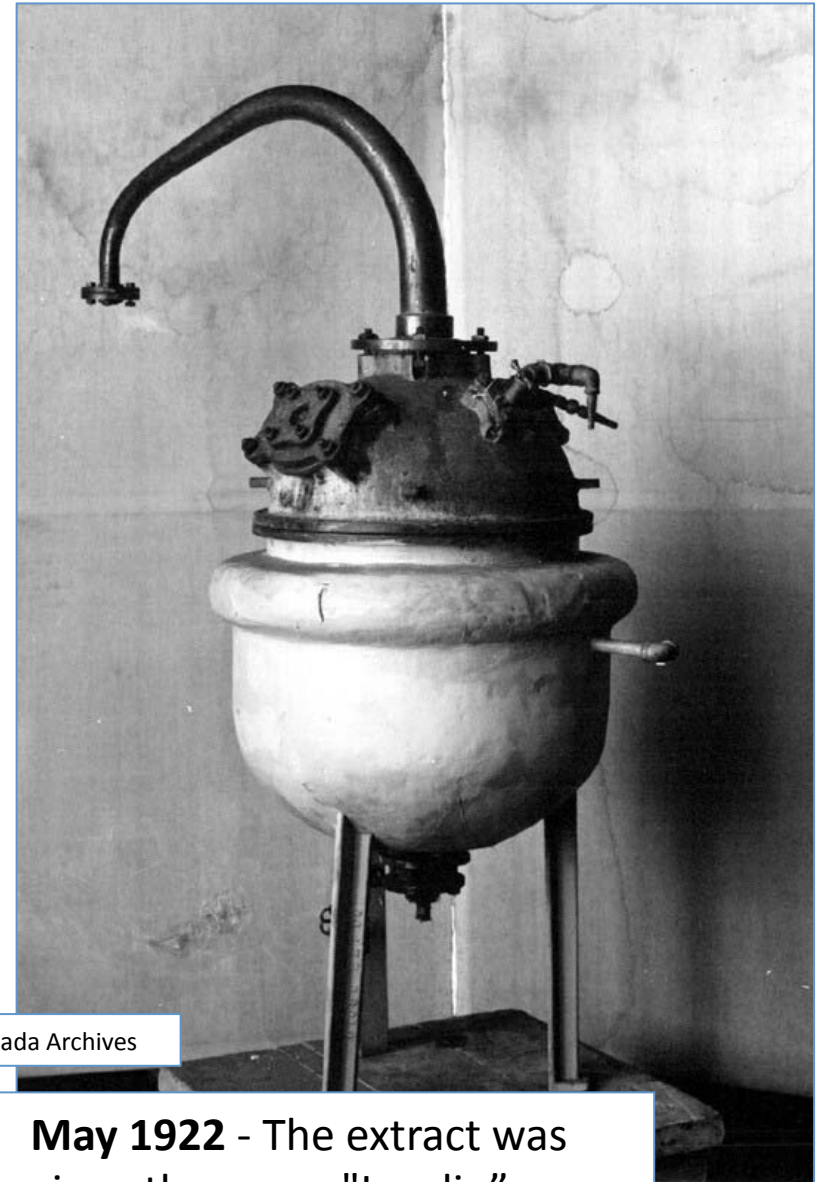
Sanofi Pasteur Canada Archives

Developing Insulin in Toronto

- Moving to large-scale insulin production was a major challenge for Connaught.
- **March-May 1922** - After frustrating failures, production was restored under Best's direction
- Connaught then dedicated its full, though modest, resources to insulin production and output rose steadily



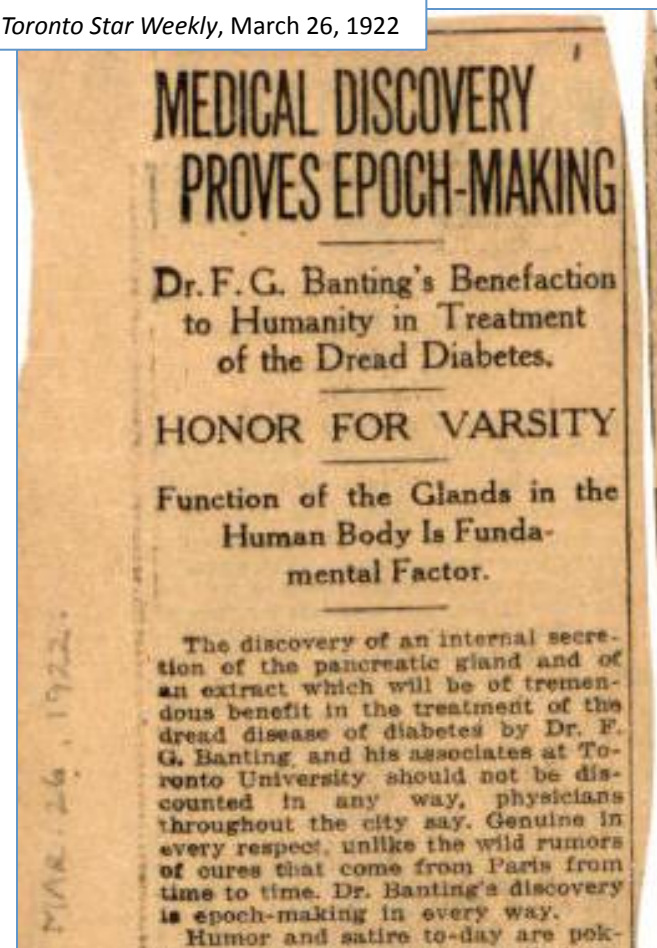
Sanofi Pasteur Canada Archives



- **May 1922** - The extract was given the name "Insulin"

Developing Insulin in Toronto

- News of the first successful use of the pancreatic extract attracted unprecedented international attention to Toronto
- It also put intense pressure on Connaught scientists to further refine and purify the extract for clinical trials and to increase production, while keeping the price as low as possible

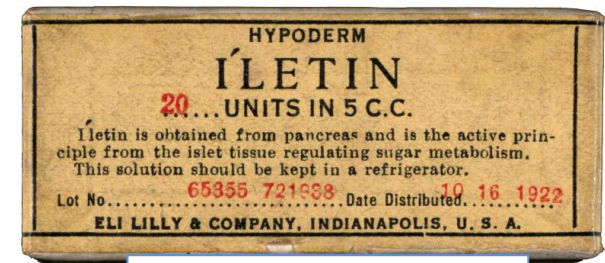
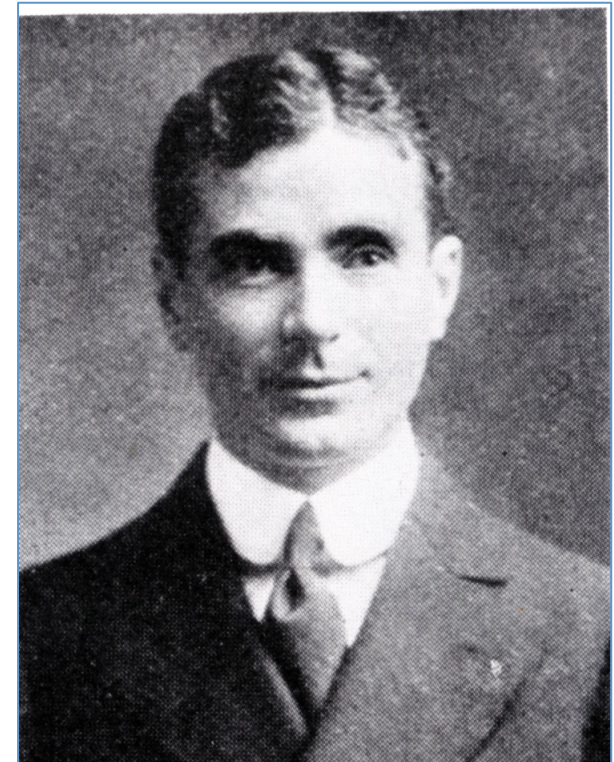


Toronto Star, March 22, 1922, p. 1



Developing Insulin in Toronto

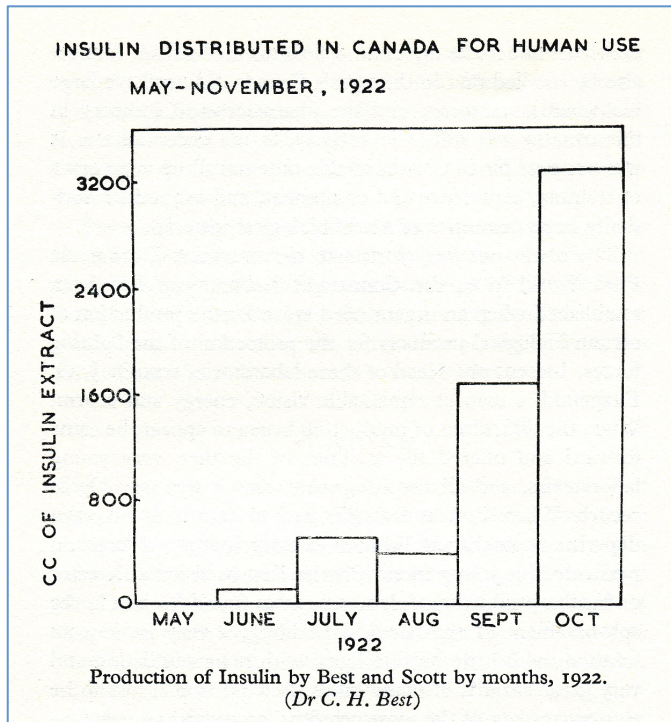
- **May 30, 1922** - A unique collaboration agreement arranged between the University of Toronto and Eli Lilly & Co. of Indianapolis, designed to expedite the the development of large scale insulin production methods
- This and other agreements relating to insulin production, licensing and patent protection was negotiated by the University of Toronto's Insulin Committee
- Charles Best assumed leadership of Connaught's Insulin production and worked closely with Eli Lilly, especially the company's Research Director, Dr. G.H.A. Clowes (right)
- The agreement granted Eli Lilly exclusive rights to supply Insulin (sold as "Iletin") in the United States until June 1924



Sanofi Pasteur Canada Archives

Insulin: From Toronto To The World

- Press coverage of insulin's first clinical trials in Toronto led to a wave of requests for this diabetes "cure" from all over the world
- The severe insulin supply challenges during 1922 meant only a few critically ill patients, mostly children, could be treated.



Toronto Star Weekly, March 26, 1922

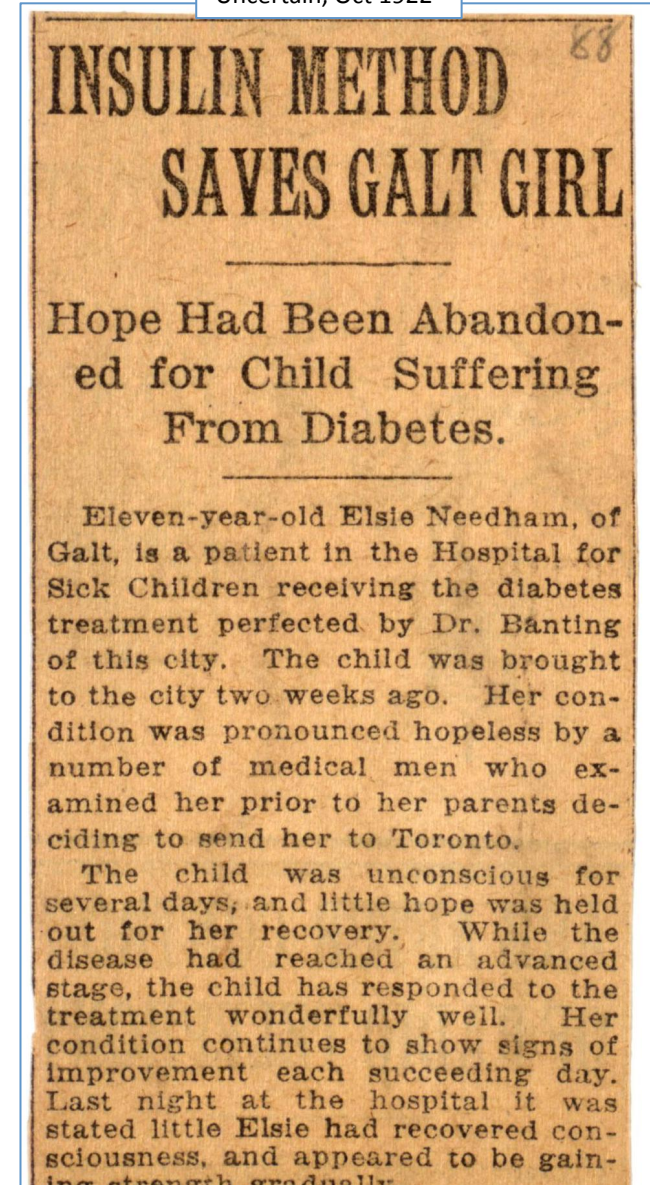
Insulin: From Toronto To The World

- Almost all of these early patients were American, some from prominent families, including Elizabeth Hughes (below)
- Elsie Needham of Galt, ON (right), was the only Canadian among this group of early patients.

Toronto Star, Aug 17, 1922

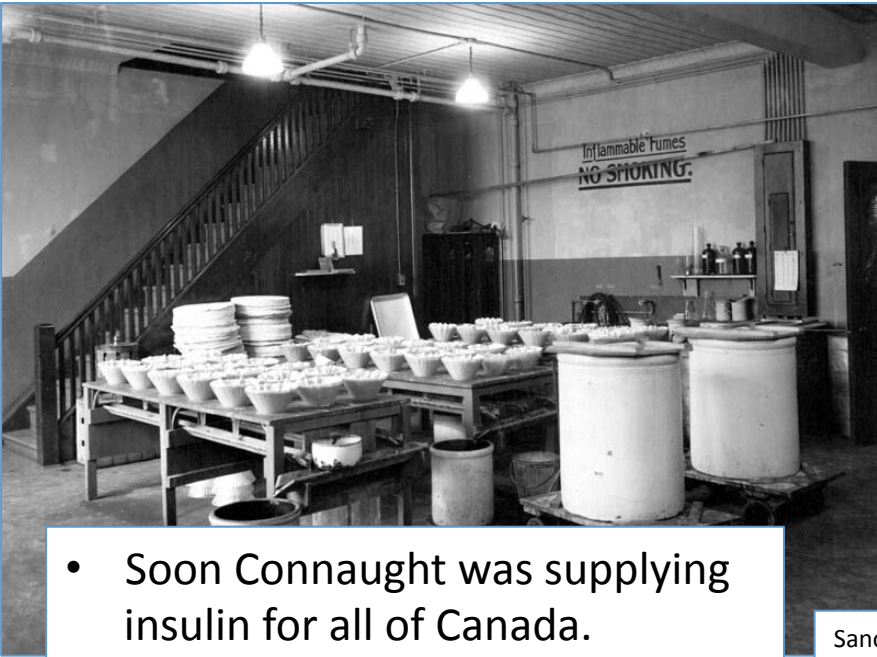


Uncertain, Oct 1922



Insulin: From Toronto To The World

- **April 1923** - Canada's insulin supply finally found a firm foothold thanks to funds from the Ontario government, a New York City diabetic, and Connaught's reserves, to establish an insulin production plant in U of T's vacant YMCA building on campus



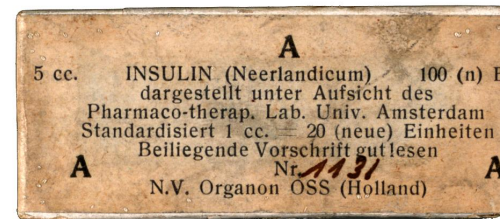
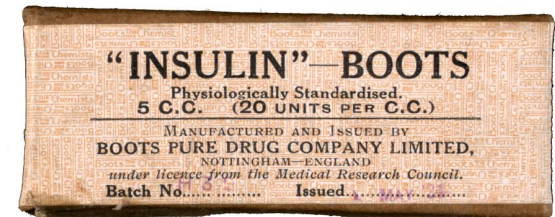
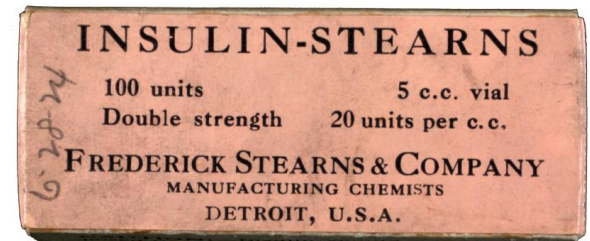
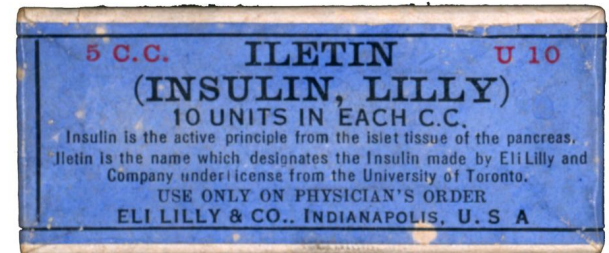
- Soon Connaught was supplying insulin for all of Canada.



Sanofi Pasteur Canada Archives

Insulin: From Toronto To The World

- As Insulin production steadily grew in Canada, the University of Toronto Insulin Committee focused on licensing its production in other countries
 - Eli Lilly had exclusive U.S. rights until 1924, when other American firms were granted licenses
 - In the U.K., the Medical Research Council was given the right to issue licenses there
 - Firms in Australia and Denmark also received early licenses
- By 1926, insulin was patented and trademarked in 44 countries, with the Insulin Committee carefully regulating who produced it



Sanofi Pasteur Canada Archives

Insulin: From Toronto To The World



SAVING LIVES WITH INSULIN
During the early 1920s, Connaught's public health partnerships grew on an international level. The discovery of insulin at the University of Toronto in 1921 and Connaught's development of large-scale production methods (in partnership with Eli Lilly) connected the Laboratories with other insulin producers around the world.

Heritage Room, Sanofi Pasteur Canada (Connaught Campus)

who produced it

Sanofi Pasteur Canada Archives

Insulin: From Toronto To The World

5 C.C. ILETIN U 10



who produced it

Insulin: Toronto's Gift To The World exhibit, MaRS Building

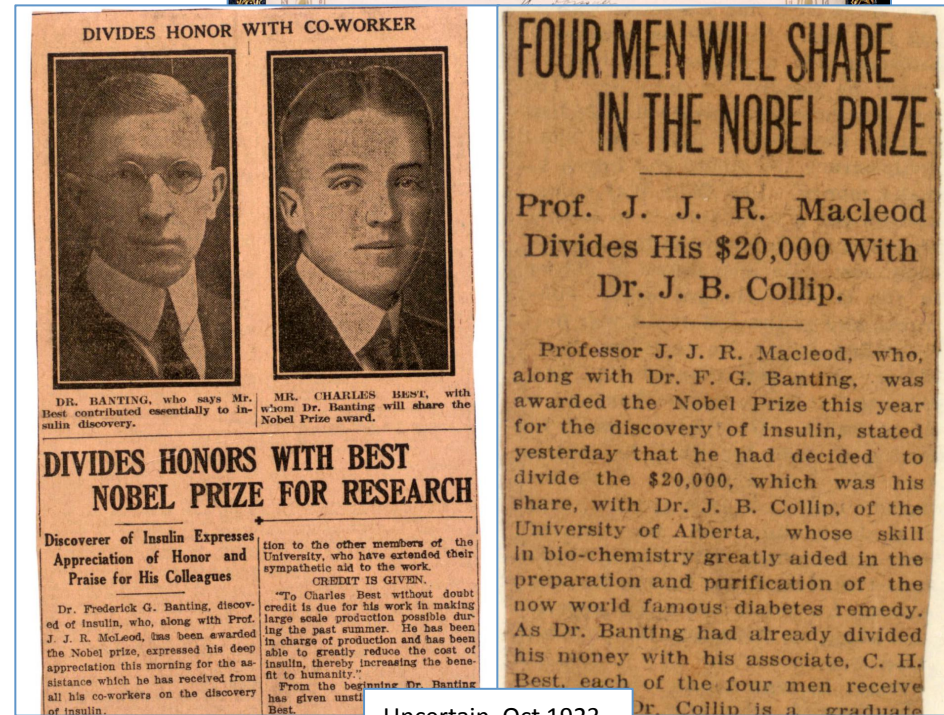
Sanofi Pasteur Canada Archives

10 New or Clinical Units
Commonwealth Serum Lab

Insulin: Honouring the Discoverers

- **May 1923** - Ontario government funded the Banting and Best Chair of Medical Research at U. of T.
- **July 1923** – Federal government awarded Banting with a lifetime annuity
- **Oct 1923** - A greater global honour came when Banting and Macleod won the Nobel Prize for Medicine

- However, recognizing that two others were similarly deserving, Banting shared his half of the Prize with Best and Macleod shared his with Collip



Insulin's Impact on Public Health

Toronto Star, Nov 29, 1923

- **1923-24** – While Connaught's Insulin production increased and the world's attention had been focused on Toronto in the wake of the Nobel Prize news, U of T's and Connaught's other public service work with vaccines production and in public health research and education, had already attracted international attention, especially from the Rockefeller Foundation



Sanofi Pasteur Canada Archives

THURSDAY, NOVEMBER 29, 1923.

INSULIN PRODUCTION 250,000 UNITS WEEKLY

And Price Has Dropped From
Five Cents to Two
Cents Per Unit

Tucked away in an obscure corner of the University of Toronto grounds, overshadowed by the new Electrical Engineering Building and flanked by a row of venerable elms, stands a two-storey, red brick building formerly occupied by the University Y. M. C. A. A year or two ago it was planned to remove the building as it was not suitable for any University purpose. To-day, housing, as it does, the only "Insulin Laboratory" in Canada, the building, together with the recently installed equipment, is worth upwards of \$35,000.

The Insulin Laboratory is one of the latest chapters in the romance of insulin. It stands as a confirmation of the success of the research of Dr. F. G. Banting and his fellow-investigator, Charles H. Best, M.A. Its management and operation are in the hands of Mr. Best, who has from the beginning been in charge of the large-scale production of insulin. The laboratory is operated as a division of the Connaught Anti-Toxin Laboratories, of which Dr. J. G. Fitzgerald is director and Dr. R. D. Defries associate director. The business administration is in charge of Dr. Fitzgerald and Dr. Defries. Mr. Best is

assisted in the new laboratories by D. A. Scott, M.A., as assistant director, and a staff of 26 persons working day and night shifts.

Big Production Now

The erection of such a completely equipped plant was made possible through the Ontario government's grant of \$25,000, the remaining \$10,000 to \$15,000 being secured from funds of the laboratory and from private donations. The plant is now producing in the neighborhood of 250,000 units a week for distribution throughout Canada, Ireland, South Africa, Central America, New Zealand, Australia, and other countries where plants have not been established. The average dosage for the diabetic patients for whom such a large quantity of insulin is being prepared varies from 15 to 20 units a day.

The price for which insulin is distributed is, as with other products of the Connaught Laboratories, governed entirely by costs of material and of production. The Connaught Laboratories are not engaged in commercial business but constitute a department of the University of Toronto. Mr. Best has called attention to the gradual fall in the price of insulin. In May, 1923, the material was sold at 5 cents per unit, in June at 3 cents, and now at 2 cents per unit.

How It is Prepared

The distribution of insulin is effected through two channels. The first is hospitals which have organized departments for the administration of insulin. The second is through physicians trained in the use of insulin. For these latter a special short course of instruction was provided at the University of Toronto last July under the direction of Professor Duncan Graham.

The preliminary stages in the preparation of the health-giving extract are conducted in a large laboratory in the north-east corner of the in-

Insulin's Impact on Public Health

- **1913** - The Rockefeller Foundation established to focus its substantial financial resources on improving medical education in the United States and Canada, and, through its International Health Commission, to further public health education and research
- **1916-18** – School of Hygiene and Public Health at Johns Hopkins University, Baltimore, established with Rockefeller funding; the 1st such School of Hygiene, with a 2nd created at Harvard in 1921
- **1920** – To improve medical education in Canada, Rockefeller Foundation pledged \$5,000,000 to be shared between Canadian medical schools, with U. of T. receiving \$1,000,000



The Globe, Nov 29, 1920, p. 1

Insulin's Impact on Public Health

- **1923** – Rockefeller Foundation contributed \$10,000 to Toronto General Hospital and the Hospital for Sick Children to support Banting's Insulin studies
- Rockefeller Foundation also looking for a 3rd institution to further showcase its support of public health education and research and U. of T. was an obvious choice
- **1923** – Rockefeller officials met with John FitzGerald, who was not shy about what was really needed:
- *A new building to house Connaught's expanding responsibilities with Insulin and other biological public health products, along with a growing program of public health teaching and research*
- **Feb 1925** – Full details announced of Rockefeller's gift to create School of Hygiene @ U. of T

**SCHOOL OF HYGIENE
AS UNIVERSITY UNIT
IS RICHLY ENDOWED**

**Work Will Begin in Spring
on Building to Cost
\$400,000**

TO GUARD PUBLIC HEALTH

Early in the spring work will start on the first School of Hygiene in Canada, and the third of its kind to be erected on the continent. The building will cost \$400,000, and will be located just north of College Street, adjacent to the old University Y.M.C.A., which at present is being used as an insulin laboratory.

To provide the building and endow the school, the Rockefeller Foundation has pledged \$650,000 to the Governors of the university. Negotiations with the Foundation have been completed, and plans are now being prepared for what will be one of the finest buildings added in recent years to the University of Toronto.

A Complete School.

The school will include the Departments of Hygiene and Preventive Medicine, Public Health Nursing and the Connaught Laboratories. The operating divisions of the laboratories—insulin and anti-toxin—which have been conducted separately, will be merged, and will constitute a public service section in the school.

Prof. J. G. Fitzgerald, Director of the Connaught Laboratories, will be in charge of the school, and the endowment from the Rockefeller Foundation will make possible several full-time appointments to the staff. It is also planned to provide additional fellowships in connection

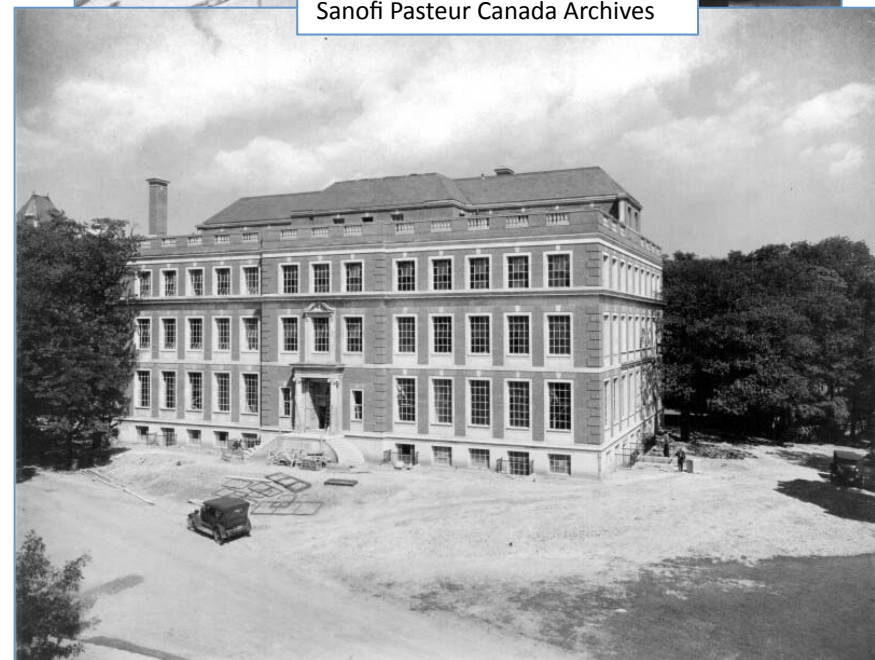
The Globe, Feb 17, 1925, p. 12

Insulin's Impact on Public Health

- **1925** – Rockefeller Foundation committed \$400,000 (or \$5.5 million today) for a new building plus \$250,000 (or \$3.5 million today) to endow a Dept. of Epidemiology & Biometrics, and a Dept. of Physiological Hygiene; a Dept. of Hygiene & Preventive Medicine would also be accommodated
- The new building would also accommodate Connaught's main production, distribution and research operations and a shared administration with the School
- The Canadian Public Health Association would also be accommodated in the new building



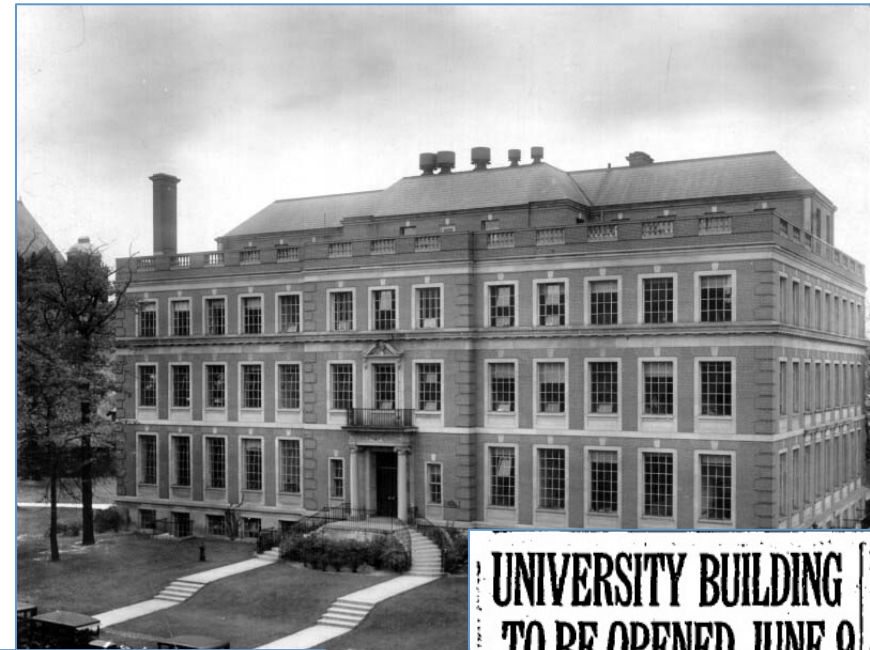
Sanofi Pasteur Canada Archives



Insulin's Impact on Public Health

- Proceeds from sales of Connaught's products were directed to the Connaught Labs Research Fund, which provided the School with a further endowment of \$250,000

- **June 9, 1927** – The School of Hygiene Building was formally opened with a special event a Convocation Hall followed by a tour led by FitzGerald along with Frederick Banting and Charles Best



Sanofi Pasteur Canada Archives



UNIVERSITY BUILDING TO BE OPENED JUNE 9

Sir George Newman Will
Officiate at School of
Hygiene Ceremony

NEW HOME OF INSULIN

Sir George Newman, K.C.B., Chief Medical Officer of the Ministry of Health for England and Wales, will officiate at the opening of the new School of Hygiene of the University of Toronto, which takes place on Thursday morning, June 9, it was announced yesterday.

The formal opening of the new building, which fronts on College Street, and is situated just east of the Mining and Electrical Buildings, and just south of the Biology Building of the university, will occur as one of the events of Commencement Week, which continues at the uni-

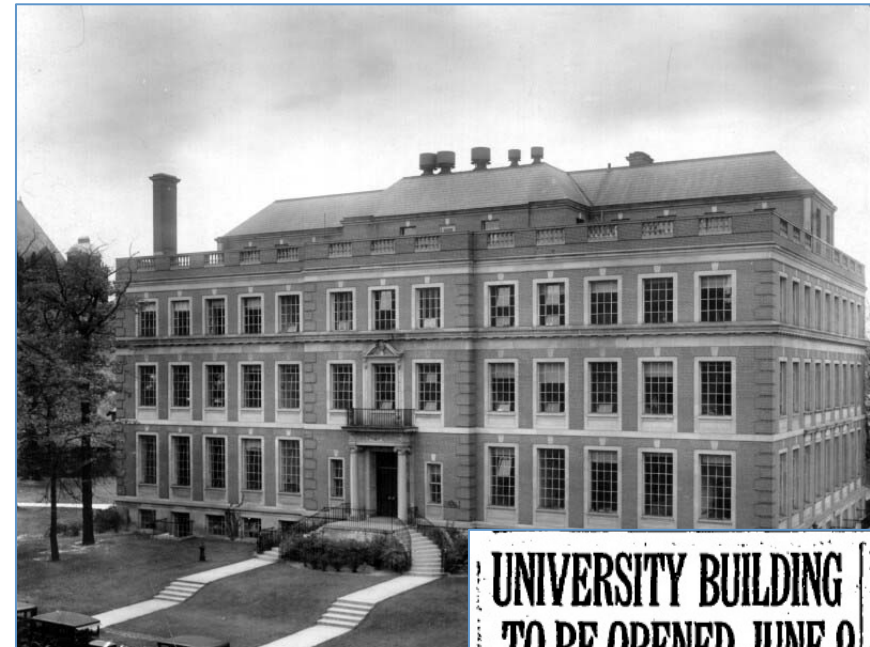
The Globe, May 5, 1927, p. 14

Insulin's Impact on Public Health

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- **June 9, 1927** – The School of Hygiene Building was formally opened with a special event a Convocation Hall followed by a tour led by FitzGerald along with Frederick Banting and Charles Best

- As was prominently noted, the new School of Hygiene Building would be the “new home of Insulin”



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UNIVERSITY BUILDING TO BE OPENED JUNE 9

Sir George Newman Will
Officiate at School of
Hygiene Ceremony

NEW HOME OF INSULIN

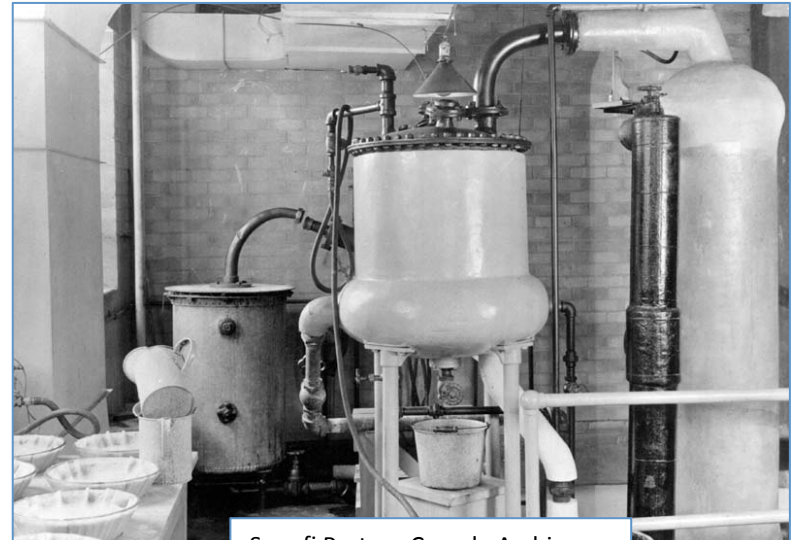
Sir George Newman, K.C.B., Chief Medical Officer of the Ministry of Health for England and Wales, will officiate at the opening of the new School of Hygiene of the University of Toronto, which takes place on Thursday morning, June 9, it was announced yesterday.

The formal opening of the new building, which fronts on College Street, and is situated just east of the Mining and Electrical Buildings, and just south of the Biology Building of the university, will occur as one of the events of Commencement Week, which continues at the uni-

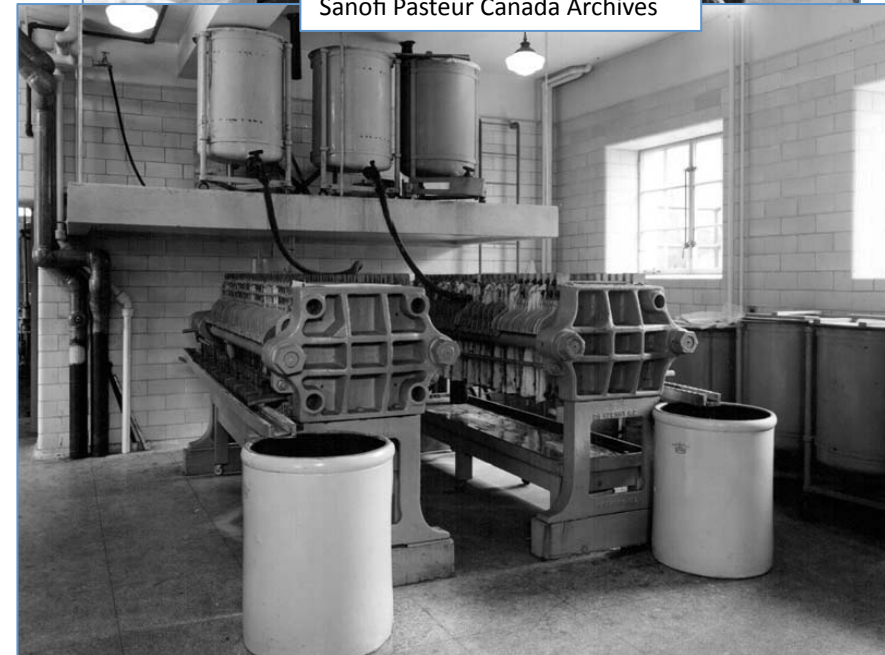
The Globe, May 5, 1927, p. 14

Insulin's Impact on Public Health

- In the Hygiene Building's new Insulin Plant, the production process began by mincing frozen beef or pork pancreas with alcohol
- Connaught made a deal with all the meat packers in Canada to secure pancreas tissue at the lowest possible price
- The insulin-containing extract was separated from the pancreas and the alcohol removed by vacuum distillation
- The remaining material was filtered and the insulin separated out by adding sodium chloride

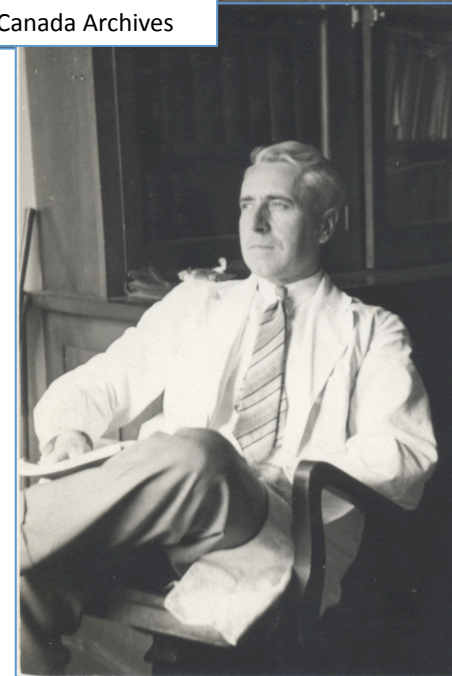


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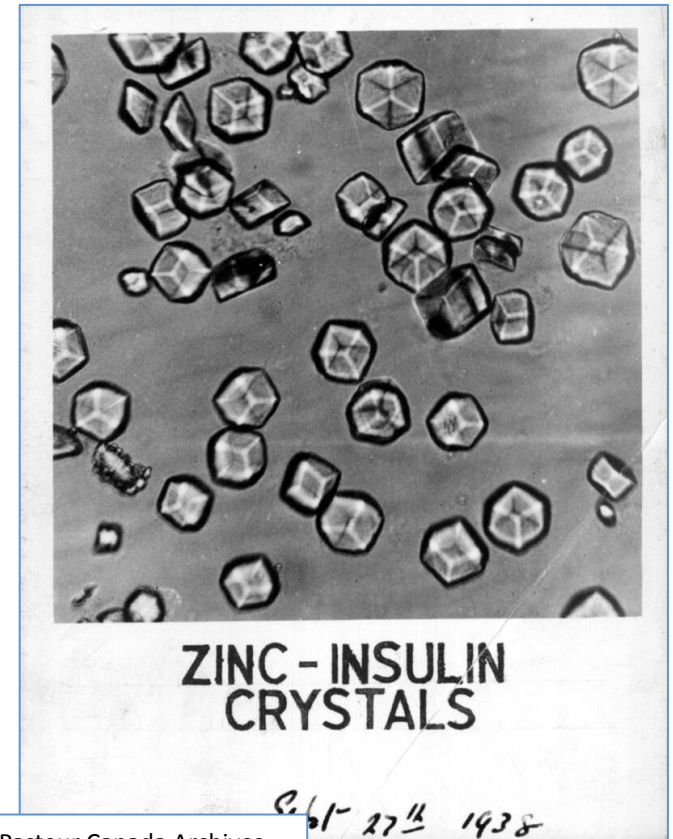
Insulin's Impact on Public Health

- **Late 1920s** - An additional process was introduced to further purify insulin into a crystalline form
- Connaught's expanded Insulin production process based on crystalizing insulin, along with the design of the Hygiene Building's Insulin plant, was led by Dr. David A. Scott
- A specialist in chemistry and mineralogy, Scott joined Connaught in 1922 and worked very closely with Best on solving Insulin production challenges



Insulin's Impact on Public Health

- **1931** – Scott also discovered that the secret to a consistent and large supply of insulin was the addition of small amounts of zinc chloride.
- This discovery led to Scott overseeing the establishment of the first international standard for insulin.



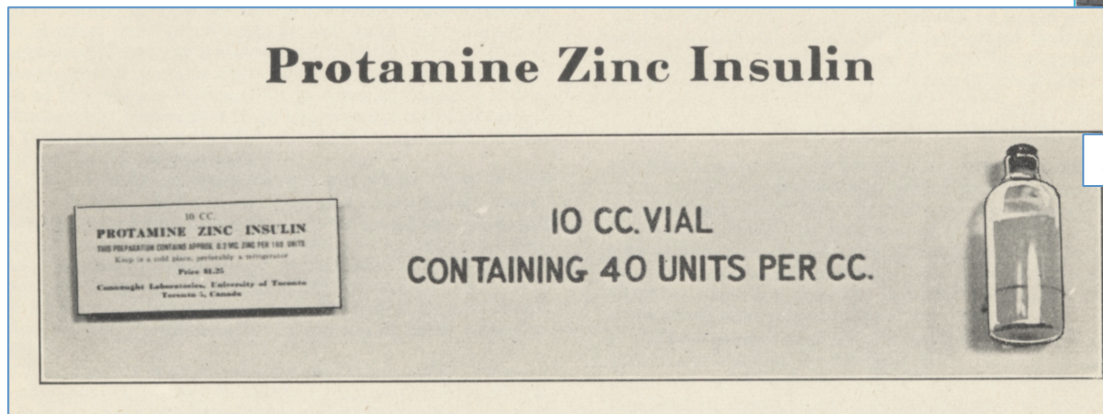
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Insulin's Impact on Public Health

- **1936** – Scott (centre) worked with Dr. A.M. Fisher (left) to improve Protamine Insulin, which was the first long acting Insulin developed by Dr. H.C. Hagedorn (right) of Nordisk Laboratories in Denmark
- They added trace amounts of zinc, resulting in a more stable and longer acting form of Insulin that was patented through the UofT Insulin Committee and rapidly adopted globally

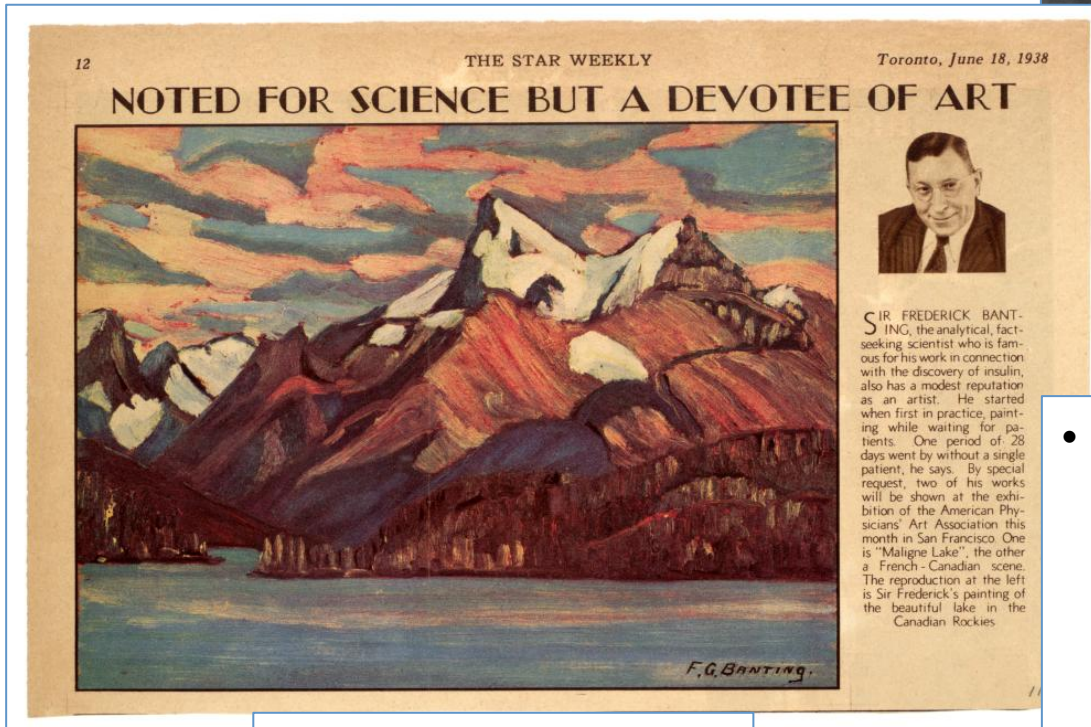
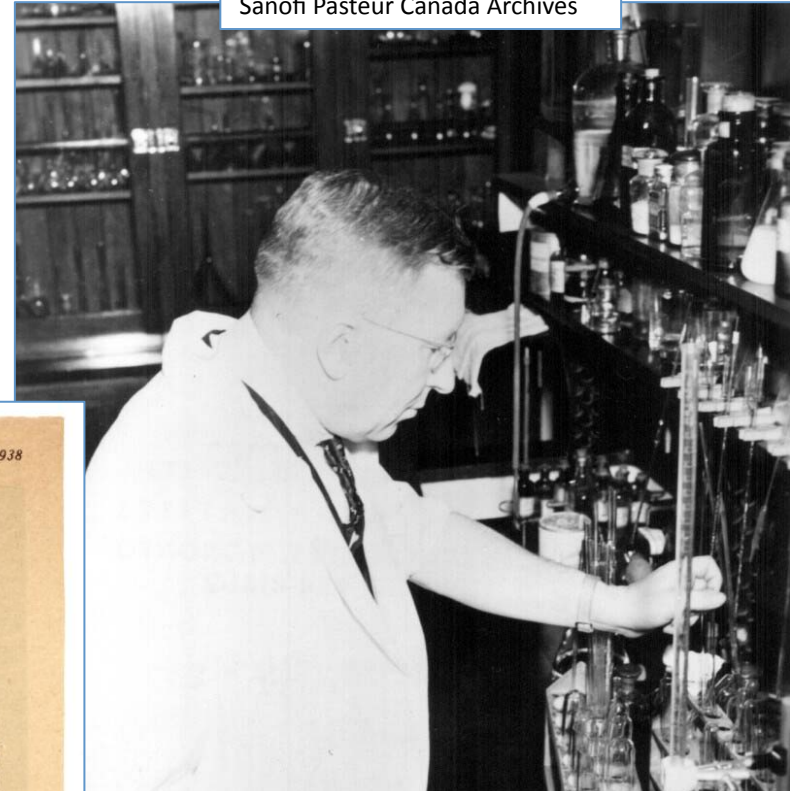


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Insulin's Impact On Its Discoverers: *Frederick Banting*

- Banting would focus on medical research, but was drawn to a growing interest in art, especially painting with A.Y. Jackson, a member of the Group of Seven



Toronto Star Weekly, June 18, 1938, p. 12

- There were great expectations that Banting would make another major medical discovery, which proved quite frustrating, and art provided an important escape

Insulin's Impact On Its Discoverers: *Frederick Banting*

- When World War II started, Banting became involved with aviation medicine studies
- He also worked closely with the British Air Force and was on a secret flight to Britain on February 20, 1941, when his small plane crashed shortly after taking off from Gander, Newfoundland
- Banting died the next day and was buried at Mount Pleasant Cemetery in Toronto.



Toronto Telegram, Feb 25, 1941, p. 1



Insulin's Impact On Its Discoverers:

Charles Best

- **May 17, 1921** - The day after graduating in Biochemistry and Physiology, Charles Best joined Frederick Banting in a small University of Toronto lab to start the work that would lead to the discovery of insulin
- Charles Best was born in Maine of Canadian parents from Nova Scotia. Inspired by his general practitioner father, Charles enrolled at the University of Toronto in 1916, but his studies were interrupted by the start of WWI; resumed in 1918, focused on Physiology & Biochemistry
- J.J.R. Macleod was impressed with Best's work and when Macleod agreed to give Banting a lab, Best was an obvious candidate to assist, although a coin toss would decide if Best, or a classmate, would get the job.

<https://insulin.library.utoronto.ca/>



Insulin's Impact On Its Discoverers:

Charles Best

- **1925** – Best completed his M.D. course amidst the insulin discovery and development period, and he also got married and then pursued postgraduate studies in Europe.
- **1927** - Best returned to Toronto to continue as Connaught's Assistant Director until 1929, and to also serve as Head of the Department of Physiological Hygiene at the School of Hygiene.
- **Late 1920s** - Best also initiated studies of liver extract as a treatment of anemia, and focused especially on the development of Heparin to control blood coagulation, this work very much involving Connaught.



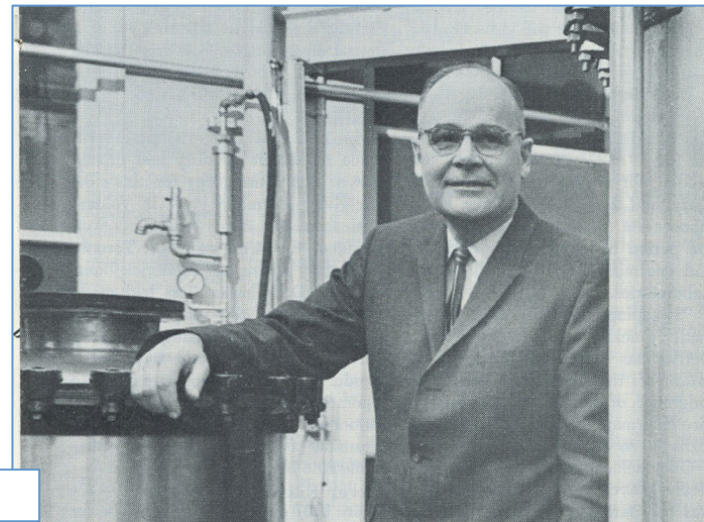
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Insulin's Impact On Its Discoverers: *Charles Best (& Dr. J.K.W. Ferguson)*



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- Dr. J.K.W. (Kenneth) Ferguson (1907-1999), who would serve as Director of Connaught Laboratories from 1955 to 1972, was the last of the Lab's Directors during its time as part of the University of Toronto
- Dr Ferguson was perhaps the last person to have known all 4 of the discoverers of Insulin, especially Charles Best



Insulin's Impact On Its Discoverers: *Charles Best (& Dr. J.K.W. Ferguson)*



Dr. Ferguson with Chris Rutty, Craig Defries (R.D. Defries' great nephew), James FitzGerald (J.G. FitzGerald's grandson), John Sparkes (Biostatistics, Connaught) @ Connaught Labs, 1996

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- I got to know Dr. Ferguson quite well during the last few years of his life through my historical work with Connaught Labs, as he was also interested in history of medicine and often visited the Connaught Labs Library & Archives, where I was often working
- Through Dr. Ferguson and a biographical project I did for him, I learned a lot about the discoverers of Insulin, and also the developers of Heparin

Read a short article I wrote about the history of Heparin here, <http://healthheritageresearch.com/Heparin-Contact9608.html>

Insulin's Sequel: *Heparin, The Miracle Blood Anti-Coagulant*

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- **1928-1937** – For Connaught Labs and Canadian biotechnology the clear sequel to Insulin's discovery and development was Heparin
- While the story of Heparin story is less known than Insulin's, its impact on medicine has been much broader, especially on the development of modern surgery and any medical technology requiring the control of blood coagulation
- Heparin is a still mysterious molecule present in various animal tissues and is responsible for regulating blood coagulation

Solution of Heparin

For laboratory and clinical investigations of prevention of thrombus formations.

SOLUTION OF HEPARIN
10 CC.
1000 units per cc.
Let _____
CONNAUGHT LABORATORIES
UNIVERSITY OF TORONTO
Toronto 3, Canada

Heparin, highly purified by processes involving crystallization, dissolved in physiological saline, and dispensed as a sterile solution. Preservative —Trikresol 0.3%.

$\left[\begin{array}{c} \text{COO}^- \\ | \\ \text{H} \\ | \\ \text{H} \\ | \\ \text{OH} \\ | \\ \text{H} \\ | \\ \text{O-SO}_3^- \\ | \\ \text{H} \end{array} \right]_1 \text{O} \left[\begin{array}{c} \text{CH}_2\text{-O-SO}_3^- \\ | \\ \text{H} \\ | \\ \text{H} \\ | \\ \text{OH} \\ | \\ \text{H} \\ | \\ \text{NH-SO}_3^- \\ | \\ \text{H} \end{array} \right]_4 \text{O}$

D-Glucuronate-2-sulfate N-Sulfoglucosamine 6-sulfate

Heparin

Insulin's Sequel:

Heparin, The Miracle Blood Anti-Coagulant

- **1916** - Heparin was discovered by Jay McLean, a 2nd year medical student at John's Hopkins University, working under the direction of physiologist William Henry Howell
- McLean extracted the anti-coagulating substance from dog liver, but did little further work with it, leaving Howell to conduct further research and name it "heparin" (derived from "hepar", the Greek term for liver)
- **Early 1920s** - A version of Heparin was produced by a Boston firm, but it proved to be toxic



THE PURIFICATION OF HEPARIN AND ITS PRESENCE IN BLOOD

W. H. HOWELL

From the School of Hygiene and Public Health, Johns Hopkins University

Received for publication November 28, 1924

In 1918 in a paper by Howell and Holt (1) a substance was described under the name of heparin which has a marked effect in preventing the coagulation of blood. The nature of its effect upon the processes of coagulation was investigated in some detail. Subsequently in a brief communication to the American Physiological Society (2) I described a second method of obtaining this material which gave a more constant and reliable product in a form suitable for laboratory experimentation.¹ On account of the high phosphorus content (about 5 per cent) of the product obtained it was assumed that the substance might belong to the group of phosphatids, but more recent work has shown that this assumption was

American Journal of Surgery, 17 (1925), p. 553

Developing Heparin: *Best Takes The Lead*

- **1928-29** – Charles Best, after spending a couple of years studying in London, UK, saw potential in revisiting Heparin and taking advantage of Connaught's expertise with insulin production to investigate preparing a purified product
- Best was newly appointed Head of the Department of Physiology at the University of Toronto, and also Associate Director of Connaught



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Developing Heparin: *Best Takes The Lead*

- **1929** - Best set out to systematically explore methods to,
 - 1), purify and then produce heparin in large, but affordable quantities
 - 2), study its effects in animals and then humans
- For the first part of the first goal, Best turned Arthur F. Charles, a specialist in organic chemistry, who was Best's graduate student when he started on the project

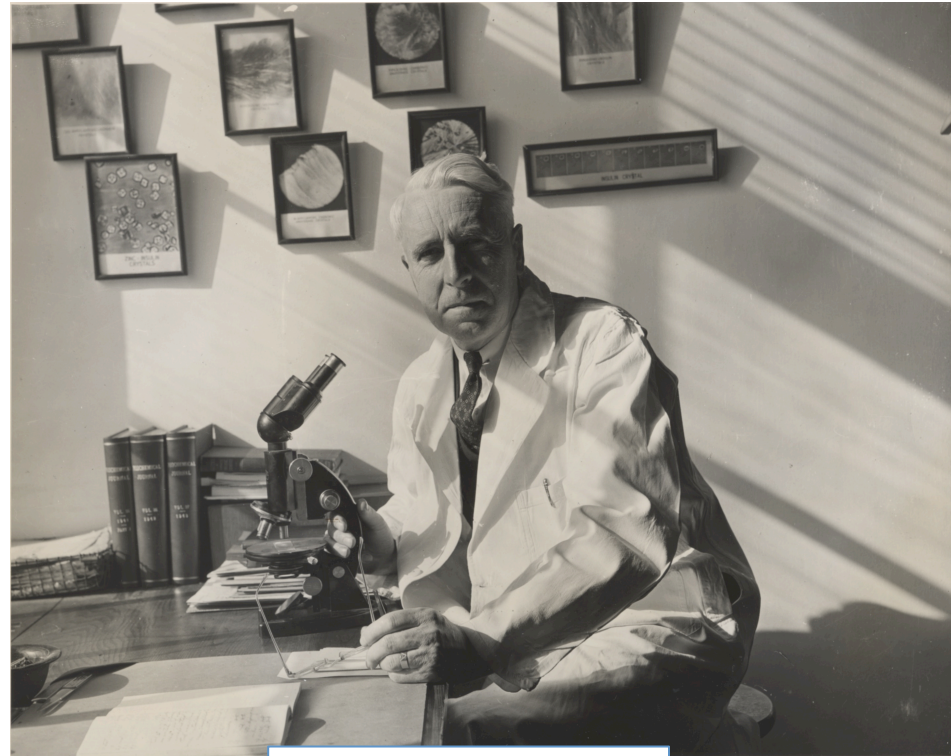


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- However, progress was steady, but slow over the next few years, focused on developing methods to extract heparin from beef liver

Developing Heparin: *Best Takes The Lead*

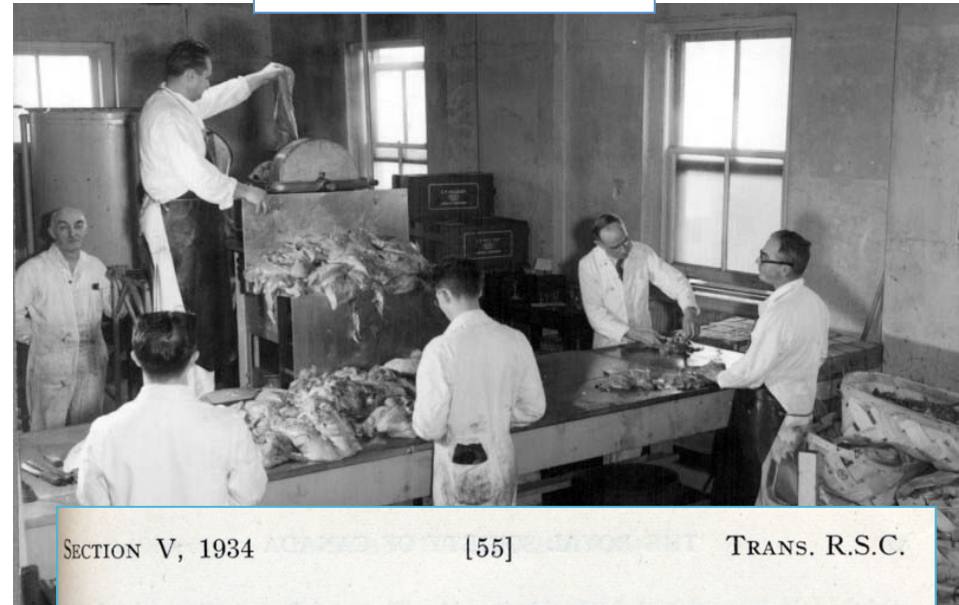
- **1933** – By this time, David Scott (right) had joined Charles in the project, utilizing his experience with insulin production to work out a method to extract heparin from not only beef liver, but also lung and intestine tissue on a larger scale
- Charles and Scott took advantage of the arrangement Connaught had with all the meat processors in the country for pancreas tissues for Insulin production to utilize for heparin work otherwise discarded beef organs



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Developing Heparin: *Purification and Production*

- **1933** – Charles and Scott published their first papers on their work, which described how the yield of extracted heparin could be doubled if the beef tissues, especially lung, were allowed to autolyse for 24 hours before extraction
- However, the smell emanating from the autolysing, or rotting tissue, was so bad that production had to move from the School of Hygiene Building up to the more open environment of the Connaught “Farm” site



SECTION V, 1934

[55]

TRANS. R.S.C.

The Preparation of Heparin from Beef Lung

By A. F. CHARLES and D. A. SCOTT

(Presented by C. H. BEST, F.R.S.C.)

In an earlier publication (1) from these laboratories, a method for the preparation of large quantities of heparin from beef liver was described. Data have also been reported (2) concerning the relative amounts of heparin obtained from various beef tissues. This work showed that, of the tissues used, liver, muscle and lung, gave the richest yields of heparin. The amount of heparin obtained from lung was somewhat greater than that from liver. In view of this fact it seemed desirable to use beef lung as a source of heparin. Further, lung is a cheap raw material. It had also been noted in certain stages of the purification of heparin from beef liver that substances antagonistic in action to heparin were present. It was hoped that these substances might not be encountered if beef lung were used as a source of the anticoagulant.

Developing Heparin: *Purification and Production*

- **1933-36** - While studying heparin's elusive and mysterious chemistry, Charles and Scott were able to develop a method to purify and finally crystalize the extract into a standardized dry form that could be administered in a salt solution
- Heparin thus became Connaught's second product, after Insulin, to be recognized as an international standard.
- While animal testing had been encouraging, It was now time to focus on preparing Heparin for clinical testing

Toronto Star, Feb 27, 1936, p. 8

DISCOVERY MAY AID ARTERIAL SURGERY

Efforts to perfect a recently discovered substance which prevents blood-clotting after arterial operations, are nearing success at University of Toronto, Dr. D. A. Scott, senior research chemist in the Connaught Laboratories, told The Star yesterday.

First obtained from the liver this substance, called heparin, can now be obtained from the beef lung in much greater quantities, but its chemical constituents are still unknown. Dr. Scott said. The new substance has been clinically applied, but is still in the experimental stage, he stated.

Testing Heparin: *Pioneering Surgical Science*

- **1935-37** – To undertake clinical studies of Heparin, Best turned to prominent Toronto surgeon, Dr. Gordon Murray (left), based at Toronto General Hospital
- Murray's experimental surgery with various animals demonstrated that Heparin effectively cleared up internal blood clots, and also seemed useful for many other dangerous operations where blood coagulated quickly
- **April 1937** – The first human tests with purified heparin were conducted, although a cruder form was tested in selected cases earlier with encouraging results



THE USE OF HEPARIN IN THROMBOSIS*

GORDON D. W. MURRAY, M.D., AND CHARLES H. BEST, M.D.
TORONTO, CAN.

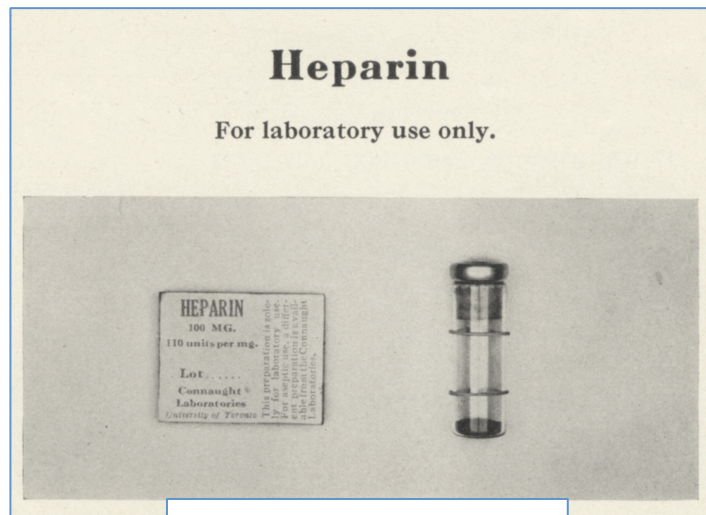
THE discovery of heparin in Howell's laboratory, in 1916, and his demonstration that it was a natural anticoagulant of blood, raised hopes that it might also be a preventive of thrombosis. Unfortunately the early experiments on animals and the clinical use of the drug as a preventive of clotting in blood transfusions were discouraging, owing to the toxic symptoms produced. In 1929, however, one of us (C. H. B.) initiated research on the purification of heparin, in the Connaught Laboratories, and Charles and Scott¹ succeeded in preparing it in the form of a crystalline, barium salt, which was 100 times more potent than the original crude material and completely free of toxic properties. This success revived our interest in the possible clinical value of the drug and encouraged us to study, both upon animals and patients, its influence on those pathologic conditions which are based upon thrombosis.

That heparin has a profound influence in preventing thrombosis has been amply demonstrated by a long series of experiments upon animals, begun in the Department of Surgery, in 1932, and reported elsewhere,² in which it was shown that the thrombosis, which normally results from mechanical (Fig.

Annals of Surgery, 108 (Aug 1938), p. 163

Testing Heparin: *Pioneering Surgical Science*

- **1937** – The early trials of Heparin soon involved hundreds of complex surgical cases during which heparin played an essential and often dramatic life-saving role.
- It was clear that Connaught's heparin was a safe, easily available and effective blood anticoagulant.



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HEPARIN AND THROMBOSIS

By C. H. BEST, *Toronto*

At the annual meeting of the Royal College of Physicians and Surgeons of Canada, held on October 30, 1937, Dr. D. W. G. Murray and the author presented a summary of their recent work on the effect of heparin on thrombus formation. A preliminary account of this investigation appeared in this *Journal*.¹

The anticoagulant heparin was discovered in 1916 by Howell and Holt. When the work on this substance was begun in the Department of Physiology of the University of Toronto (1929) it appeared that two problems had to be solved before its effect on thrombus formation in human subjects could be investigated. It was necessary to secure a pure, non-toxic form of heparin and to prove that the anticoagulant prevented the formation of thrombi in experimental animals. The problem of the purification of heparin was attacked by Dr. Arthur Charles and Dr. D. A. Scott in the Connaught Laboratories. Each new preparation of heparin which they prepared was tested on experimental animals, and later some of the purer ones were administered to a group of human subjects. A detailed report of an

Canadian Medical Association Journal, 38 (Jan 1938), p. 59

Testing Heparin: Pioneering Surgical Science

- Best's heparin team had opened the door to such operations as organ transplants and open-heart surgery, as well as the artificial kidney that was pioneered by Murray



Globe & Mail, Nov 2, 1939, p. 13

Organs May Be Transplanted, Using New Drug, Says Graham

Cambridge, Mass., Nov. 1 (AP).—Advances in surgery and post-operative treatment made public with the drug heparin, which is obtained from the lung of the ox, were described today by Dr. Roscoe E. Graham of the University of Toronto.

(Today, in the journal of the American Medical Association, other investigators told of the possibility of using heparin, which prevents clotting of blood, in the treatment of acute endo-

was the exact cause," he said, "we found that in 400 cases treated with heparin following operations, pulmonary embolism failed to occur. I believe heparin has some merit here."

He declared the drug, by keeping blood fluid and preventing clots, had made possible an operation involving the cutting away of a section of artery, and substituting in the gap a section of vein, an operation which previously had been dangerous because of blood clots.

Moreover, he said, the effectiveness of the substance now estab-

Success With Heparin in Toronto Is Welcomed by British Surgeons

London, June 13 (CP). — Use of heparin to prevent blood-clotting was described to the Royal College of Surgeons today by Dr. D. Gordon Murray of Toronto, who told of success in purifying the drug in the departments of physiology and surgery of the University of Toronto.

Heparin, extracted from liver, lung and other tissues, never has been successful because of the toxic reaction it produced when administered to living animals. The University of Toronto's laboratories have produced it in a non-toxic, crystalline powder form.

Dr. Murray's experiments showed that in addition to prolonging

blood-clotting, heparin can prevent thrombosis in injured or diseased blood vessels. By continuous administration of the drug, through a needle tied into a vein, injured blood vessels can be healed, Dr. Murray said.

The practical value of the studies has been demonstrated on a series of persons suffering from embolism of the peripheral arteries, the Toronto doctor announced. It has also been possible to excise a segment of a large artery and replace it with a segment of vein obtain elsewhere in the patient's body, still maintaining a normal circulation through the damaged vessel, Dr. Murray said.

Globe & Mail, June 14, 1939, p. 2

Producing Heparin

- Connaught continued to prepare Heparin and developed methods to increase its potency and reduce its price.
- Ironically, this work made heparin more easily produced elsewhere and by the early 1950s, Connaught had stopped producing a crucial life-saving product that it had pioneered.

Globe & Mail, Oct 14, 1939, p. 17

Cites Value of Heparin To Prevent Thrombosis

Minneapolis, Oct. 13 (AP).—Par-

tial success in preventing coronary thrombosis, a fatal clotting of the heart's main artery and a common cause of death, through use of a compound called heparin, was reported today by Dr. Charles H. Best of Toronto, co-discoverer of insulin.

Dr. Best's paper dealing with his work was read at a meeting of scientists in connection with observance of the University of Minnesota Medical School's fiftieth anniversary.

While saying that many more cases must be studied before the matter is settled, Dr. Best declared:

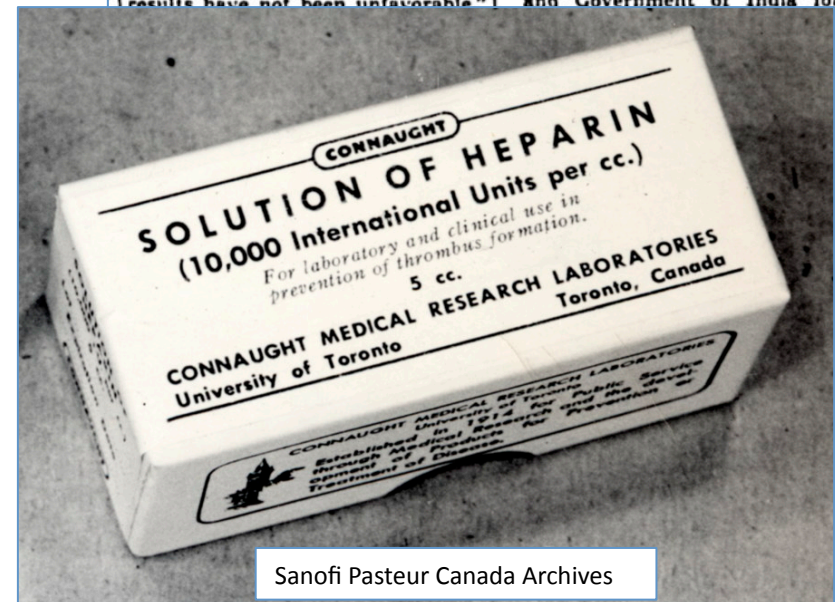
"While it will perhaps be almost impossible to secure scientific proof of the effects of heparin under these conditions (referring to certain operative procedures), the results have not been unfavorable"

Sure Dalai Lama Is Reincarnation

(Wireless to The New York Times and The Globe and Mail.)

(Copyright.)

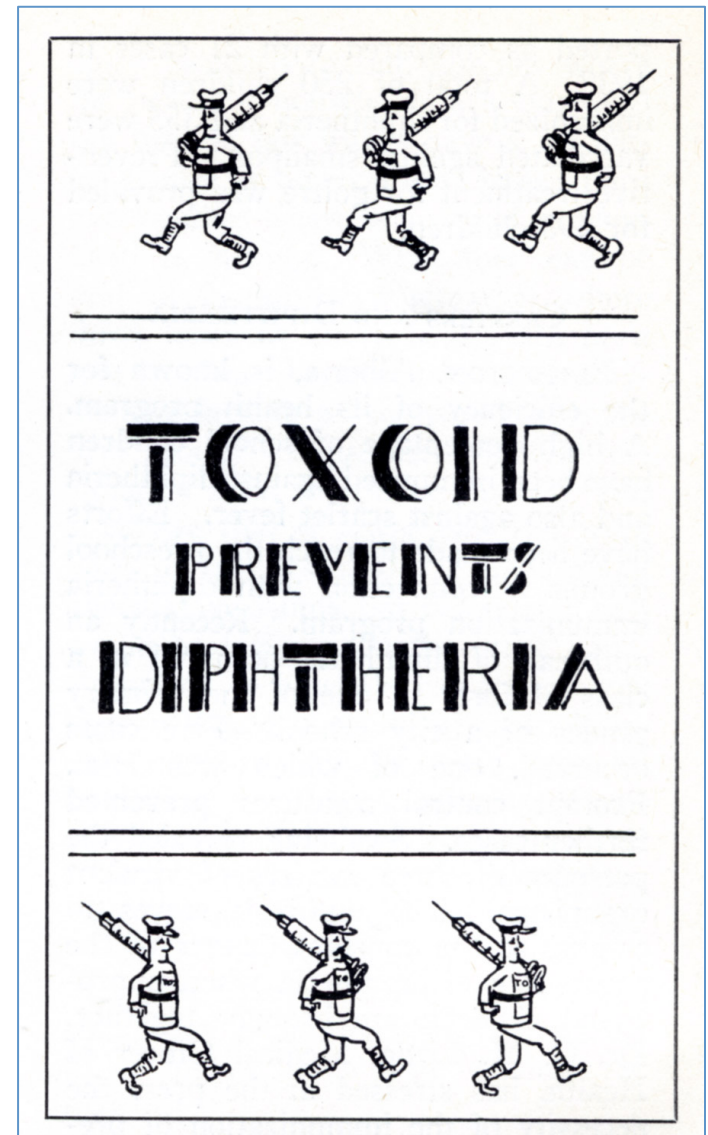
Delhi, India, Oct. 13.—A telegram received by the political officer at Sikkim from the Kashag (Tibetan Cabinet) expresses the conviction that the boy now figuring in the ceremonies at Lhasa is the "true reincarnation of the Dalai Lama without a shadow of doubt." The message thanked the British Government and the Viceroy and Government of India for



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Public Health Transformations: 1920s to 1930s & The Eve of War

- As was emphasized at the end of the last class, much had changed and progressed in Canadian public health between the start of the 1920s and the end of the 1930s
- From the perspective of preventing infectious diseases, the key driving force of such progress was Canada's pioneering attack on diphtheria with diphtheria toxoid



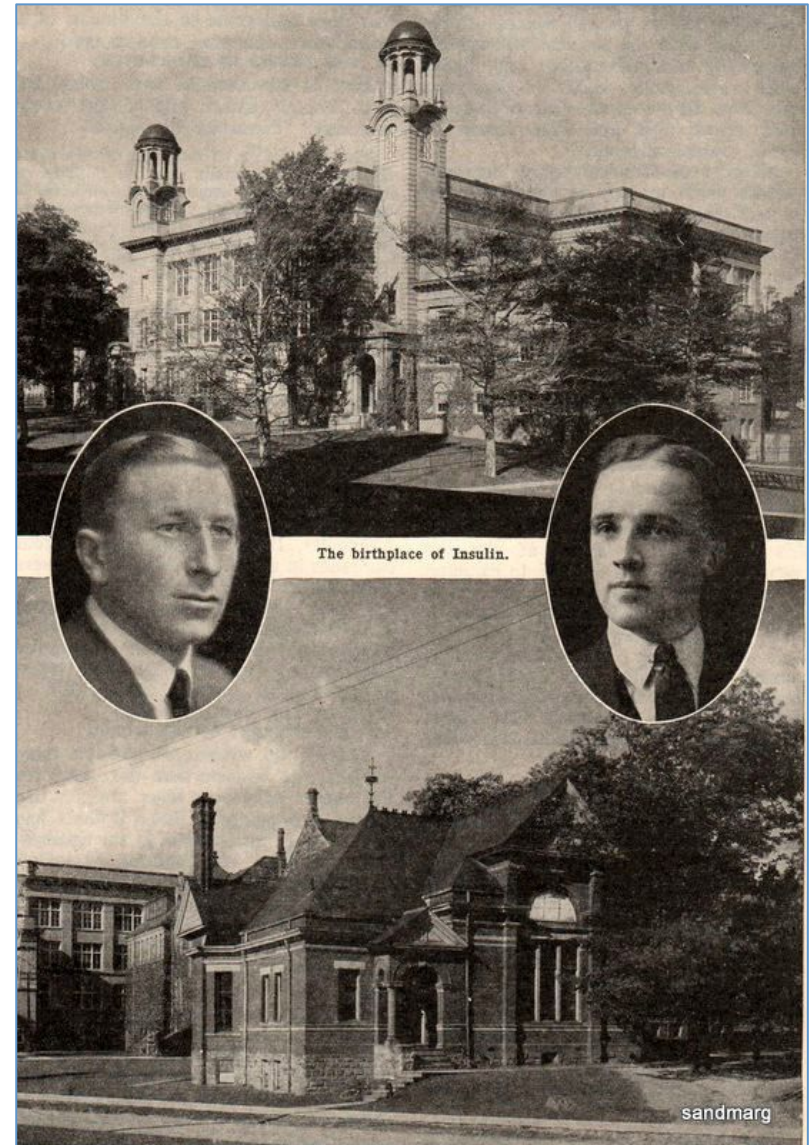
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Public Health Transformations: 1920s to 1930s & The Eve of War

- As we've seen in today's class, the other key driver of public health progress in Canada during the same two decades, from the perspective of controlling a non-infectious but inevitably deadly disease with a biological product, was Insulin



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Public Health Transformations: 1920s to 1930s & The Eve of War

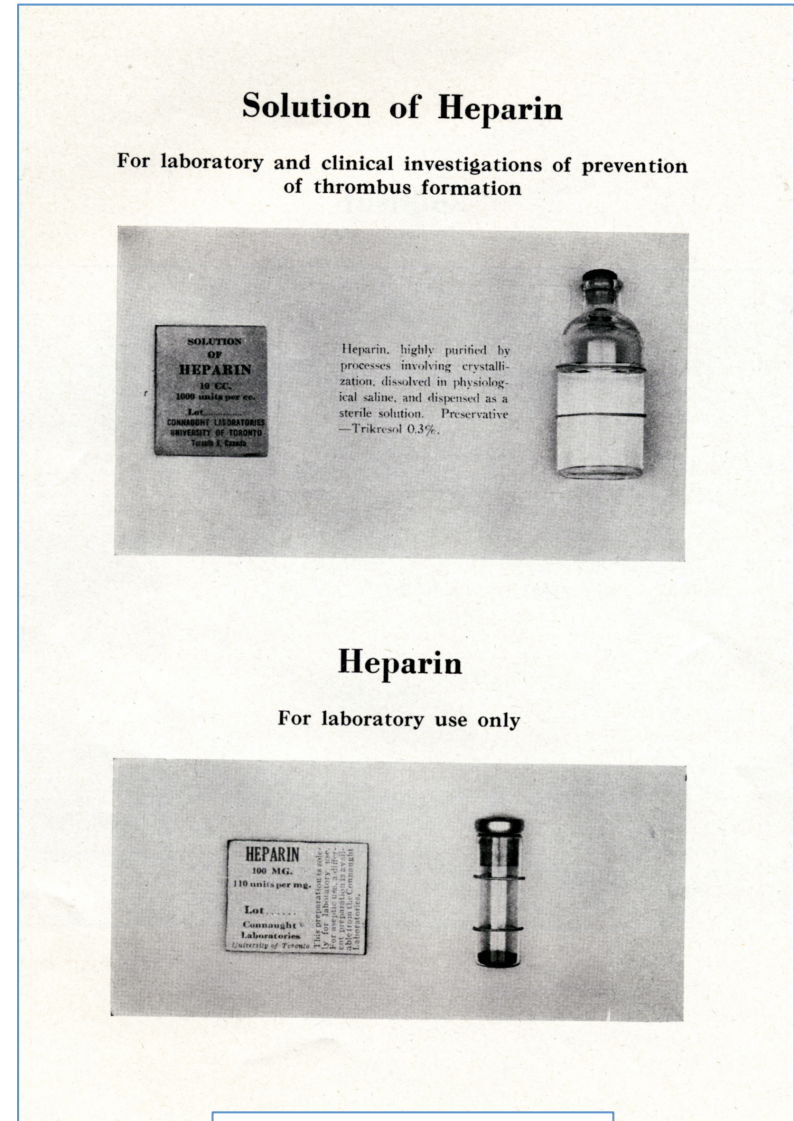
- Not only did the discovery of insulin at the University of Toronto revolutionize diabetes treatment, almost literally resurrecting the dead, its development at Connaught Labs fuelled the rapid expansion and consolidation of Canada's public health infrastructure during this period that was based in the School of Hygiene



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Public Health Transformations: 1920s to 1930s & The Eve of War

- As we have also seen, Insulin's development at Connaught Labs very much made the development of Heparin possible, making it possible to save lives on an even broader scale



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Public Health Transformations: 1920s to 1930s & The Eve of War

- However, as the 1930s ended and as the Second World War began, there was an uncomfortable recognition within the public health community, as reflected by the editors of the *Canadian Public Health Journal*, that despite significant progress against many communicable diseases in Canada, there was a need to acknowledge “our imperfections, if not failures,” and reassess public health strategies against infectious diseases

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HOW MUCH DO WE CONTROL COMMUNICABLE DISEASE?

AT the annual meeting of the Ontario Health Officers Association in 1928 the late Dr. Wade Frost, Professor of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, discussed the control of communicable diseases. He directed attention to the fact that many high hopes of effectual control had not been realized; he pointed out the necessity for recognizing our failures, for casting off those methods which had proved to be of little or no value and for adopting, when possible, new methods based on adequately controlled observations and experience. He emphasized that public health work, including control of communicable disease, should be re-assayed in order to determine the current value of methods which might have been established and evaluated under other conditions. In short, he made a plea that health officials of all grades should keep an eye open to both success and failure and that practice should be based on previous results.

The fact that now, over ten years later, nearly one whole general session of the recent annual meeting was given over to presentation and very lively discussion of current practice in control of communicable disease is evidence at least that we are cognizant of our imperfections, if not failures. Some progress has been made since Dr. Frost indicated the serious limitations in our practices. Diphtheria is to a large extent controlled through active immunization with toxoid; the misconception of the “irreducible minimum” in typhoid fever has largely disappeared and the sporadic residual typhoid that still persists is receiving attention as well as the epidemic outbreaks; tuberculosis is treated, not merely spoken of, as a communicable disease and sources of infection are recognized and where possible, and as soon as possible, segregated or otherwise controlled. Gratifying results have been obtained, too, in other fields. Therein is encouragement.

But some features are less encouraging—especially the lack of factual information in regard to the value of current practice. Is it true, for instance, that whooping cough mortality in the United States has decreased very decidedly while in Ontario the level of thirty years ago is, for practical purposes, maintained? Has control been achieved south of the border and not achieved north of it? Have control measures been applied in the United States so much more effectually than here in Ontario? Or is the difference in the apparent decline

Public Health Transformations: 1920s to 1930s & The Eve of War

- There was a need to see better results from many public health initiatives, and “in order to preserve respectability, or more important, self respect, public health practice must be based on fact; fancy, untested, is little better than fallacy”
- As we’ll see in Class #5, the onset of World War II would severely limit available resources for many public health initiatives, but it would also provide new opportunities to test their effectiveness...

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HOW MUCH DO WE CONTROL COMMUNICABLE DISEASE?

AT the annual meeting of the Ontario Health Officers Association in 1928 the late Dr. Wade Frost, Professor of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, discussed the control of communicable diseases. He directed attention to the fact that many high hopes of effectual control had not been realized; he pointed out the necessity for recognizing our failures, for casting off those methods which had proved to be of little or no value and for adopting, when possible, new methods based on adequately controlled observations and experience. He emphasized that public health work, including control of communicable disease, should be re-assayed in order to determine the current value of methods which might have been established and evaluated under other conditions. In short, he made a plea that health officials of all grades should keep an eye open to both success and failure and that practice should be based on previous results.

The fact that now, over ten years later, nearly one whole general session of the recent annual meeting was given over to presentation and very lively discussion of current practice in control of communicable disease is evidence at least that we are cognizant of our imperfections, if not failures. Some progress has been made since Dr. Frost indicated the serious limitations in our practices. Diphtheria is to a large extent controlled through active immunization with toxoid; the misconception of the “irreducible minimum” in typhoid fever has largely disappeared and the sporadic residual typhoid that still persists is receiving attention as well as the epidemic outbreaks; tuberculosis is treated, not merely spoken of, as a communicable disease and sources of infection are recognized and where possible, and as soon as possible, segregated or otherwise controlled. Gratifying results have been obtained, too, in other fields. Therein is encouragement.

But some features are less encouraging—especially the lack of factual information in regard to the value of current practice. Is it true, for instance, that whooping cough mortality in the United States has decreased very decidedly while in Ontario the level of thirty years ago is, for practical purposes, maintained? Has control been achieved south of the border and not achieved north of it? Have control measures been applied in the United States so much more effectually than here in Ontario? Or is the difference in the apparent decline