# Insulin – Querelen um den Nobelpreis

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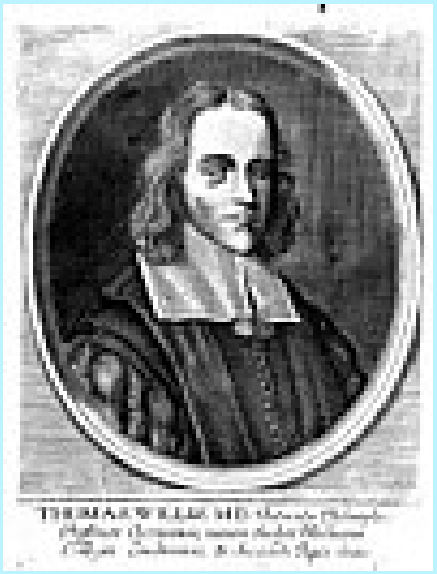
ETH Zürich

- Insulin und Diabetes als Paradigma der Medizingeschichte.
- Rolle der Industrie: kein Insulin ohne *Eli Lilly?*
- Prioritäten und Nobel-Preise.

# First steps in history of diabetes mellitus



***Thomas Willis***
(1621-1675)
*British anatomist and physician:*
diabetes associated with a sugar-like (sweet) substance

***Francis Home***
(1719-1813)
*British Army physician:*
sugar in urine.

***John Rolo***
(1749-1809)
*British Army physician:*
sugar in blood.

# The role of pancreas in diabetes

***Oskar Minkowski***
(1858-1931)
*German physician*

***Joseph von Mering***
(1849-1908)
*German physiologist*

Diabetes in dogs after dissection of pancreas (1889)

# Diabetes mellitus: statistics

**Prevalence (Western countries): 1 - 5% of the total population**

**USA** (275 mill. inhabitants)

- incidence: 0.07% (newly 200,000 cases per year)
- prevalence: 4.4% (12 mill. people)
- eighth leading health-related cause of death (50% mortality because of coronary disease)

Genetic predisposition (USA): relative prevalence (age adjusted) in subpopulations

- *blacks / whites 191%*
- *Hispanics / whites 161%*
- *other races / whites 143%*
- *females / males 122%*

Prevalence in age groups (USA, 1988-1989)

- *18-34 years 1.6%*
- *65-74 years 12.5%*

# Diabetes mellitus: classification

## WHO 1980

| DM type | subtypes | insulin secretion | comment |
|---|---|---|---|
| Type I: IDDM ("juvenile") | I a: juvenile-onset<br>I b: aduld-onset (up to 35 years) | no | 10-20% of all diabetics<br>HLA-associated: groups DR3, DR4, DR3/DR4 |
| Type II: NIDDM | II a: obesity<br>II b: no obesity | normal to enhanced | metabolic syndrome (associated with II a) |

# Etiology of diabetes mellitus

## Type I

- Autoimmunity against secretory cells probably provoked by unspecific viral infections;
- Genetic predisposition (HLA-associated: groups DR3, DR4, DR3/DR4);
- Toxic or infectious processes (Prion infections).

## Type II

- Multifactorial genesis, largely unknown;
- Dysfunction(s) of cell signaling pathways in pancreatic b-cells;
- Genetic predisposition?
- Risk factors: pregnancy, obesity, etc.

# Pathologic consequences of insulin deficiency

***Glucose uptake into body cells decreased;***

***Glucose oxidation decreased;***

***Glycogen production (liver, extra-hepatic organs) decreased; glucose release from liver enhanced;***

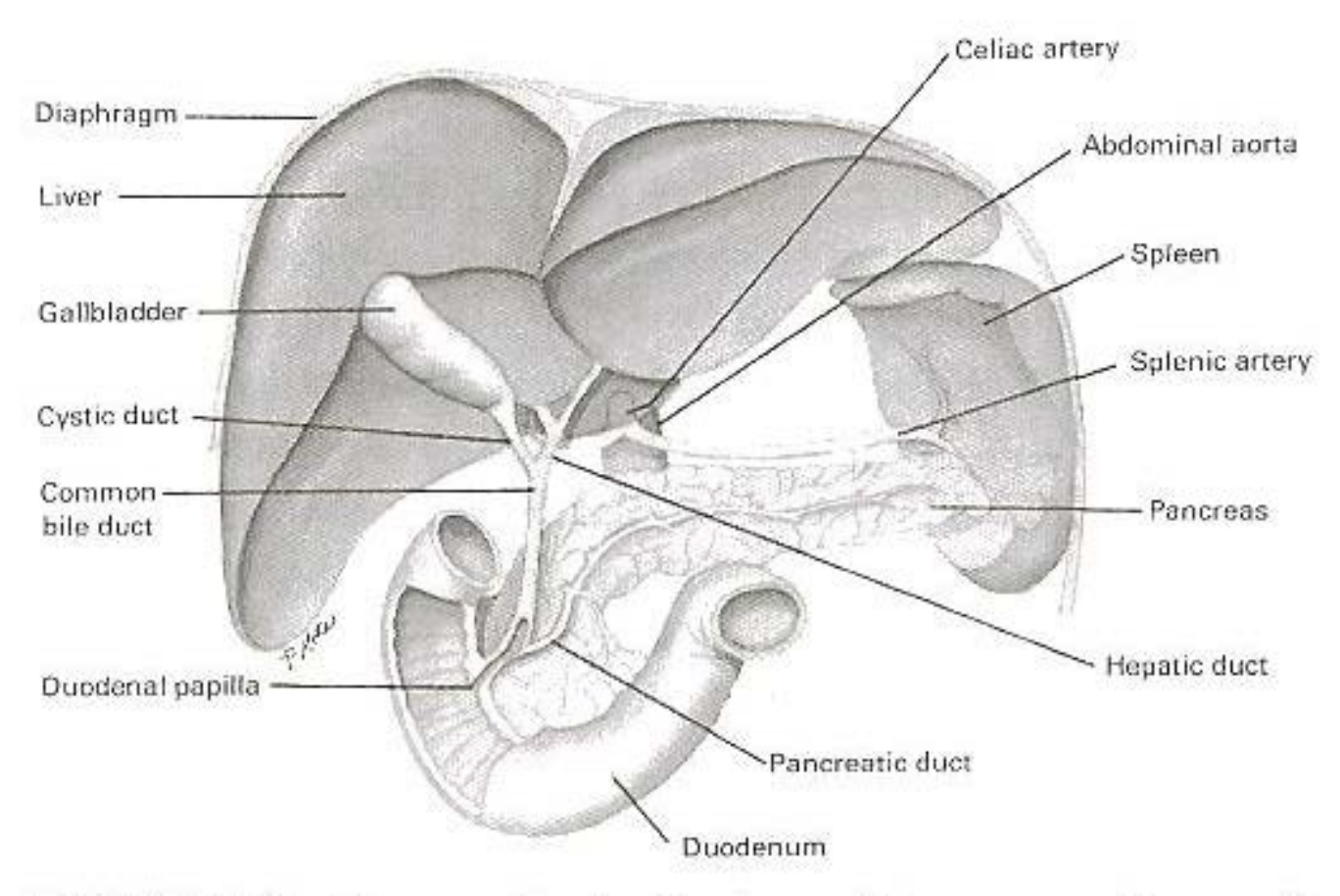
***Lipogenesis decreased, cholesterol production increased;***

***Protein and peptide synthesis impeded;***

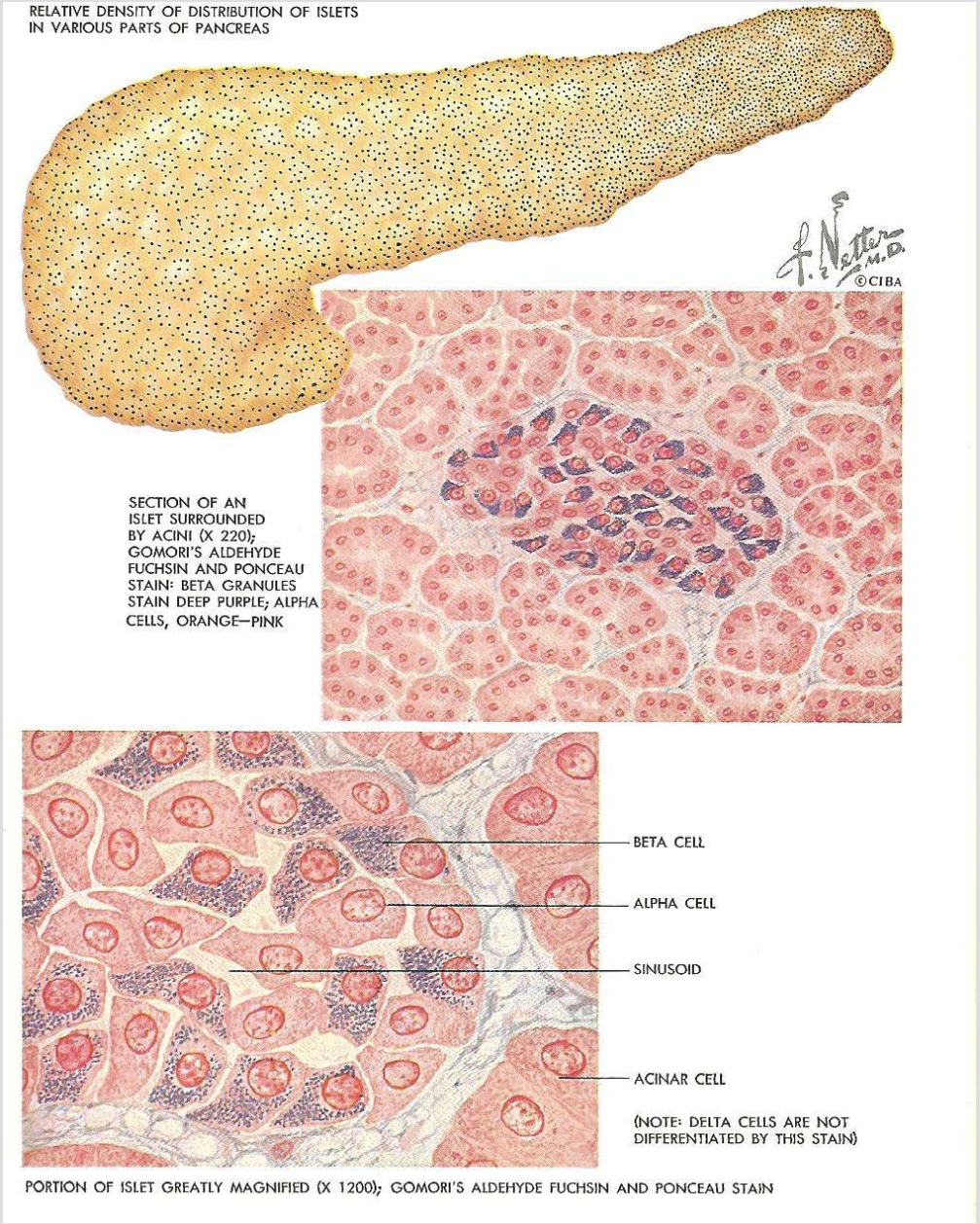
***Disturbances of energy metabolism;***

***Occurrence of keto-acidosis (increased $H^+$ concentration in blood plasma, pH < 7.38).***

# Pancreas: anatomic location



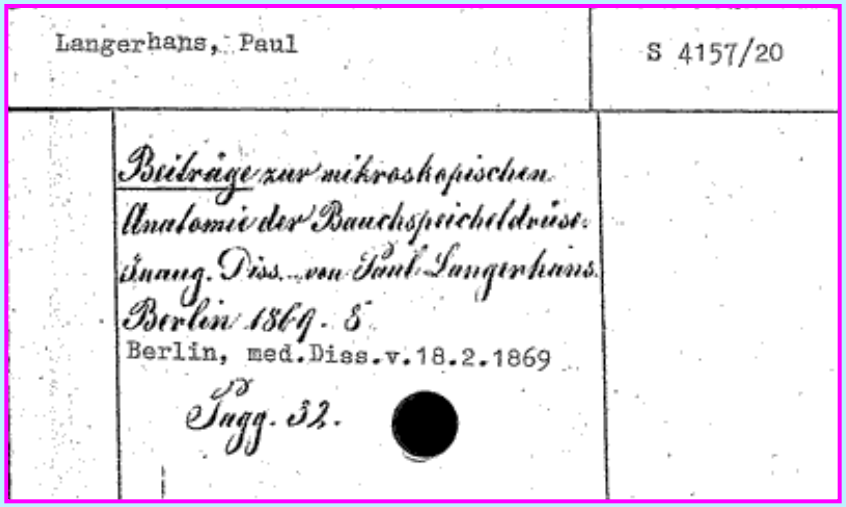
# Insulin and glucagon:
## pancreatic secretory tissue



# Further steps in history

***Paul Langerhans***
(1847-1888)
*described in his M.D. thesis*
*islet cells in pacreatic tissue*

***Gustave-Edouard Laguesse***
(1861-1927)
*assumed an endogenous secretion from the pancreatic islets (1893)*


Langerhans, Paul

S 4157/20

Beiträge zur mikroskopischen
Anatomie der Bauchspeicheldrüse.
Inaug. Diss. von Paul Langerhans
Berlin 1869. 8.
Berlin, med.Diss.v.18.2.1869
Sagg. 32.

*M.D. thesis (Berlin 1869) of P. Langerhans (examiner: Rudolf Virchow)*

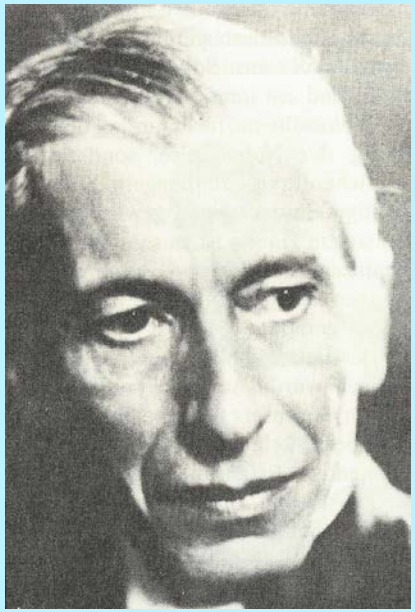
# Scientists who were close to the discovery of insulin

## *Eugene Lindsay Opie*
(1873-1971)

*American pathologist.*

Discovered (1901) that diabetes is caused by the destruction of the islets of Langerhans. He was the first to recognize the specific role of the islets. First extracts of pancreas used in treatment of diabetic patients.

## *Nicolas Constantin Paulesco*
(1869-1931)



*Romanian physiologist, working earlier with Minkowski & von Mering.*

Apparently reached similar results as Banting and Best, in roughly the same period of time.

## *Georg Ludwig Zuelzer*
(1870-1949 or 1952)

*Pediatrician and diabetologist in Berlin.*

Calf pancreatic extract ("Acomacol") seemed to possess antidiabetic activity (1908). Abandoned due to numerous side effects (hypoglycemia?)

## *Marcel Eugène Émile Gley*
(1857-1930)

*Professor of Physiology, Collège de France (Paris).*

Investigation of pancreatic extracts already in 1890ies. Their preparation and hypoglycemic effects were very similar to that of Banting and Best. For unknown reasons, he didn't publish his results.

# Discovery of insulin

## 1921-1922

Charles Herbert Best (1899-1978)

Frederick Grant Banting (1891-1941)

# Eine erfolgreiche Geschichte aus Toronto

30. Okt. 1920:
Frederic Banting liest einen Artikel in *Surgery, Gynecology and Obstetrics* über die Beziehung pankreatische Lithiase – Diabetes (Autor: Moses Barron).

7. Nov. 1920:
Besuch von Banting bei Prof. John J.R. Macleod.
"*I found that Dr. Banting had only a superficial text-book knowledge of the work that has been done on the pancreatic extracts in diabetes*" (1922).
Macleod trotzdem einverstanden mit einer zeitlich beschränkten Durchführung der Versuche am Physiologischen Institut der Universität Toronto.

Anfang Mai 1921:
Charles Best angestellt als Assistent für die von Banting vorgeschlagenen Versuche.

15.-17. Mai 1921:
Beginn der Versuche. Wechselnde Erfolge und Misserfolge mit der antidiabetischen Wirkung der Extrakte.

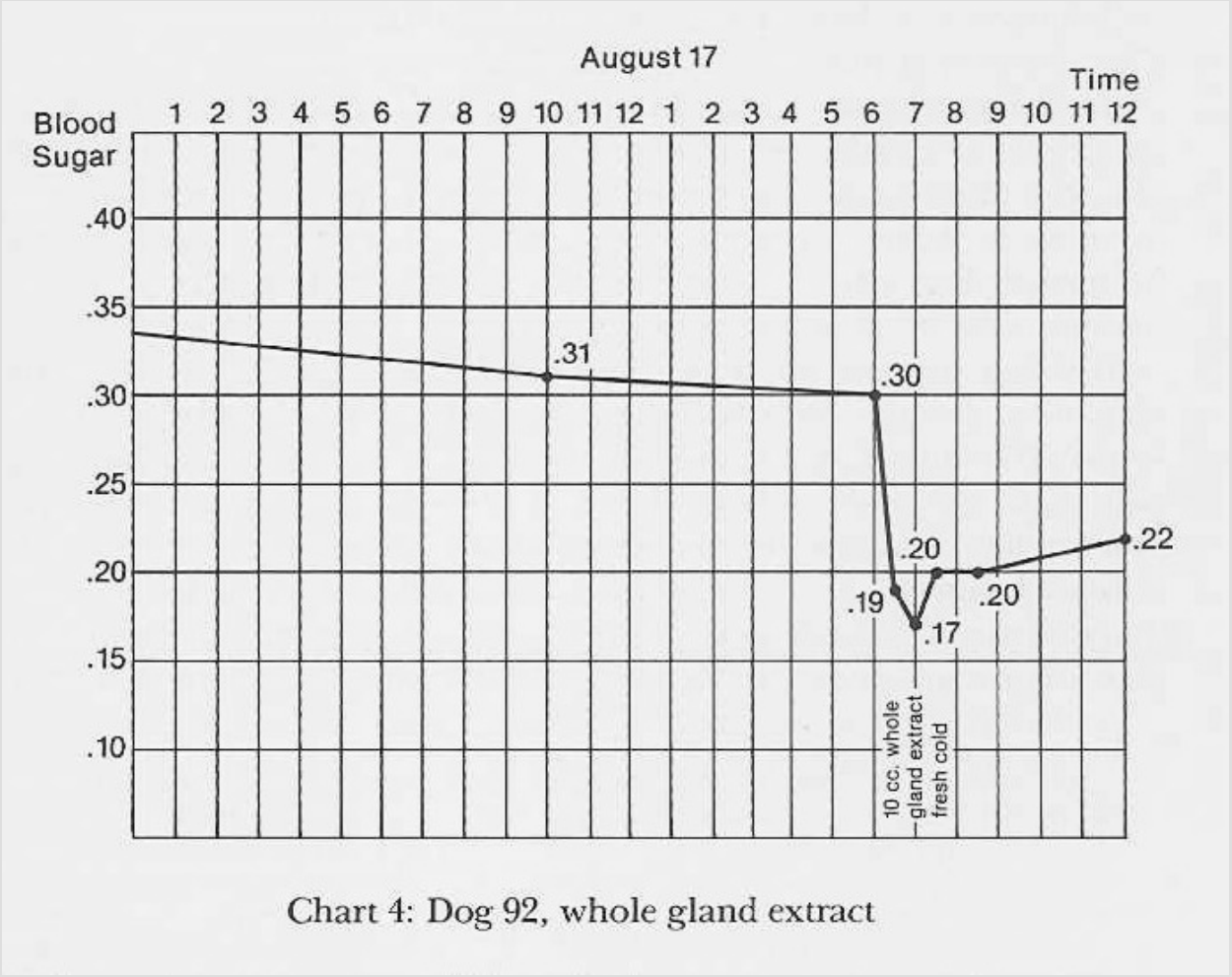



Chart 4: Dog 92, whole gland extract

from M. Bliss: *The Discovery of Insulin*. Paul Harris Publishing, Edinburgh, 1983. P. 76

Ende September 1921:
Macleod lehnt neue Forderungen von Banting ab (Räume, Laborhilfe).
Macleod zu Banting: "*As far as you are concerned, I am the University of Toronto.*"

Okt. 1921:
Fortsetzung der Versuche mit Hilfe von Prof. Velyien Henderson (Pharmakologisches Institut, Universität Toronto).

Dez. 1921:
Auf Vorschlag von Macleod beschäftigt sich der Biochemiker Prof. James Bertram Collip (University of Alberta) mit der Gewinnung und mit der weiteren Reinigung des Insulins. Bereits im Februar 1922 besitzt er ziemlich reine Insulin-Präparate.

Weihnachten 1921:
Banting, Best und Macleod berichten zum ersten Mal über ihre Resultate am Meeting of the American Physiological Society in New Haven, CT. Dr. Lewells Barker (John Hopkins Hospital) informiert weitere Kliniker und den Forschungsdirektor von Eli Lilly Company, Dr. George H.A. Clowes, über die viel versprechenden Resultate aus Toronto.

11. Jan. 1922:
Extrakte von Banting und Best wurden zum ersten Mal einem diabetischen Patienten (Leonard Thompson, 14-jähring) in Toronto General Hospital verabreicht. Der behandelnde Arzt, Dr. Walter Campbell (Diabetic Clinics) bezeichnete das Präparat als "a thick brown muck". Resultate nicht völlig überzeugend: Absinken der Glukose um 30% im Blut, 18% im Urin.

22. Jan. 1922:
Durchbruch: Derselbe Patient wird über 14 Tage mit gereinigten Präparaten von Collip behandelt. Dauerhaftes Absinken der Blutglukose auf ca. 7% (unter die Normwerte!), Glykosurie verschwunden. (Thompsom starb an Pneumonie im Jahre 1935, nach 13 Jahren Therapie mit Insulin).

April 1922:
Ein junges Mädchen mit schwerem Diabetes (Zustand *ante mortem*) wird mit Collip'schen Extrakten behandelt; dramatische Besserung. Es starb jedoch, als die Therapie wegen Mangel an Extrakt unterbrochen wurde.

17. Mai 1922:
Macleod gibt die Entdeckung von Insulin am Kongress der Association of American Physicians in Washington, DC, bekannt.

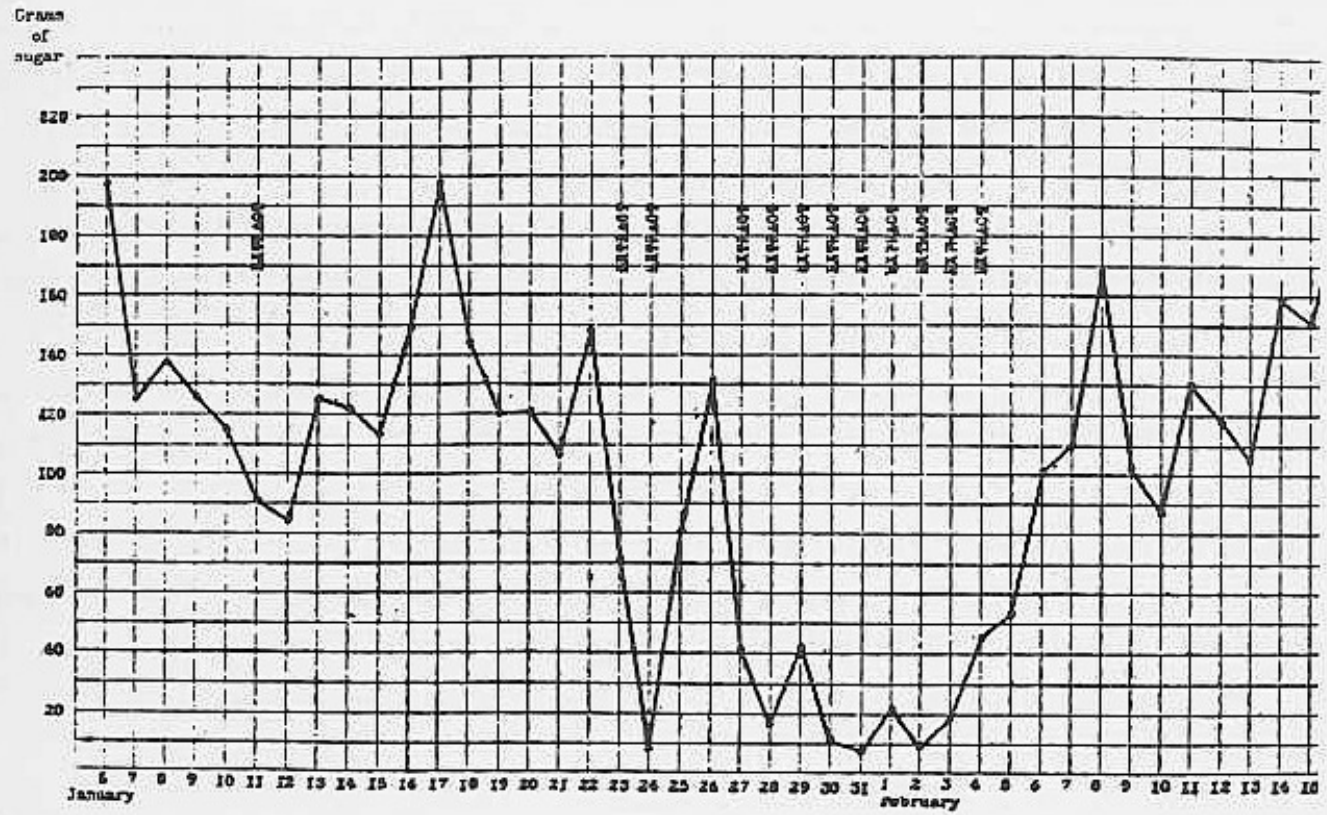


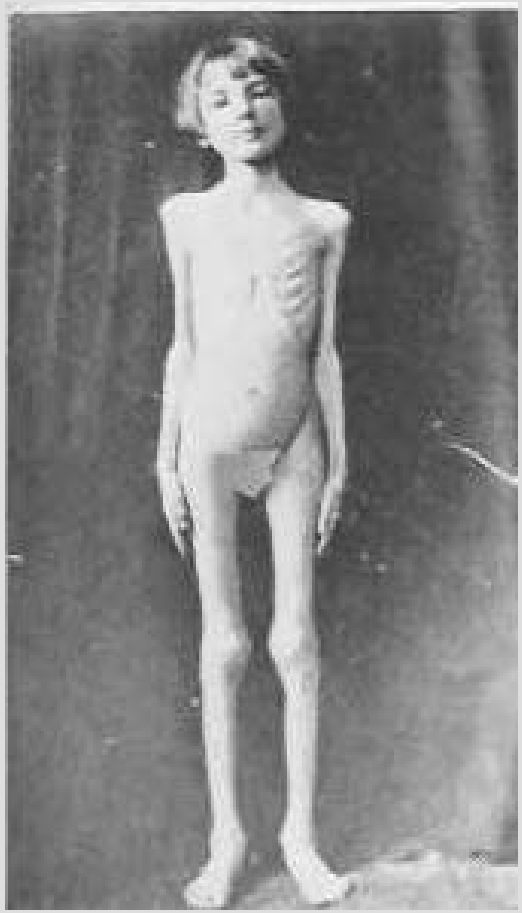

Chart 5: The effect of extract on the sugar in Leonard Thompson's urine. Taken from the 1922 published report.

from M. Bliss: *The Discovery of Insulin*. Paul Harris Publishing, Edinburgh, 1983. P. 121

# Patient “J.L., age 3 years

Before insulin. December 15, 1922
weight 6.8 kg

After insulin. February 15, 1923
weight 13.2 kg



**Before and after insulin treatment pictures of a 1922 patient of Dr. H. Rawle Geyelin.**

Vereinigung ›Ärzte gegen Tierversuche‹ e.V.

*Herzlich willkommen!*

**Cristeta Brause**
Der Tierversuch in der Diabetes-Forschung - genauer betrachtet!

**Alle brauchbaren Erkenntnisse, die den »roten Faden« in der Diabetes-Geschichte von der Antike bis in unser Jahrhundert bilden, basieren auf tierversuchsfreien Methoden!**

**Tierexperimente haben**

- **zu keiner neuen Erkenntnis geführt,**
- **Bestenfalls eine auf anderem Wege gewonnene Erkenntnis in ihrer Reproduzierbarkeit gezeigt, und**
- **insgesamt gesehen der Diabetesforschung eher geschadet als genützt, da sie Anlass zu falschen Theorien gaben.**

http://aerzte-gegen-tierversuche.tierrechte.de/textversion/content/de/infokrankheiten/diabetes.php4

# Industrielle Herstellung des Insulins

Ende März 1922:
Eli Lilly Company (G.H.A. Clowes) schlägt der Toronto-Gruppe eine Kooperation zwecks industrieller Insulinproduktion vor. Gemäss einer ursprünglichen Vereinbarung sollte die Gruppe mit keiner „major manufacturing company" zusammenarbeiten und keine Insulin-Patente anmelden.

Agreement signed by F.G. Banting, C.H. Best, J.B. Collip, J.J.R. Macleod, January 25, 1922:

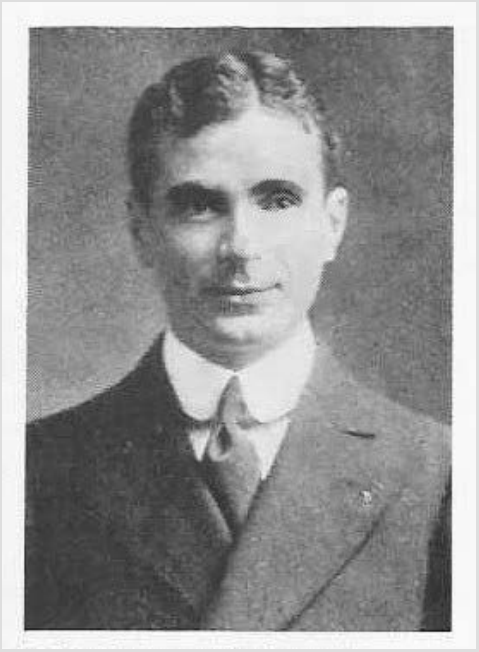
1. Dr. Banting, Mr. Best and Dr. Collip each agrees not to take any steps which will result in the process of obtaining an extract or extracts of pancreas, being patented, prepared by any commercial firm with aid of any of the above or otherwise exploited during the period of co-operation with the Connaught Anti-Toxin laboratories.
2. That no step involving any modification in policy concerning these researches be taken without preliminary joint conference between Dr. Banting, Mr. Best and Dr. Collip, and Professor Macleod and Professor Fitzgerald be held.


Erste Niederlassung der Firma in Indianapolis, IN

Lilly

1876 Gründung in Indianapolis, IN

Elias Lilly (1838-?) Gründer der Firma in Indianapolis, IN (1876)



Dr. George H.A. Clowes, Forschungsdirektor Eli Lilly and Company

12. April 1922:

Die Therapieerfolge verlangen eine schnelle industrielle Produktion des Insulins (grosse Nachfrage seitens der Kliniker). Vorschlag der Bedingungen für Patentierung in Zusammenhang mit der Produktionsübernahme durch Eli Lilly im Brief an Sir Robert Falconer (Präsident der Universität Toronto).

Letter by F.G. Banting, C.H. Best, J.B. Collip, J.J.R. Macleod & J.G. Fitzgerald (Connaught Anti-Toxin Laboratories) to Sir Robert Falconer, April 12, 1922:

The patent would not be used for any other purpose than to prevent the taking out of a patent by other persons. When the details of the method of preparation are published anyone would be free to prepare the extract, but no one could secure a profitable monopoly.

The Board of Governors of the University of Toronto agreed to the arrangement. An application was filed for a Canadian patent in the names of Collip and Best.

30. Mai 1922:

Vertrag zwischen Board of Governors of the University of Toronto und Eli Lilly and Company.

Juni 1922:

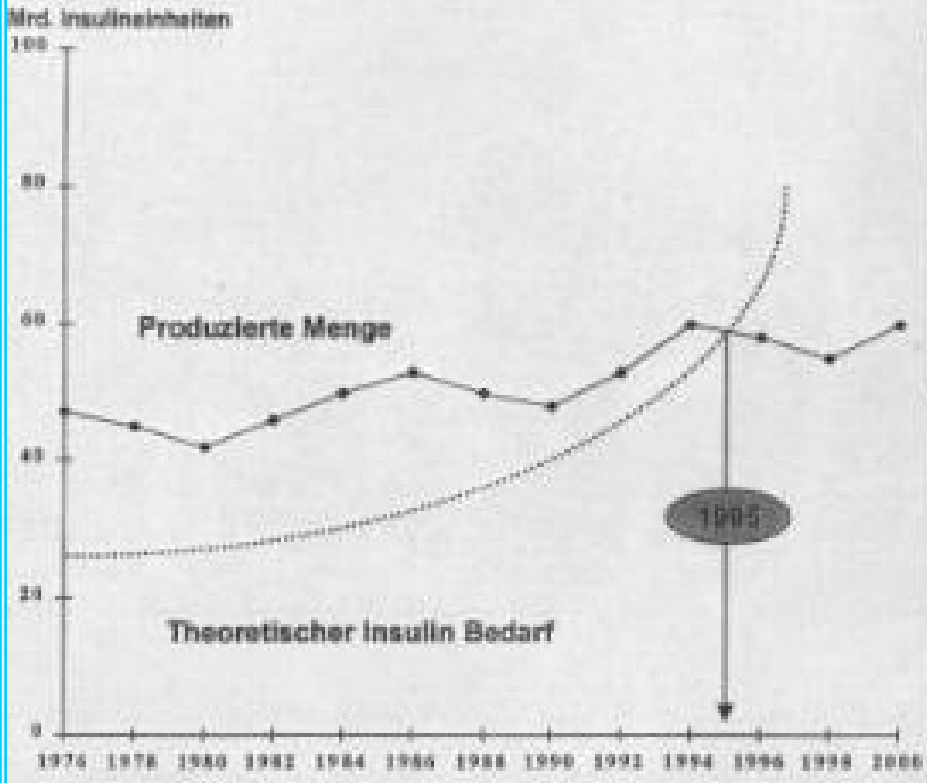
Eli Lilly beginnt mit Produktion des Insulins aus Schweine-Pankreaten.

# Isoliertes Schweineinsulin: prognostizierter Produktions-Engpass (1995)

**Abb. 6: Insulinbedarfsentwicklung**

Aventis

## Insulinversorgung in den USA Prognose 1976




**Unberücksichtigt blieben:**

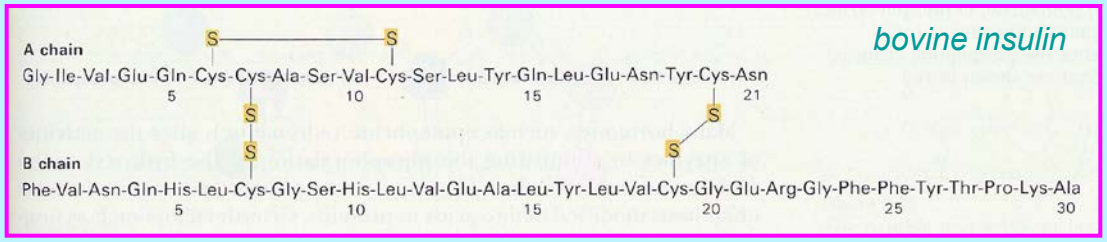
- Bessere Nutzung verfügbarer Drüsen
- Verfügbarkeit von
  - Drüsen aus dem Ausland
  - Insulin aus dem Ausland
- Mögliche Ausbeuteverbesserungen
- Bessere orale Antidiabetika
- Durchbrüche in der Genforschung

**Fakten**

- Ein gesunder Mensch produziert rund 2 mg Insulin pro Tag
- Ein Typ-I-Diabetiker verbraucht ca 1,5 mg tierisches Insulin pro Tag
- Ein Schweinepankreas ergibt tierisches Insulin für 10 Tage
- Seit 1982: gentechnisch hergestelltes Humaninsulin

Quelle: A Study of Insulin Supply and Demand, NIH 1976

# INSULIN: 1955




A.P. Ryle, F. Sanger, L.F. Smith, R.Kitai:
Disulphide bonds of insulin.
*Biochem. J.* ***60*** *(1955) 541-556*

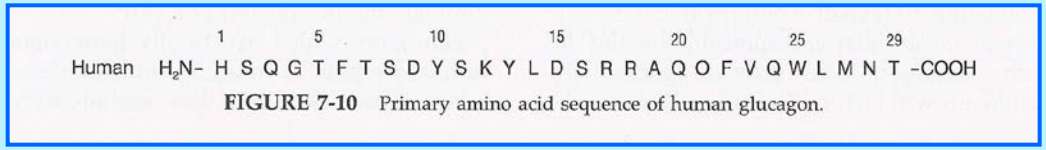


FIGURE 7-10 Primary amino acid sequence of human glucagon.

Nobel Prize (Chemistry) 1958
***"for his work on the structure of proteins, especially that of insulin."***

Frederick Sanger
(*1918)

# INSULIN: structural studies

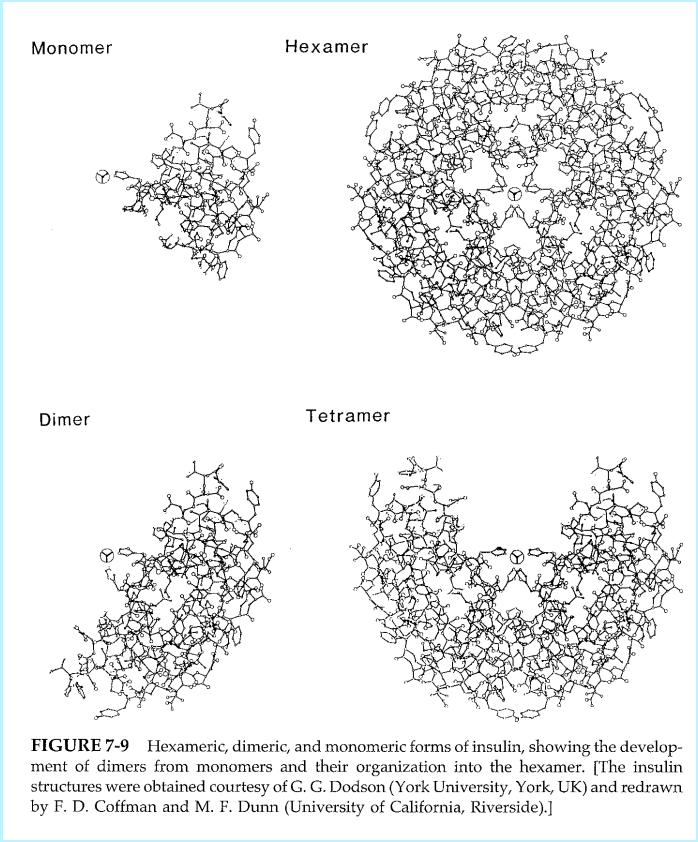



**FIGURE 7-9** Hexameric, dimeric, and monomeric forms of insulin, showing the development of dimers from monomers and their organization into the hexamer. [The insulin structures were obtained courtesy of G. G. Dodson (York University, York, UK) and redrawn by F. D. Coffman and M. F. Dunn (University of California, Riverside).]

Nobel Prize (Chemistry) 1964
***"for her determinations by X-ray techniques of the structures of important biochemical substances."***

Dorothy Crowfoot Hodgkin
(1919-1994)

# Synthetische Insulin-Analoga: gentechnisch hergestellte Arztneimittel

| Substanz | Struktur[b)] | therapeutische Charakteristik | Produzent (*Präparat*) | Produktionslinie[d)] |
|---|---|---|---|---|
| Humaninsulin (normal) | | | | *E. coli*<br>*S. cerevisiae* |
| HPN-Humaninsulin (***n**eutrales **p**rotamin-verzögertes Insulin **H**agedorn)[a)] | Protamin-gebundenes Insulin[c)] | langwirkend, mischbar mit normalem Insulin | Eli Lilly, Aventis, Novo Nordisk, Berlin-Chemie, B. Braun/ratiopharm | *E. coli*<br>*S. cerevisiae* |
| Insulin Lispro | Pro(B28)Lys; Lys(B29)Arg | schnell verfügbar, schneller Einsatz des Effekts | Eli Lilly (*Humalog 100 / Liprog*) | *E. coli* |
| Insulin Aspart | Asp(B28)Pro | schnell wirkend | Novo Nordisk | *S. cerevisiae* |
| Insulin Glargine | Asn(A21)Gly; Arg(B31); Arg(B32) | langwirkend | Aventis (*Lantus*) | *E. coli* |

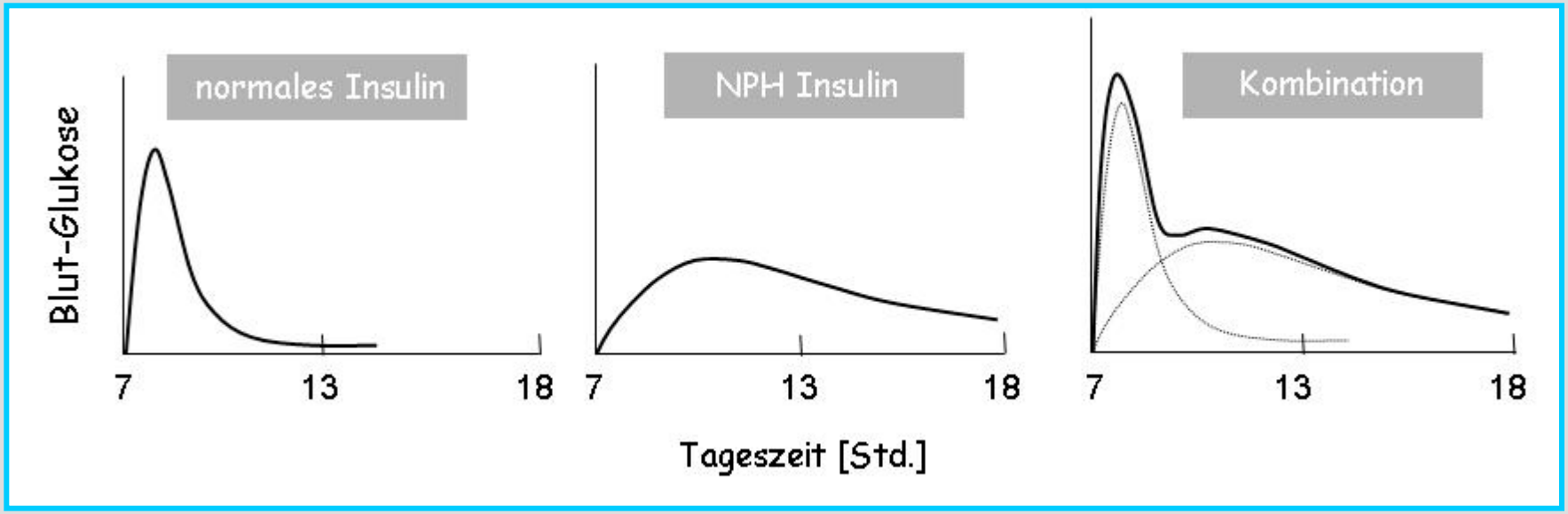
[a)] Das Verzögerungsprinzip (Bindung an Protamin) wurde von W. Hagedorn entwickelt.

[b)] z.B. Pro(B28)Lys bedeutet, dass die 28. Aminosäure *Pro*lin der B-Kette des menschlichen Insulins durch die Aminosäure *Lys*in ersetzt wurde. Arg(B31) : *Arg*inin wurde der B-Kette als 31. Aminosäure zugefügt.

[c)] Protamine: einfache basische Proteine aus Fischsperma.

[d)] Für die Produkution benützte Mikroorganismen: Darmbakterium *Escherichia coli* und Bierhefe *Saccharomyces cerevisiae*.

# Pharmakokinetik: Insulin und NPH-Insulins



# Discovery of insulin

Nobel Prize (Physiology or Medicine) 1923

***Frederick Grant Banting***
(1891-1941)

***John James Richard Macleod***
(1876-1935)

Nobel Prize deserved but not received

***Charles Herbert Best***
(1899-1978)

*Summer student with F. Banting*

***James Bertram Collip***
(1892-1965)

*Canadian biochemist, on sabbatical with J.J.R. Macleod*

# "There is in insulin glory enough for all."

Comment by Dr. Lewellys Barker on the speeches given by J.J.R. Macleod and F. G. Banting at the banquet of University of Toronto, November 26, 1923.

(Published in *Star, Telegram, Globe,* and other journals, Nov. 27, 1923)

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