PONTIFICIA
ACADEMIA
SCIENTIARVM

COMMENTARII

VOL. II N. 57

CHARLES H. BEST

THE HISTORY, THE DISCOVERY AND THE PRESENT POSITION OF INSULIN

EX AEDIBVS ACADEMICIS IN CIVITATE VATICANA

PONTIFICIA
ACADEMIA
SCIENTIARVM

COMMENTARII
Vol. II - N. 57
pag. 1-48

THE HISTORY, THE DISCOVERY AND THE PRESENT POSITION OF INSULIN

CHARLES H. BEST
Pontifical Academician

SVMMARIVM — Diabetis historia exponitur et eventus narrantur, qui effecerunt ut Auctor insulinam reppererit; minuta quaedam commemorantur circa operam, quae anno 1921 Toronti facta est; breviter autem perpenditur quae sit nunc insulinae sors, quaeque in futurum sperare liceat.

1972 marks the 50th Anniversary of the testing and the clinical use of the antidiabetic hormone insulin. The history of this remedy goes far back into antiquity and is, of course, closely related to that of diabetes. Traces of what may have been diabetes are described in records which go back to 1500 years before the birth of Christ. My students from India, Japan, China, and from the Arabic countries, tell me that references to the disorder have been passed from expert to expert and that the first references may be earlier than the one to which I have referred.

I will begin my brief review of the History of Diabetes with the physician Celsus who lived here in Rome from

---

Paper presented on April 13th, 1972 during the Plenary Session of the Pontifical Academy of Sciences.

30 B.C. to 38 A.D. (Slide 1). He recorded a good description of diabetes. Later, about 250 years after the birth of Christ, Aretaeus of Cappadocia (Slide 2) gave an even better description and coined the word « diabetes » which means "to flow through" or to "syphon off". The word "mellitus" was later added.

The next (Slide 3) shows a picture of Claude Bernard who has been one of my heroes as a first great experimental physiologist. He discovered many important facts relating to diabetes, such as the presence of the complex sugar glycogen in liver and the fact that diabetes could be produced by a pin prick in certain parts of the brain in animals. I was working on the nerve pathway by which these impulses produced diabetes just before the work on insulin in Toronto began.

In 1869 a young medical man, Paul Langerhans (Slide 4) who had graduated from the University of Berlin, published his inaugural dissertation on cells in the pancreas glands which had never been described before. Langerhans made many other contributions to the histology of the pancreas but he suggested no function for the cells which bear his name. He was immortalized by Laguesse who first called these cells the Islands of Langerhans. In the next (Slide 5) is a picture of a single human Island of Langerhans showing the blood vessel going in to carry nutrients and the blood vessel coming out which would carry insulin.

In 1889 two German investigators, BARON VON MERING (Slide 6) and OSCAR MINKOWSKI (Slide 7) proved conclusively that the removal of the pancreas from dogs produced rapidly fatal diabetes. MINKOWSKI was really the moving spirit. I had correspondence with him and sent him his first insulin, but never had the pleasure of meeting him. He died before the Nazi regime but his wife was rescued from prison-camp with funds sent from Toronto through our Swiss colleagues.

Aulus Cornelius Celsus. First century.

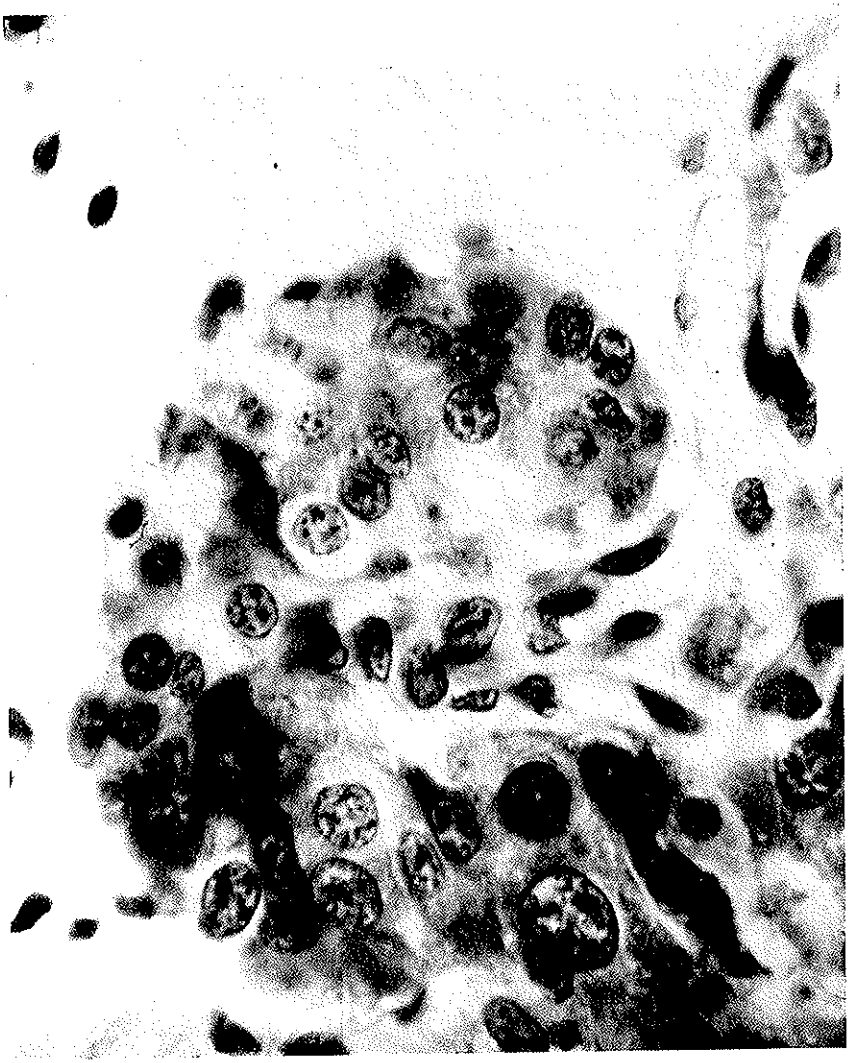
SLIDE 1 — CELSUS

Aretaeus, the Cappadocian.

SLIDE 2 — Aretaeus of Cappadocia

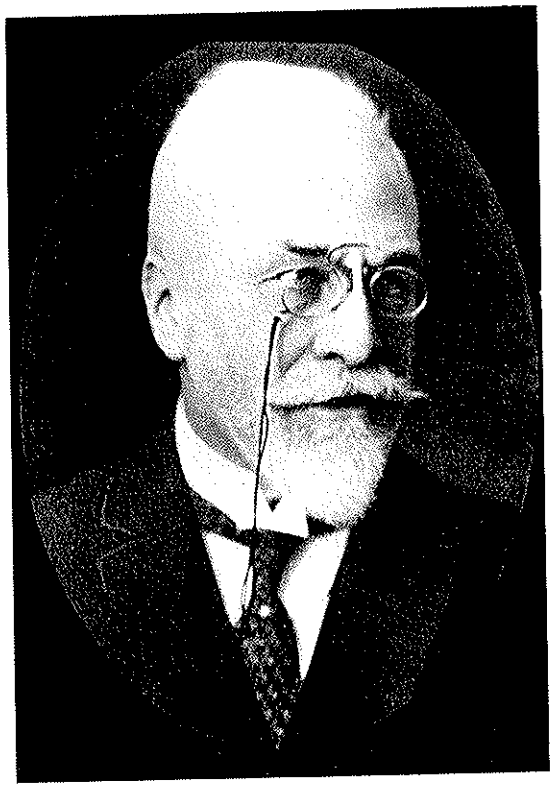
SLIDE 3 — CLAUDE BERNARD

SLIDE 4 — PAUL LANGERHANS



SLIDE 5 — Single human ISLAND of LANGERHANS

SLIDE 6 — VON MERING

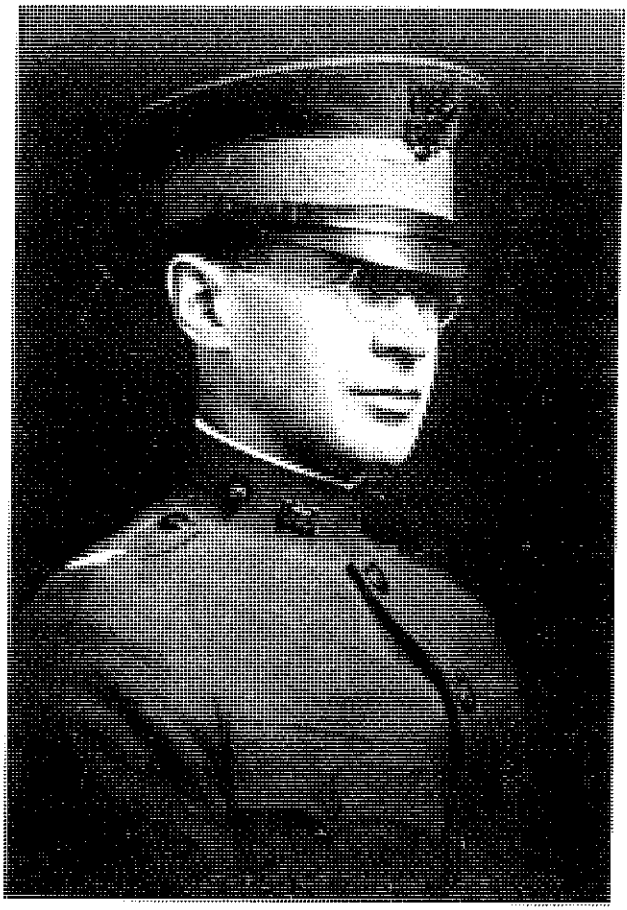


SLIDE 7 — MINKOWSKI

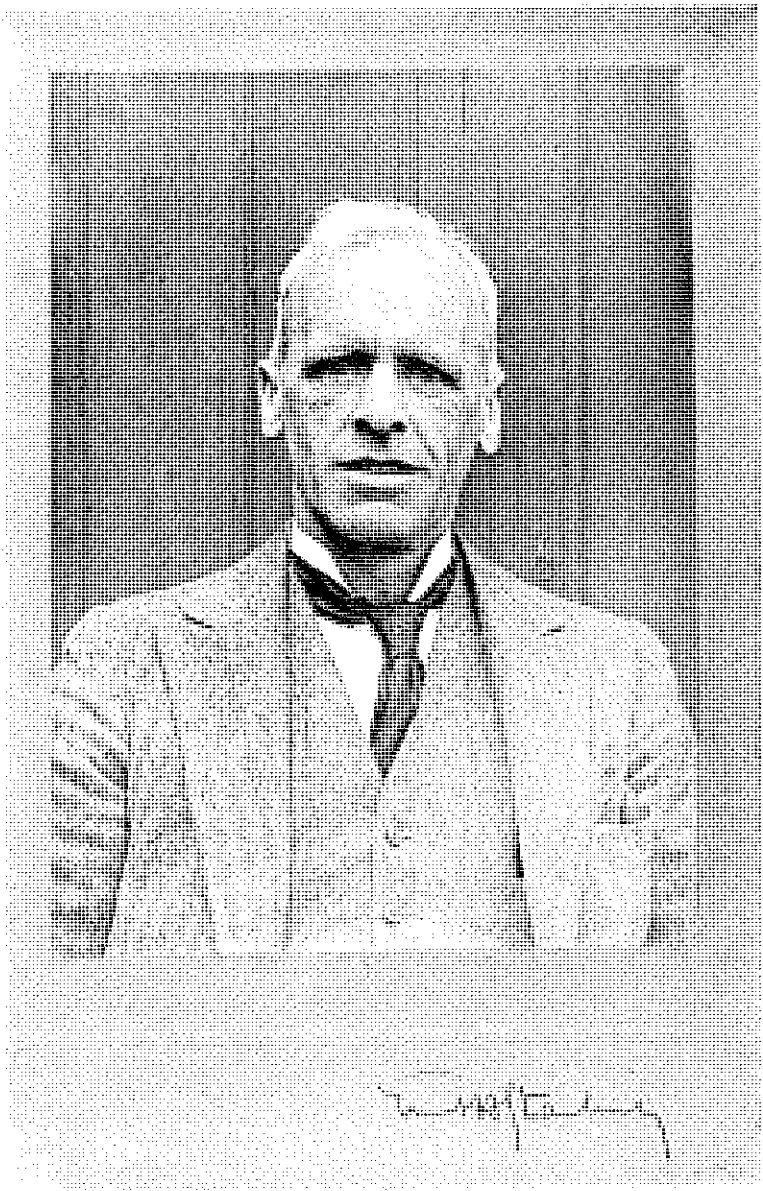
She went to join her daughter in South America where I called upon her when I was a visiting lecturer in Professor Houssay's laboratory for some six weeks. She gave me several most interesting books from OSCAR MINKOWSKI'S library.

There were many attempts to extract an active principle from the pancreas after VON MERING and MINKOWSKI'S work. MINKOWSKI made extracts himself but recorded only negative results. I will mention a few of the many others who made these experiments. The next (Slide 8) is of Dr. GEORG ZUELZER whose experimental work was not significant but who made extracts of pancreas and administered them to human patients in MINKOWSKI'S Clinic. He produced a fall in blood sugar but certainly no clinical improvement and the study had to be discontinued because of the toxic effects of the extracts. Nothing more was heard of ZUELZER'S work, which was completed in 1909, until after the work on insulin in Toronto. The next (Slide 9) shows Dr. E. L. SCOTT of New York who made extracts of pancreas and secured some lowering of blood sugar in depancreatized dogs. But he was worried about his chemical methods and spent most of the rest of his active life in trying to improve them. I mention him because he was one of those who tied the pancreatic ducts as we did later. Professor ERNEST STARLING (Slide 10) had evidence of the presence of insulin but his findings were severely criticized by my mentor in Torouto, Professor J. J. R. MACLEOD, and Sir ERNEST withdrew his claims. The next (Slide 11) shows his statement in 1920. The next picture (Slide 12) is of Prof. J. J. R. MACLEOD who taught me a great deal about carbohydrate metabolism and experimental diabetes in the course of 60 lectures in 1920. He thought that the Islands might be detoxifying centres and remove a poison, the accumulation of which might produce diabetes. He made extracts of pancreas but completely failed to secure any definite antidiabetic effect. His comments are shown in the next (Slide 13).

SLIDE 8 — DR. GEORG ZUELZER



SLIDE 9 — DR. E. L. SCOTT



SLIDE 10 — DR. ERNEST STARLING

WE DO NOT YET KNOW HOW THE PANCREAS AFFECTS SUGAR PRODUCTION OR UTILISATION IN THE NORMAL ANIMAL. IT IS GENERALLY ASSUMED THAT IT SECRETES INTO THE BLOOD STREAM A HORMONE WHICH MAY, ACCORDING TO THE VIEW OF THE NATURE OF DIABETES WHICH WE ADOPT, PASS TO THE TISSUES AND ENABLE THEM TO UTILISE SUGAR, OR PASS TO THE LIVER AND INHIBIT THE SUGAR PRODUCTION IN THIS ORGAN. A VERY SMALL PORTION OF THE PANCREAS IS SUFFICIENT FOR THIS PURPOSE, BUT WE HAVE BEEN UNABLE TO IMITATE THE ACTION OF THE PANCREAS STILL IN VASCULAR CONNECTION WITH THE BODY BY INJECTION OR ADMINISTRATION OF EXTRACTS OF THIS ORGAN.

MARCH 1920. ERNEST H. STARLING'S TEXTBOOK.

SLIDE 11 — Statement by Dr. STARLING

SLIDE 12 — J. J. R. MACLEOD

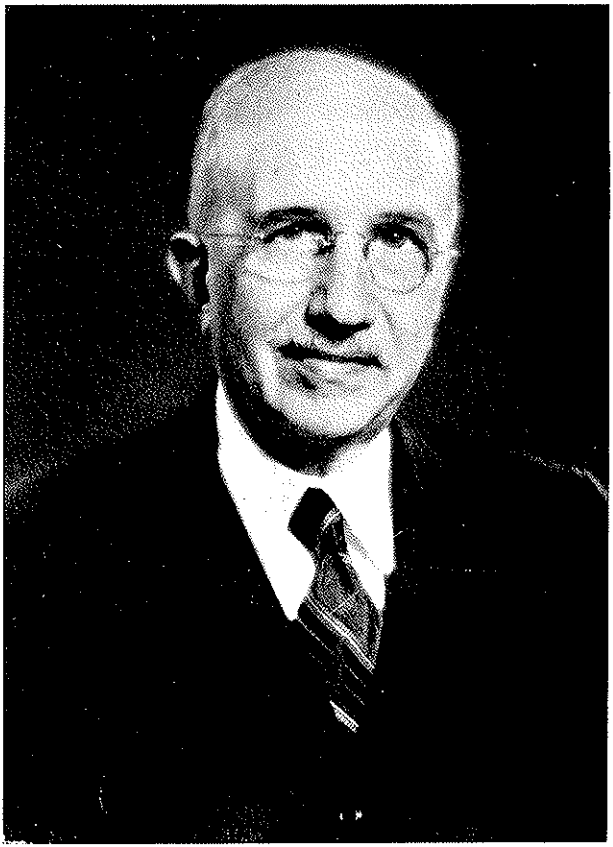
THE REMOVAL OF SOME HORMONE NECESSARY FOR PROPER SUGAR METABOLISM IS, HOWEVER, BY NO MEANS THE ONLY WAY BY WHICH THE RESULTS CAN BE EXPLAINED, FOR WE CAN ASSUME THAT THE PANCREAS OWES ITS INFLUENCE OVER SUGAR METABOLISM TO SOME CHANGE OCCURRING IN THE COMPOSITION OF THE BLOOD AS THIS CIRCULATES THROUGH THE GLAND - A CHANGE WHICH IS DEPENDENT ON THE INTEGRITY OF THE GLAND AND NOT ON ANY ONE ENZYME OR HORMONE WHICH IT PRODUCES.

1920. J.J.R. MACLEOD'S TEXTBOOK.

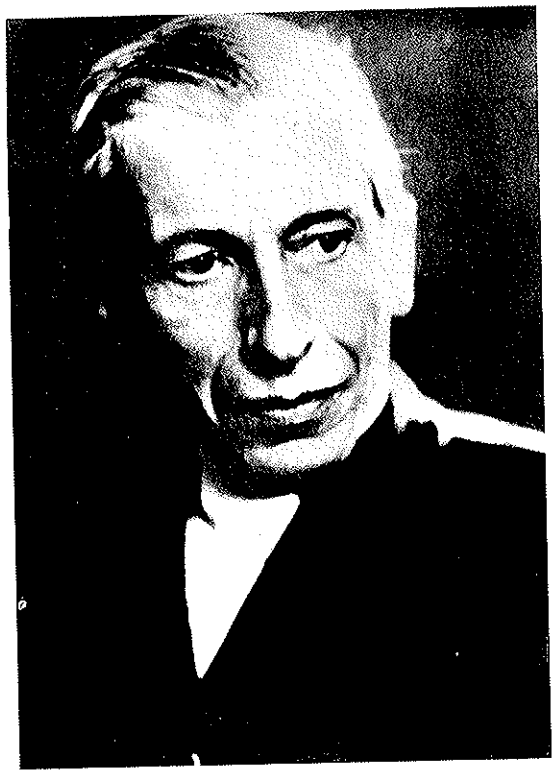
SLIDE 12 — J. J. R. MACLEOD

Another investigator who came close to success was Dr. ISRAEL KLEINER of The Rockefeller Institute in New York (Slide 14). He made emulsions of pancreas and succeeded in lowering the blood sugar but he was bothered by thrombosis produced by the particles in his suspension and contented himself with recording his findings and stating that someone should filter his extracts and see if they were still potent. Another prominent investigator who had not published prior to the beginning of our work in Toronto, was Professor PAULESCO of Roumania (Slide 15). His acute experiments were very successful. The blood sugar of his dogs after pancreatectomy did not rise as high as they usually did in our animals. He produced a very low blood sugar and it is very puzzling why these animals did not show profound signs of hypoglycaemia. He lowered not only the blood sugar but the ketone bodies with his extracts. In contrast with onr experiments he did not observe his dogs for prolonged periods — never more than 4 days. He did not attempt to purify his extracts as we did with acid alcohol and fat solvents and his studies did not lead directly to the clinical use of insulin which was, of course, the goal which we achieved.

The next (Slide 16) is my favourite picture of FRED BANTING taken in our laboratory in 1921. The experiments in Toronto were initiated by BANTING who had the idea that if the pancreatic ducts were tied it might be possible to extract the antidiabetic hormone. This procedure had, as I told you, been used many times before but without snccess. The next (Slide 17) shows a portrait of FREDERICK BANTING which hangs in the entrance of the Banting Institute in Toronto. The next (Slide 18) illustrates our first success. It is not very startling but it was encouraging. However, during the following months we had scores of dramatic lowering of the blood sngar and of the improvement of the clinical condition of the animals. The next (Slide 19) is a page from our



SLIDE 14 — DR. ISRAEL KLEINER



SLIDE 15 — PAULESCO

SLIDE 16 — F. G. BANTING

SLIDE 17 — DR. F. G. BANTING

Dog 410.
July 30th.
Blood Sugar - .20
10-15 - injected 4 cc. of extract (Ringers solution used) of degenerated pancreas from dog - 391 -
11-15 - Blood sugar - .12
Injected 5 cc. of extract -
(1.00 - extract was frozen) salt water removed & de water put around basin.
12-15 - Blood Sugar .11
Dog drinking
Injected 5 cc. of extract -
Vol urine 5 CC
(No sugar - Ben. qual.
2-15. Blood Sugar - .14
Vol urine 10 CC (5 cc per hr)
Ben. qual. neg.
- Injected intravenously 5 cc. extract
- 20 gms sugar in 200 cc water injected into stomach.
- (twice first passed into lung dog nearly drowned! completely recovered in 15 min.

47

5-oc P.M. dog in good condition

Aug. 7th

12 midnight (Aug 6 - Aug 7th)

Blood sugar — .43

Vol urine from 2 PM to 12 midnight — 175 cc.

(the last 30 cc being catheter specimen seperate sugar estimation)

← 10 hour total sugar — 3.36 g.

" " nitrogen — 1.20 g

" G : N ratio — 2.8

① 8 cc Isletin given

1. A.M.

Blood sugar — .37.

no urine obtained by catheter dog about same - able to stand up + walk, has not vomited since yesterday aft

② 8 cc Isletin given.

2 A.M. Blood Sugar .33

③ 8 cc Isletin no urine obtained

3. AM. Blood Sugar — .29

④ 8 cc Isletin no urine obtained

SLIDE 19

notebook showing the lowering of blood sugar. The next (Slide 20) continues this record. In the next (Slide 21) the dramatic lowering of blood sugar from a very high level to the normal level, is illustrated. And in the following (Slide 22) is shown the first use of extract of foetal calf pancreas. From this material we produced an extremely potent and relatively pure material which would — as we later showed — give excellent clinical results. The next (Slide 23) shows the lowering of the blood sugar to a level below the normal and the animal had the characteristic symptoms which are seen to-day in patients who take too much insulin. In the next (Slide 24) a summary of our results which appeared as the conclusion of our first paper. This (Slide 25) is a picture of FRED BANTING and myself in 1921 with the laboratory where we worked, as a background, with the first dog that received insulin. The following (Slide 26) is of the dog that lived for 70 days and showed dramatic improvement. She was the first dog in history to demonstrate the prolonged beneficial effect of daily injections of insulin. (Later on animals lived for 10 to 12 years with daily injections). This dog was called "Marjorie" and a bas-relief was made of her by a physician in the United States and I have a cast of this plaque in my office (Slide 27).

Professor MACLEOD who had been sceptical and who had been away for 4 months in the summer of 1921, heard BANTING and me present our results at a University of Toronto Medical Seminar on the 14th of November, 1921. He was completely convinced (Slide 28) and thereafter turned his own attention and that of his laboratory to the development of insulin. The next (Slide 29) shows the suggestion which FRED BANTING made for a plaque to be put up in the room where we had carried on our experiments.

In 1920, before the discovery of insulin, I became engaged to a beautiful girl (Slide 30) who took a very great interest in our work. Indeed she helped us write the first paper, and

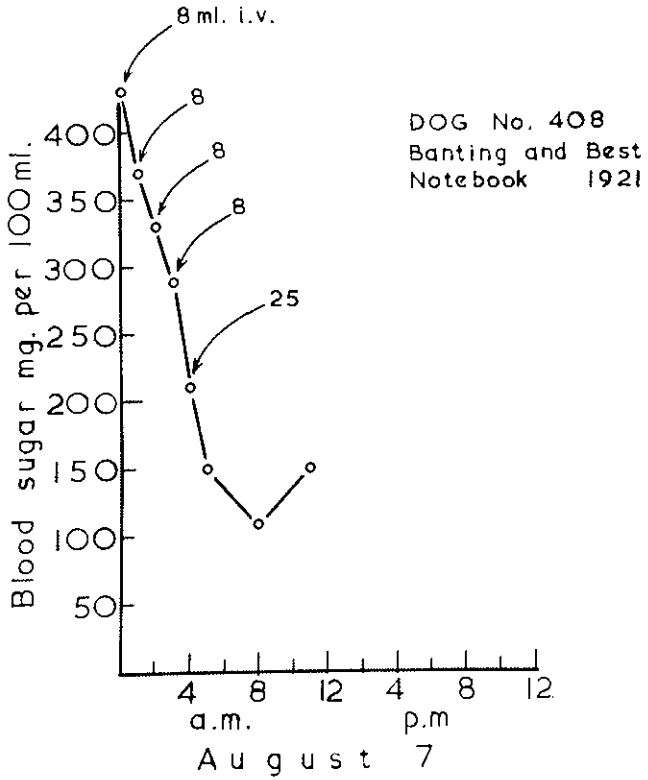
48

4.00 P.M. dog 408. Aug. 7th Blood sugar - .21
The extract of Aug 1st + the remainder of Aug 5th extract mixed - and somewhat diluted
⑤ making 25 cc in all injected
no urine obtained.
Blood Sugar - .15
5.00, P.M. Dog suddenly became lifeless & appeared to be dying. 30 cc Ringers sol injected intraperitoneally
6.00 P.M. - 50 cc ringers sol intravenously - slightly improved. Bowels moved twice during last ½ hour saliva drubbled from mouth.
7.00 P.M. - dog slightly improved
8.00 P.M. Blood Sugar - .11
dog still more improved + is now able to stand up

SLIDE 20

EFFECT OF INJECTION OF EXTRACT OF PANCREAS ON BLOOD SUGAR OF DEPANCREATIZED DOG

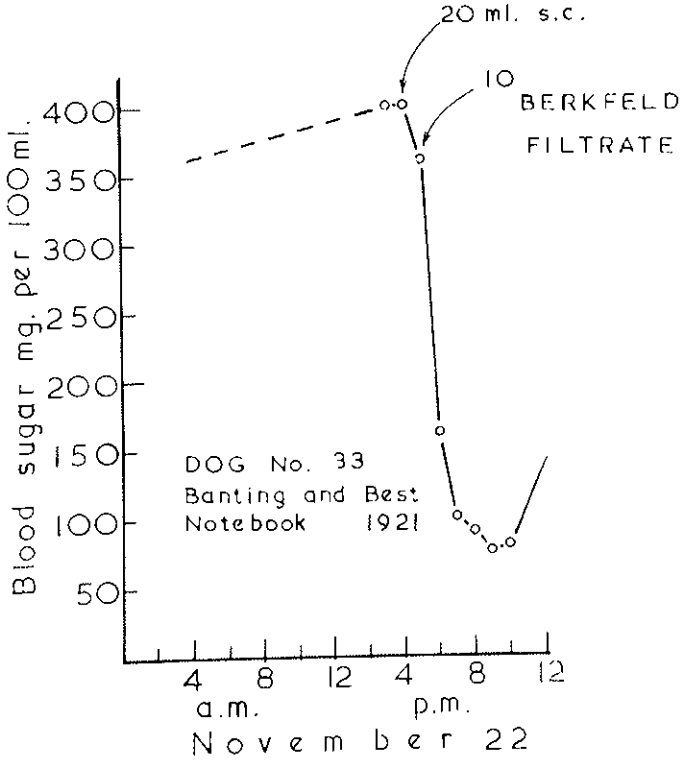
SALINE EXTRACT OF DEGENERATED PANCREAS



SLIDE 21

EFFECT OF INJECTION OF EXTRACT OF PANCREAS ON BLOOD SUGAR OF DEPANCREATIZED DOG

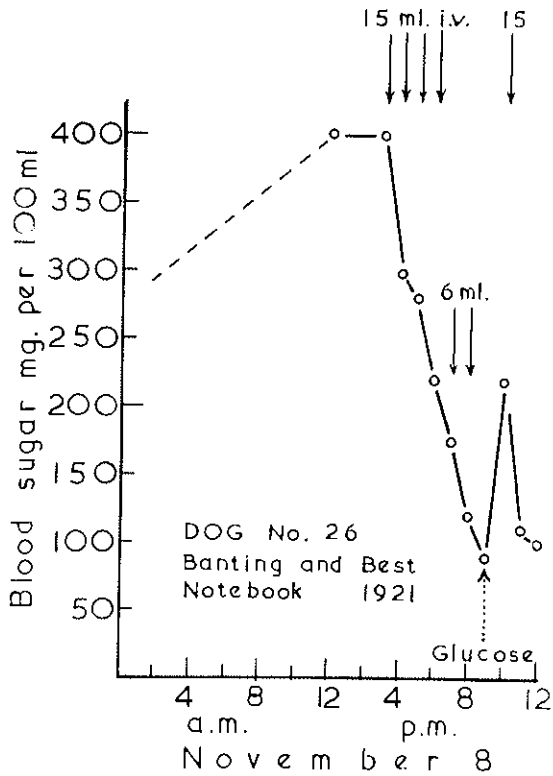
SALINE EXTRACT OF FOETAL CALF PANCREAS



SLIDE 22

EFFECT OF INJECTION OF EXTRACT OF PANCREAS ON BLOOD SUGAR OF DEPANCREATIZED DOG

SALINE EXTRACT OF DEGENERATED PANCREAS

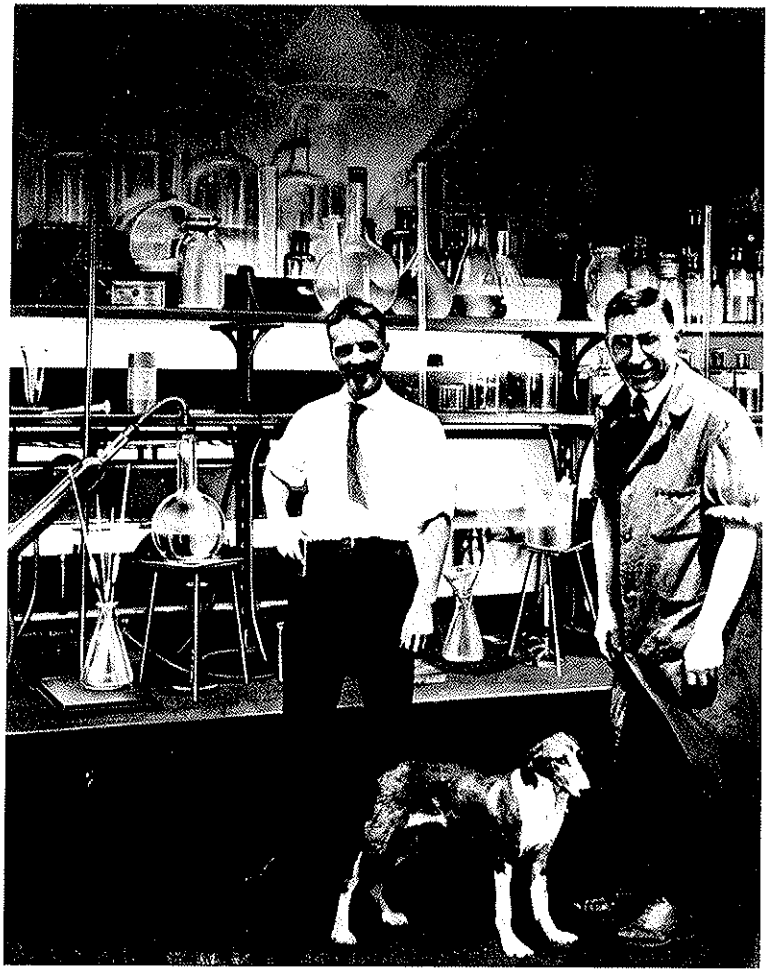


SLIDE 23

"IN THE COURSE OF OUR EXPERIMENTS WE HAVE ADMINISTERED OVER SEVENTY-FIVE DOSES OF EXTRACT FROM DEGENERATED PANCREATIC TISSUE TO TEN DIFFERENT DIABETIC ANIMALS. SINCE THE EXTRACT HAS ALWAYS PRODUCED A REDUCTION OF THE SUGAR OF THE BLOOD AND OF THE SUGAR EXCRETED IN THE URINE, WE FEEL JUSTIFIED IN STATING THAT THIS EXTRACT CONTAINS THE INTERNAL SECRETION OF THE PANCREAS."

("THE INTERNAL SECRETION OF THE PANCREAS"
By: F. G. BANTING AND C. H. BEST,
The Journal of Laboratory and Clinical Medicine,
St. Louis, Vol. VII, No. 5, Feb. 1922)

SLIDE 24



SLIDE 25 — C. H. BEST (left) - F. G. BANTING (right) with dog

SLIDE 26 — "Marjorie"

SLIDE 27 — Bronze plaque of "Marjorie"

PROFESSOR J.J.R. MACLEOD WROTE:

"BY THEIR INDUSTRY AND PATIENCE THESE TWO WORKERS (FREDERICK G. BANTING AND CHARLES H. BEST) SUCCEEDED, IN A FEW MONTHS, IN OBTAINING FINDINGS WHICH I CONSIDERED TO BE PERFECTLY CONVINCING."

SLIDE 28

REPLY TO
F. G. BANTING
CHAIR OF MEDICAL RESEARCH

UNIVERSITY OF TORONTO

"In this room, in 1921, Banting and Best carried out the early experiments which led to the discovery of Insulin."

Yours respectfully

F. G. Banting.

SLIDE 29

SLIDE 30 — MARGARET MAHON

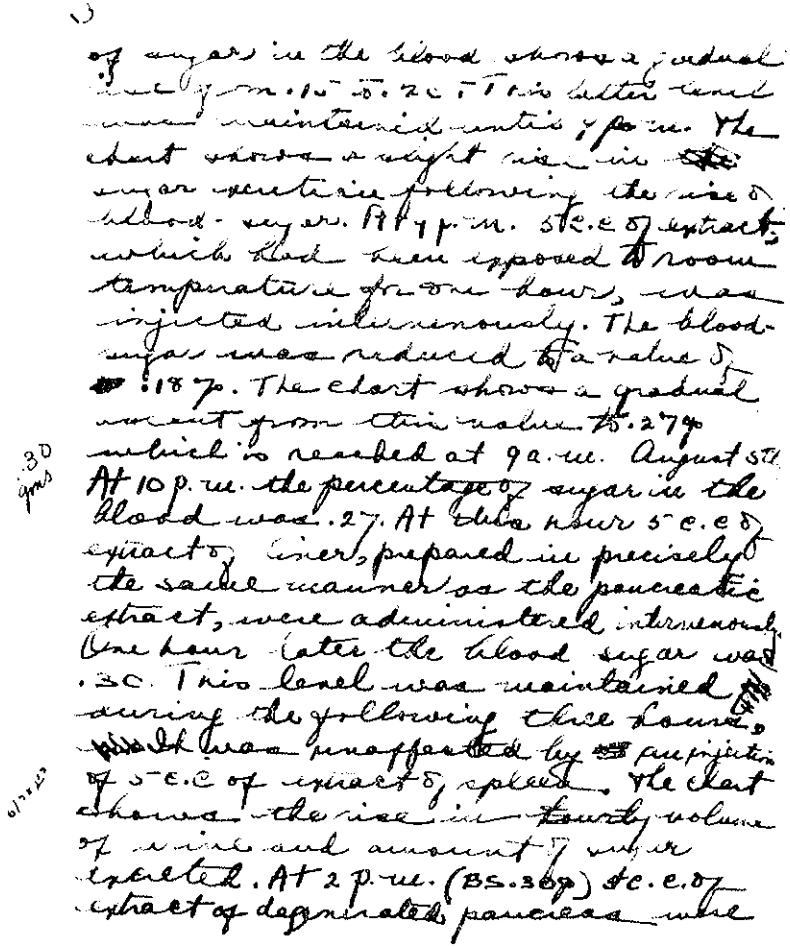
three pages of this document are her handwriting. As many of you know she goes with me everywhere and we have never been busier than in 1971 and 1972. This next (Slide 31) shows her handwriting, the following one (Slide 32) that of FRED BANTING, while the next one (Slide 33) is part of the manuscript in my own hand.

I will not have time to go into the developments of insulin in the 1920's and 1930's but insulin was crystallized by Professor J. J. ABEL of JOHNS HOPKINS University. His picture is shown in the next (Slide 34). Professor H. C. HAGEDORN of Copenhagen (Slide 35) was the first to make a slow-acting insulin and this was followed by the work of many others until a great variety of insulin preparations are now available.

On January 11th, 1922, the first diabetic patient received insulin. BANTING and I had given each other injections of our material and then it was sent over to the Toronto General Hospital for clinical use. I have always been sorry that we did not use the material from foetal calf pancreas because it was ten to 20 times as potent but it was felt that material from a commercially available source, that is, beef pancreas, would be preferable.

In December, 1922, Professor J. B. COLLIP joined our group. He was an experienced biochemist and using the data which we made available to him he was able to purify our extracts so that they could be given freely to diabetic patients. Unfortunately after several weeks he lost the secret of making insulin on a larger scale. He was recalled to his own CHAIR in Alberta before he could recover the secret. That was a hectic period for me but after six weeks with a greatly modified method, the procedure was recovered and, of course, has never been lost.

In January, 1922, LEONARD THOMPSON (Slide 36) was the first patient to receive insulin. A little later Dr. JOSEPH GILCHRIST (Slide 37) was the first medical man to receive



of sugars in the blood showed a gradual fall from .15 to .2 c. This latter level was maintained until 7 p.m. The chart shows a slight rise in the sugar reaction following the rise of blood-sugars. At 7 p.m. 5 c.c. of extract, which had been exposed to room temperature for one hours, was injected intravenously. The blood-sugar was reduced to a value of .187. The chart shows a gradual ascent from this value to .27% which is reached at 9 a.m. August 5th. At 10 p.m. the percentage of sugar in the blood was .27. At this hour 5 c.c of extract of liver, prepared in precisely the same manner as the pancreatic extract, were administered intravenously. One hour later the blood sugar was .3c. This level was maintained during the following three hours, when it was unaffected by the injection of 5 c.c of extract of spleen. The chart shows the rise in hourly volume of urine and amount of sugar excreted. At 2 p.m. (BS. .36%) 5 c.c. of extract of degenerated pancreas was

30 gms

6/7/22

SLIDE 31 — Page of the original manuscript by BANTING and BEST: "The Internal Secretion of the Pancreas", in the handwriting of MARGARET MAHON

8

Chart No. I contains the record of Dog 410. This experiment is not one of the most conclusive of those we submit but is very interesting to us at least since ~~it~~ we administered to this animal the first dose of the extract of degenerated pancreas.

As will be seen from the chart ~~on July 11th~~ the pancreas with the exception of the processus uncinatus was removed on July 11th. In the interval between this initial operation & the removal of the pedicle on July 18th the percentage of sugar in the blood remained at the normal level (.090 average of 30 normal observations on 30 normal dogs by the Lewis-Benedict method). The Benedict qualitative tests showed no sugar excreted. Animal decreased in weight from 6.5K to 5.8K. Volume ranged from 250 cc to 300 cc per day. The day following removal of pedicle percentage of bl. sugar rose to .12 and 8.03 gms sugar were excreted in the urine. On the following two days the % blood sugar rose slightly;

SLIDE 32 — Page of the original manuscript in the handwriting of F. G. BANTING

(1) This is the original manuscript on Insulin which was presented as an oral communication by Banting and Best on November 14, 1921 to the University of Toronto Physiological Society. The hand-written copy was then typed and sent as the first report on Insulin to the journal of Laboratory and Clinical Medicine. F.G.B.

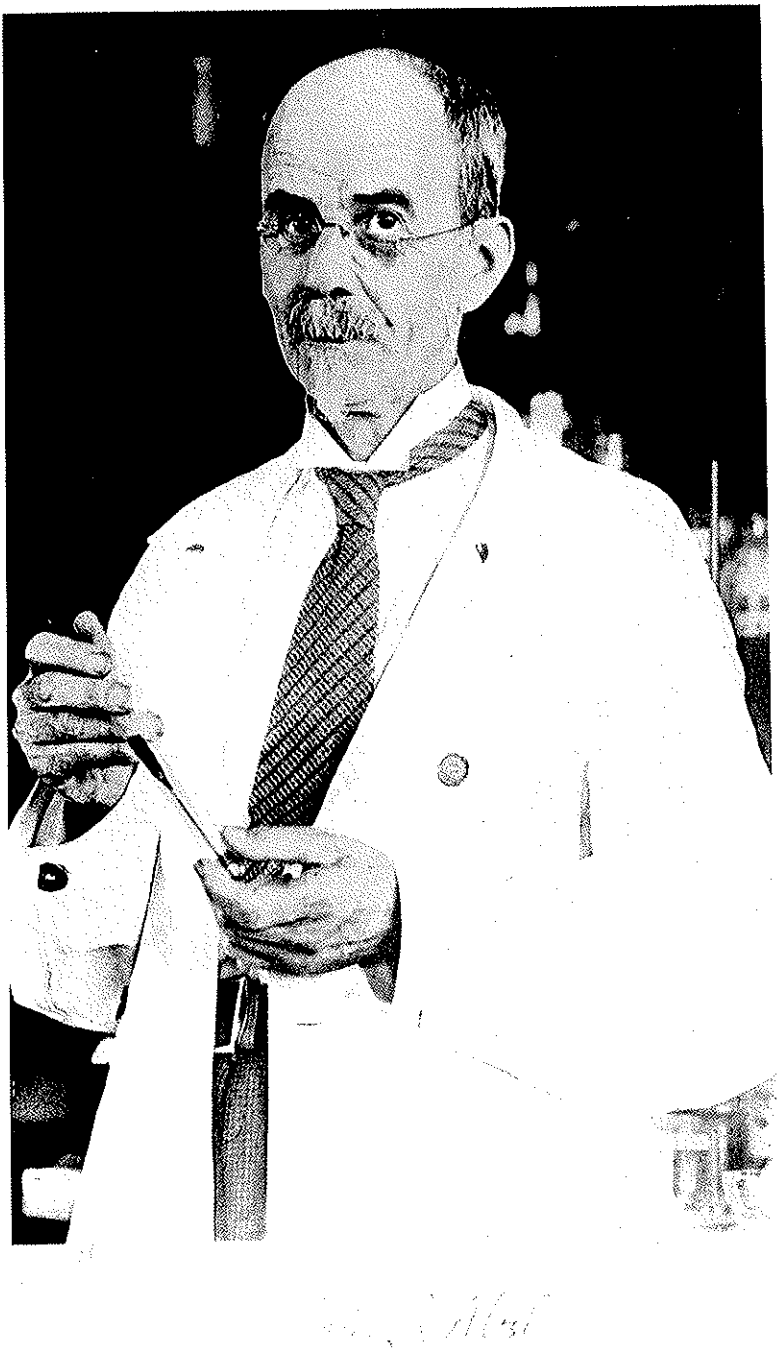
The Internal Secretion of the Pancreas

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 (F.G.B.) while reading an article dealing with the relation of the islets of Langerhans to diabetes. 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 antecedent hypothesis was that trypsinogen or its derivatives was antagonistic to the internal secretion of the gland. The failure of other workers in this much-worked field were thus accounted for.

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

SLIDE 33 — Page of the original manuscript in the handwriting of C. H. BEST



Slide 34 — Professor Abel

SLIDE 35 — Professor HAGEDORN

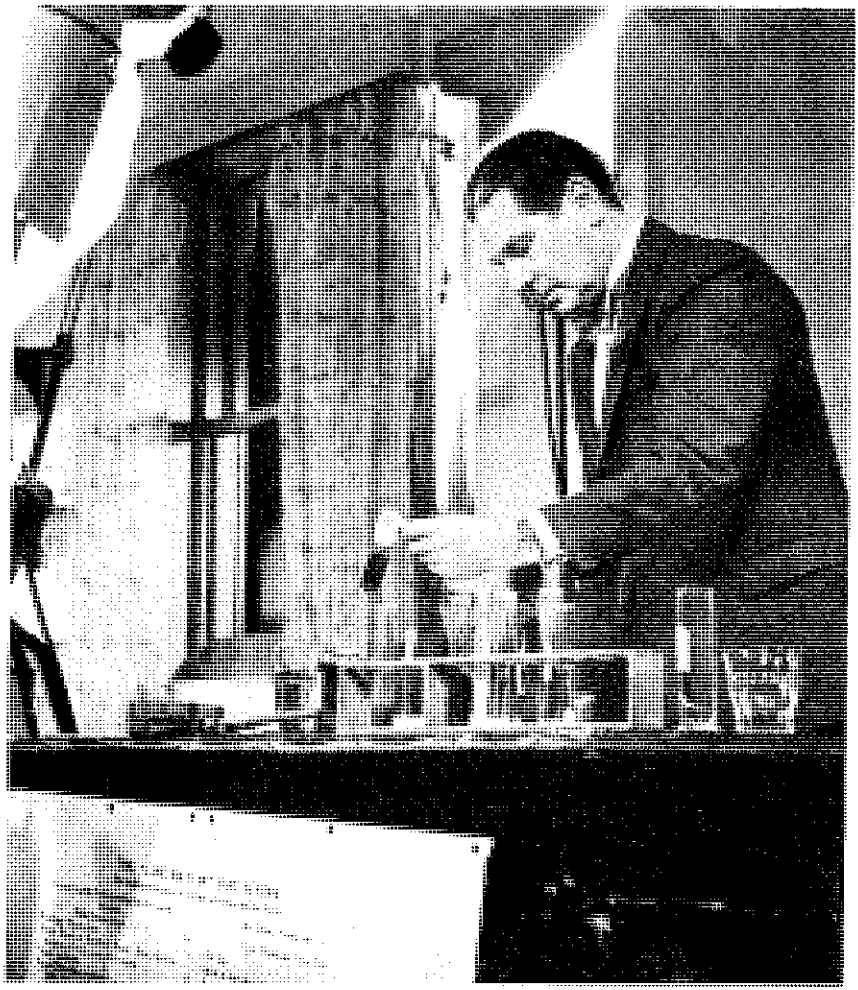
SLIDE 36 — LEONARD THOMPSON

SLIDE 37 — DR. JOE GILCHRIST

the hormone. He volunteered for many experiments and when we gave him insulin in the laboratory the first demonstration of increased burning of sugar in a human diabetic was secured. The next slide shows Dr. R. D. LAWRENCE (Slide 38) one of the early patients in Great Britain. He became their most eminent diabetic specialist. I am sure that my colleagues could cite early cases from many countries in the world. The next (Slide 39) shows the first patient in the United States, JAMES HAVENS, who became a celebrated artist, and the following (Slide 40) is of Dr. GEORGE MINOT, a severe diabetic who was treated by the celebrated diabetic specialist Dr. ELLIOTT P. JOSLIN of Boston. After his recovery he devoted himself to work on pernicious anaemia and, with Drs. MURPHY and WHIPPLE, he discovered the treatment for that disorder. This was the beginning of a romantic pyramid and I know that people with pernicious anaemia have made many contributions to medicine, arts and sciences.

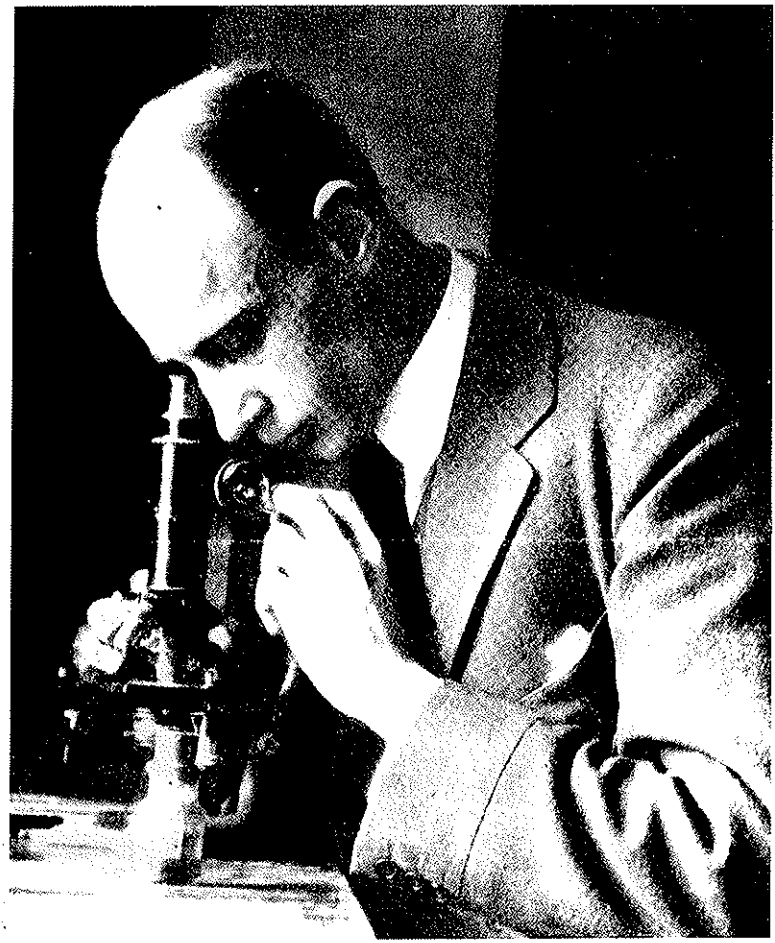
I have said enough about the discovery phase of insulin and will make a few remarks about the present position. Approximately one hundred and thirty million people have taken insulin since 1922. Some of them have lived for 50 years. Many of them have had no complications but others have suffered from disorders relating to diseases of the blood vessels which may affect the heart, the limbs or other organs. So one of our main problems is to learn more about these complications and how to prevent them. I have advocated for a long time, a direct attack, using diabetic animals in which these complications may be seen. I am sure that success will reward the efforts of our successors.

As many of you know, there are oral agents which can be used in the treatment of some diabetics. The pioneer work was done by Professor LOUBATIÈRES of Montpellier, France. These exert their effect by stimulating the pancreas to liberate insulin. A great many patients can be controlled



Slide 38 — Dr. R. D. Lawrence

SLIDE 39 — JAMES HAVENS



SLIDE 40 — DR. GEORGE MINOT

by diet alone — some need these oral agents and others, the more severe cases, require insulin.

There are many triumphs which I could record. A great one was the determination of the constitution of insulin by Dr. FREDERICK SANGER of Cambridge. His was a great advance in protein chemistry and was rewarded by the Nobel Prize. His findings laid the foundation for the synthesis of insulin which was accomplished at about the same time in China, in Germany, and in the United States. The making of insulin on a large scale in the laboratory has not yet been accomplished but will, I am sure, be realized before the supply of natural insulin from pancreas is exhausted. The three-dimensional structure of insulin has been largely worked out by Dr. DOROTHY HODGKIN and her colleagues.

As shown by Dr. DONALD STEINER of Chicago, insulin is made from a precursor, proinsulin, and the exact site of this intracellular synthesis in the conversion of proinsulin to insulin, is now well-established. Professor PAUL LACEY of St. Louis has shown how the granules of insulin are formed and how they migrate to the cell margin and discarge their contents into the extracellular fluid. Thus we have a great deal of information on the formation and secretion of the hormone. Many physiological and pharmaceutical substances stimulate this process.

The action of insulin is a subject in which I am most interested and we know a great deal about it. The various organs in which insulin works, the fact that it increases the penetration of sugar in amino acids and other substances into the cell, that it stimulates a number of enzymes which synthesize glycogen, protein and glyceride. We know a great deal about the destruction of insulin by specific enzymes. Of course, in every field which I have mentioned, much more remains to be done.

In 1971 we had twelve conferences on insulin in various parts of the world so that I think research workers are better

informed than they have ever been before; they are certainly highly motivated and the level of knowledge which has now been reached will serve as a platform on which great advances will be built.

I could predict that many important experimental and clinical advances will be made before we celebrate the 60th Anniversary of Insulin in 1981.