Milestones in the 60-Year History of Insulin (1922–1982)

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Important events in the discovery of insulin and in its 60-yr history are presented. DIABETES CARE 5 (SUPPL. 2): 1–3, 1982.

A few remarks on the discovery and development of insulin will serve as a background to the exciting reports on human insulin presented at this symposium.

It all started in 1889, when von Mering and Minkowski demonstrated that total pancreatectomy led to severe diabetes in the dog.[1] Subsequently the pancreatic hormone, though not yet located, was named insulin. It soon became apparent that the acinar tissue, subserving a digestive function, was not concerned with blood sugar regulation. After spontaneous atrophy, or that induced by tying the pancreatic ducts, the islets of Langerhans survive as the acinar tissue atrophies. Thus it was clear by 1893 that the islets were independent and serving some endocrine function.[2]

Why then did over 30 yr elapse between the demonstration of pancreatic diabetes and the isolation of insulin? It was due to the tragic fact that the trypsin of the acinar tissue released in isolating insulin destroyed it. Yet a large number of researchers claimed to have isolated insulin prior to the conclusive work of Banting, Best, and Macleod that led to the discovery of insulin in 1921.

L. B. Zuelzer made extracts in 1907 of animal pancreases and obtained some hypoglycemic activity in diabetic patients. However he had to give up his work because of anaphylactoid reactions and some possible hypoglycemic episodes as well.

G. W. Scott around 1917 perfected an acid alcohol extraction of the pancreas and showed a very definite hypoglycemic effect in dogs. However he had to stop further work on the project because the potency of the various hypoglycemic extracts was inconsistent and also because of the lack of funds at the University of Chicago. Nonetheless his method of extraction was subsequently mentioned prominently in the original paper on the isolation of insulin by Banting, Best, and Macleod. Scott subsequently became famous for crystallizing insulin by the addition of zinc and later by stabilizing protamine insulin with zinc.

There were two particularly strange claims made: Gley in Paris had deposited a sealed letter at the Societé de Biologie in Paris in 1905 and had the contents read publicly after the discovery of insulin in 1922. It revealed that active hypoglycemic extracts had been obtained, but the variability in potency led to discontinuance of his work.

Nicholas Paulesco of Bucharest in 1921 described pancreatic extracts that reduced blood sugar and ketone bodies in the dog and also decreased urea nitrogen. It was deemed by all the experts that this was probably not the consequence of insulin but rather of the pH of the extracts. From these examples it becomes quite clear that the time for the discovery of insulin was at hand.

In 1920, Moses Barron of Minneapolis published a paper titled, "The relation of the islets of Langerhans to diabetes with special reference to cases of pancreatic lithiasis."[3] He showed that with obstruction of the pancreatic ducts there was atrophy of the acinar tissue with complete preservation of the islets and no diabetes. This paper was discovered, read, and reread avidly by F. G. Banting. He was a young orthopedic surgeon who had been wounded in the war and had come back to London, Ontario, to practice. He was unhappy and determined to do research in the department of physiology of the University of Toronto, of which J. J. R. Macleod was chairman. It was the paper by Barron that inspired him to start work on insulin in late 1920. During the summer of 1921, he prepared dogs for insulin extraction by ligation of the pancreatic ducts. C. H. Best, a somewhat impecunious graduate student in physiology was assigned by Macleod to assist Banting in his work. Best's assistance became invaluable, for he acquired a technique for blood sugar determinations using a Dubosque Colorimeter, exhibited to this day in London, Ontario. Professor Macleod allowed Banting and Best to work in his own laboratory after he set off on a vacation of grouse shooting in Scotland. The two investigators made rapid progress in their work. Banting communicated much of it by mail to Macleod in Scotland. Upon

his return Banting presented the repeated findings of a fall in blood sugar and a rise in respiratory quotient when giving extracts of the islets to depancreatized dogs.

At first Professor Macleod like a good scientist, remained skeptical and demanded more experiments. These were carried out quite feverishly. By December 1921 there was no doubt but that active hypoglycemic extracts, containing insulin, had been obtained repeatedly. At a meeting of the American Physiological Society, December 28, 1921, in New Haven, Connecticut, the first report on the isolation of insulin was given by Professor Macleod, flanked by his two bench workers.

The next few months are clouded in controversy. Banting and, to some extent, Best felt that the support given them by Macleod was rather limited and that he stood in the way of a quick use of insulin in diabetic patients.

A letter Macleod later wrote to the Board of Regents of the University of Toronto was finally made available by Lloyd B. Stevenson and published in 1978.[4] In it Macleod accounts for the discovery and development of insulin step by step. His positive role in the venture was also commented on effectively in 1928 by Professor J. M. D. Olmsted, Chairman of Physiology at the University of California in Berkeley.[5]

On the other hand, there appears to be much documented material at the University of Toronto, which is still under lock and key and has never been published, that discredits the role of Dr. Macleod. The supporters of this point of view cite the fact that neither Banting nor Best remained in the department of physiology for more than 1 yr before leaving for the department of pharmacology and medical school, respectively.

This sort of thing appears to happen with many scientific discoveries in which there is collaboration of two or three people. *The Double Helix,* by James Watson on the discovery of the structure of DNA, became a bestselling book, but there is no such frank publication in the insulin field as yet.

During the 1921 Christmas meeting at New Haven, a middle-aged gentleman by the name of G. H. A. Clowes, vice president of Eli Lilly and Company, was a most attentive listener.[6] At the conclusion of the meeting he spoke with Macleod about a possible cooperation between industry and academia. He was both well versed and persistent, and had been given power by the Board of Directors of Eli Lilly to go all out. A preliminary pact was drawn up whereby Eli Lilly was to take over the production of insulin in the United States, supervise the manufacture of insulin by the Connaught Laboratories, a subsidiary of the University of Toronto, and in return furnish insulin free to the investigators in the university for as long as it was financially possible.

The original group in Toronto[7] was reinforced even before serious negotiations with Eli Lilly took place by the addition of J. B. Collip, a biochemist on sabbatical in Toronto at that time.[8] He proved invaluable in preparing potent and more reliable extracts of insulin, but even with help there was a 6-mo hiatus during which the extracts showed no insulin-like activity whatsoever. It was then that the decisive and final negotiations between the insulin committee now established at the University of Toronto and Eli Lilly Company began and were most fruitfully concluded. Essentially Eli Lilly was granted exclusive license for the period of 1 yr to develop a clinically acceptable product. They were to manufacture the insulin in the United States after obtaining a U.S. patent and to acquire patents elsewhere in the world. In turn they were to provide the University of Toronto with insulin at no charge for research. Clowes started a team at Eli Lilly with three biochemists as section leaders. One of these was D.A. Scott, who had first used alcohol extraction before in Chicago. The University of Toronto was to hold the patent as a public trust, and they in turn decreed that insulin was to be made available to any needy diabetic patient in the Province of Ontario free of charge in perpetuity.

On June 21,1922, the first large-scale run of insulin was completed at Eli Lilly Company, and Banting received a shipment of potent and fairly pure insulin that allowed him and his colleagues to start on clinical trials on a reasonable scale. By 1923, 2 yr after these negotiations had taken place, Eli Lilly produced enough insulin to treat 10,000 diabetic patients.

At this point Eli Lilly reluctantly had to admit that they could no longer supply insulin for human use free of charge, but at the same time licenses for the use of the patent in a number of countries had been granted and the survival of countless diabetics in the world was assured.

All of these happenings represent the fruitful cooperation of academia with industry in the best way possible and will serve for succeeding generations as a model for similar developments.

Even before this time, though, two individuals had received insulin. The first was Dr. Joe Gilchrist, a young diabetic physician who began insulin treatment experimentally in early 1922. It was he who gave the first description of hypoglycemia experienced after the injection. The physicians at the institute called him the "human rabbit."

The second was Leonard Thompson. With an injection on January 11, 1922, his blood sugar fell and he survived 15 yr on insulin until he died in 1937 at age of 29 of bronchopneumonia.[8]

Between the University of Toronto and Eli Lilly, prominent diabetologists all over the world were mobilizing to start giving insulin and reporting on its effects. The saving in human lives was phenomenal in the type I group—then called juvenile diabetics.

I personally had much at stake in all of this, as I developed diabetes myself in 1925 at age 9 after a frightening attack by robbers while passing through a dense forest. I have now had diabetes for 57 yr and I am still around. This I owe entirely to the fact that I was put on insulin within a week after the discovery of my diabetes—only 2½ yr after it became commercially available. I went through anaphylactic, peptone, and insulin shocks, insulin atrophy and dystrophy, but year by year these matters improved as better preparations became available.

The complete purification of insulin was rather halting. Danish firms did better initially than did Eli Lilly and Squibb. Whereas the insulin preparations were only 95% pure in 1970, they are now 99.9% pure, as all firms have been able to produce "highly purified" insulins. This has cut down significantly on atrophy at the site of injections; hypertrophy is still a problem, but this obviously is not related to the purity of insulin.

The water-soluble insulin, with a peak action at 3 h and duration of action of only 6 h necessitated four injections a day for perfect control. The need for prolonged action was paramount. This was achieved by the development of protamine and then protamine zinc insulin in 1937. Thereafter intermediate-acting insulin was developed first as the NPH series and then the Lente series. At the present time most type I diabetic patients are treated with tailor-made mixtures of these various preparations. Antibody formation, maximal with beef insulin and minimal with pork insulin, is still a problem. Human insulin may do away with this.

Now the latest achievement in the insulin story is at hand: human insulin produced by either recombinant DNA methodology (Eli Lilly) or by chemically substituting the terminal alanine of pork insulin with threonine (Novo Industries, Copenhagen, Denmark).

One hopes that human insulin, not being fixed to antibodies in the tissues, will act much more rapidly and thereby simulate the normally secreted insulin more closely. It is my belief that the relatively slow action of subcutaneous insulin accounts for high postprandial blood glucose levels, which exert a glucotoxic effect and thereby contribute to the long-range vascular diseases of diabetes. The advent of protamine zinc insulin, while a "mother's dream," was perhaps the worst event in diabetic treatment since it precludes high-level activity of insulin.

What was the ultimate fate of the co-discoverers of insulin? Dr. Banting met an untimely death on military service in 1941. Engaged in creating a pressure suit for allied aviators, he was to bring the prototype to England to have it tried out under combat conditions. He obtained a ride on a bomber; conditions were icy, visibility was poor, and the plane failed to gain altitude in time, struck a tree, and crashed. Banting survived his serious injuries for only 24 h.

Dr. Best had an illustrious career in Toronto as Director of the Charles H. Best Institute and Director of the Banting and Best Department of Medical Research. He died of natural causes in 1978.

Professor Macleod, after spending 10 yr as chairman of physiology in Toronto, went to Aberdeen, Scotland, as the Regius Professor of Physiology and died in 1935 of natural causes.

J. B. Collip became Professor of Biochemistry at McGill University (where he isolated parathyroid hormone). He became dean of the school of medicine at the University of Western Ontario and died in 1965.

The success of insulin was a good example of having the right men together at the right time in the right place and obtaining the help of industry immediately after the fundamental discovery.[9]

The year 1925 was a year of triumph for Macleod and Banting. As they stood before the king of Sweden in September to receive the Nobel Prize, accorded them in record time, Banting declared then and there that he would give half of the prize to Best (who thereupon bought his first home). Macleod, not to be outdone, declared that half of his prize would go to Collip. This regal attitude of the recipients could not have failed to impress the king of Sweden.

Banting ended his Nobel lecture by saying, "Insulin is not a cure for diabetes, it is a treatment."[10-12] Thus the next step in research will be to find the cure, presumably by DNA manipulations. Meanwhile, we shall further improve the treatment by the use of human insulin.

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