THE EARLY STORY OF INSULIN

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Excerpts from a speech delivered by Dr. Banting on October 11, 1934, at the dedication of the Lilly Research Laboratories, Indianapolis, Indiana

. . . To go back to July, 1920, after spending four years' postgraduate work in surgery at military and civilian hospitals, I commenced the practice of medicine in London, Ontario. After I had observed the conventional office hours of 2 to 4 p.m. and 6 to 8 p.m. for twenty-eight consecutive days, my first patient presented himself. At the end of the month I had four dollars on the books. The succeeding months were not much more gratifying. However, in October, when the medical school opened, I was successful in obtaining an appointment as demonstrator in the Departments of Physiology and Anatomy which gave me access to these laboratories. On 30th October, it so happened that in the early part of the evening I was preparing a lecture on the relation of the pancreas to diabetes, and when the lecture was completed I commenced the perusal of the newly arrived November number of *Surgery, Gynecology and Obstetrics*. This journal contained an article by Moses Barron in which he pointed out the analogy between the degenerative changes which follow the experimental ligation of the pancreatic duct, and the blockage of the duct by gallstones.

After reading the article by Barron I was unable to sleep. There seemed to be in some vague way a relation between the islet cells of the pancreas and clinical diabetes. There seemed also to be a means of attacking the problem of extracting the islet cells by ligating the pancreatic duct. It was not until two o'clock in the morning that I was able to crystallize the idea into a form that would lend itself to experimentation. At this hour I arose and wrote in my notebook the following words: "Ligate pancreatic ducts of dogs. Wait six to eight weeks for degeneration. Remove the residue and extract." The following morning I consulted a number of the professors at London concerning the idea, and inquired as to the possibilities of obtaining facilities for experimental work. Unfortunately, it so happened that since the new medical school was not completed, facilities and assistance could not be provided. On the advice of Professor Miller, I went to the University of Toronto, my Alma Mater, to consult Professor J. J. R. Macleod. I had never met Professor Macleod until this time, but his reputation as an authority on carbohydrate metabolism was well known.

After I had presented my case, Professor Macleod asked me what I hoped to accomplish when the best-trained physiologists had not succeeded in establishing or proving that there was an

internal secretion of the pancreas. My request was that I should be given ten dogs, an assistant for eight weeks, and facilities for doing blood- and urine-sugar estimations.

I further consulted the late Dr. C. L. Starr, Dr. Gallie, and Dr. Robertson, under whom I had worked when resident surgeon at the Children's Hospital, and it was agreed that I should continue practicing and teaching in London, throughout the remainder of the term. Consequently I returned to London.

The next four months were spent in reviewing the available literature. By Easter I was so keen to proceed with the work that I asked Professor Macleod that I be allowed to tie the pancreatic ducts of a number of dogs so that they would be ready in May for the final experiments. But Professor Macleod considered that it would be better to wait until May and have the animals under my personal supervision from the beginning.

Work was commenced on the 16th of May, 1921. It was arranged that I should have ten dogs and the use of the laboratory for eight weeks. Mr. Best and Mr. Noble were appointed as assistants, each to give four weeks. They tossed a coin to decide who would give the first four weeks, and Mr. Best won the toss. At the end of the four weeks, however, Mr. Noble did not return and Mr. Best stayed with me and was associated with me throughout the entire work.

We first ligated the pancreatic duct of a number of dogs. Following this we did a number of pancreatectomies in normal dogs to familiarize ourselves with the blood and urinary findings and the general clinical behavior of the dogs following this operation. At the end of seven weeks (July 6th) we chloroformed a couple of the dogs which had had their pancreatic ducts ligated. To our great disappointment, it was found that the pancreas was not degenerated. Careful examination showed that the ligature was still present in a bulbous sac in the course of the duct. It was therefore necessary to operate on all the duct-tied dogs a second time and to exert particular care as to the tension put on the ligature. If the ligature was applied too tightly it cut through the duct and a serous exudate laid down on the surface over the ligature resulted in recanalization. If the ligature was applied too loosely the duct was not blocked. We, therefore, in some cases applied two or three ligatures at different tensions. In re-operating we found some of the dogs had fairly well degenerated glands, but it was decided to leave them another two weeks.

On 27th July, 1921, we had a depancreatized dog and we decided to begin treatment. A duct-tied dog was chloroformed and the degenerated residue was removed. It was chopped into small pieces in a chilled mortar and frozen in brine. The mass was ground up and about 100 cc. saline were added. Five cc. of this extract were administered intravenously into the depancreatized dog. Samples of blood were taken at half-hour intervals and showed that the blood sugar had fallen from 0.200 to 0.11 percent in two hours. The clinical condition of the dog was markedly improved.

Another dog treated with extract from duct-tied pancreases was kept in good condition for eight days following pancreatectomy. At the end of this time we had used up all the available supply of what we then called "isletin." . . . It was hoped that the old classroom experiment

of injecting secretin to stimulate the production of pancreatic juice could be continued long enough to exhaust the acinous cells.

The following morning a normal dog was anesthetized and while Mr. Best extracted secretin from its intestinal mucosa a cannula was placed in its pancreatic duct. For four hours secretin was continuously injected and pancreatic juice was collected. At the end of this time no more juice was secreted in spite of the continued injection of secretin. The vagi were then stimulated below the diaphragm and a few more drops of pancreatic juice were obtained. The exhausted pancreas was then rapidly removed, frozen, minced, and extracted. This extract was carefully administered to the depancreatized dog. Even before the blood-sugar results were obtained the dog showed clinical improvement . . .

The exhausted gland extracts were not practical, but they served as contributory evidence in favor of the main theory of obtaining extracts of the island cells free from the products of the acinous cells.

Experiments with degenerated gland extract and exhausted gland extract showed that these extracts produced lowering of blood sugar, disappearance of sugar from urine, increased utilization of intravenous glucose, and marked clinical improvement with increased duration of life in depancreatized dogs.

It was then inevitable that a more practical means of obtaining extract must be found if progress was to be made. Laguesse had found that there were relatively more islet cells in the pancreas of a new-born than in the adult pancreas. The first idea was to extract the pancreas of new-born animals. It seemed reasonable to conclude that the pancreas of a partly developed fetus might contain even more abundant islet cells. It was finally conjectured that if one could obtain the pancreas of a fetus at the end of the first third of pregnancy the internal secretion of the islet cells would be present since other internal secretions (e. g., epinephrine) are present at this stage of development. At the same time, it seemed reasonable to conclude that since digestion is not called into play until after the birth of the animal there would not be powerful digestives present in the fetus. . . . The next morning at nine o'clock, having obtained sterile instruments and containers, Mr. Best and I proceeded to the abattoir where we obtained the pancreases of nine fetal calves varying from three to four months' gestation.

An extract was made in the usual way and carefully administered intravenously to a depancreatized dog on 19th November, 1921. Following the injection the blood sugar fell from 0.33 to 0.17 in one hour. This result was confirmed by subsequent injections. We were thus able to maintain an adequate supply of the active principle of the islands of Langerhans with no expense to the laboratory, and in quantities which provided for repeated trials and various extractions. It was found that the active principle could be extracted from the fetal gland with acetone and alcohol, and that it was not destroyed by chloroform or ether.

We then proceeded to make extracts from the whole gland of the adult beef. The first extracts made from the whole adult gland were extracted with alcohol, and the alcohol removed by distillation *in vacuo* at low temperature. Various percentages of alcohol were used for the

extraction and it was found that the active principle was not soluble above 90 percent.

The various extracts used up to this time were tested for potency and toxicity on depancreatized animals, the extract being administered subcutaneously or intravenously. We had kept one dog alive for seventy days after its pancreas was removed by giving it daily injections of various extracts.

On 11th January, 1922, the first patients were treated with extract in the Toronto General Hospital. Following the injections there was a typical lowering of blood sugar and a slight decrease of the sugar in the urine. But since the percentage of protein in the extracts was high, a sterile abscess developed at the point of injection.

Our results in the human were, however, sufficiently encouraging to change the whole trend of the research. Professor J. J. R. Macleod abandoned his work on anoxemia and turned almost his whole laboratory staff to the problem of the physiological activity of this pancreatic extract.

Dr. J. B. Collip was given the problem of chemical refinement, and in a short time he was able to run the scale of fractional precipitation from 60 to 90 percent alcohol and thereby succeeded in producing a less toxic and more active product. Unfortunately, when Dr. Collip endeavored to do this on a large-scale production, he encountered serious difficulties. After a few months' delay Mr. Best took up the problem of production and refinement and he is still in charge of the production of insulin in the Connaught Laboratories at the University of Toronto. He and those associated with him were responsible to a very large extent for many refinements now used in the manufacture of insulin.

Insulin was not the first name used among our group of workers. As early as August, 1921, the word "isletin" occurs in our notebooks. Professor Macleod insisted that the internal secretion of the pancreas should be called "insulin." Later it was found that Sharpey-Schafer of Edinburgh suggested this name about 1910.

With a group of workers attacking various problems under Professor Macleod's directions, rapid progress was made. The first endeavor was made to find a test-tube reaction for determining the potency of insulin, but none was found. Therefore it was necessary to develop a biological method of standardization. In the early work Collip had found that when a normal rabbit was given a certain dose of insulin, in four hours the rabbit developed a trend of symptoms characterized by intermittent convulsions and coma. The rabbit rapidly recovered when given injections of glucose and could be used again for another test. It was therefore decided to use the rabbit in making a biological assay.

Following pancreatectomy the glycogen content of the liver rapidly fell to less than 0.5 percent. It was found that by the administration of insulin and glucose to a depancreatized dog the liver could store glycogen in even larger quantities than that stored by a normal dog. Following pancreatectomy the respiratory quotient was lowered to the level which indicates the burning of fat and protein. The administration of glucose had little or no effect in raising

the respiratory quotient in totally depancreatized dogs. However, when insulin was given with glucose the respiratory quotient was raised, showing that insulin enabled the totally depancreatized dog to burn sugar. It was found that an overdose of insulin produced a characteristic group of symptoms and that these were associated with hypoglycemia.

During the spring of 1922, Dr. Best succeeded in producing quantities of insulin sufficiently large and sufficiently purified to prove thoroughly the value of insulin to diabetic patients. A large number of hopeless severe diabetics began to come to Toronto. It was the ideal of all those associated in the work to obtain the largest quantities of insulin at the lowest possible price for the rapidly increasing clinical needs.

When the first report of insulin was made at New Haven in December, 1921, Dr. G. H. A. Clowes offered to put the resources of the Eli Lilly Company at our disposal whenever we felt that our laboratory experiments had reached the point at which their practical co-operation might be of benefit. About April, 1922, we accepted his kind offer. From this time the Eli Lilly Company collaborated with us and were of the greatest assistance in the development of the large-scale production. There was an intimate reciprocation of all results between the two laboratories, and in the early days when we were unable to make sufficient insulin for our clinical needs Mr. Lilly and Dr. Clowes were good enough to assist us from their inadequate supply. It is interesting now to look over the telegrams and letters that went back and forth between Toronto and Indianapolis at that time. They recall the terrific pressure under which we were all working in the common endeavor to provide a purified product for widespread distribution. . . .

In the autumn of 1922 the product was still extremely impure and we were experiencing great difficulty with deterioration and sensitization reactions. By the middle of November the Eli Lilly Company were first able to effect a very substantial purification and concentration of the product by developing the iso-electric method of precipitation. This product had the added advantage of being reasonably stable. The yields at that time were still very small, but by January (1923), as a result of work carried out in the Connaught Laboratories and the Eli Lilly Company, we were able to provide insulin to about 250 clinicians.

I would like once more to express to the Eli Lilly Company, and particularly to Dr. Clowes, my personal thanks for their whole-hearted co-operation in those trying days which meant so much in the early story of insulin. The Eli Lilly Company joined the Toronto group in their ideal of providing insulin to the greatest number of diabetics at the lowest possible price. It was largely through the untiring and well-directed efforts of Dr. Clowes and his associates that this ideal was fulfilled in such a short time. The high traditions that have always been associated with the name of the Eli Lilly Company were well exemplified in their ethical associations with the Toronto Insulin Group. . . .

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