

as I know, he was only occasionally in trouble with his secretive superiors!

Impressive, too, was Banting's unerring instinct in dealing effectively with the public; he felt the public was entitled to know what was going on in scientific laboratories—war or no war—and he took great trouble to explain the nature of scientific developments in language which the layman could readily comprehend. Few scientists were as conscientious as he in dealing with such things, and his efforts were warmly appreciated by the population at large.

In short, it seems to me that during the fifteen years since Banting's untimely death he has grown in stature on many scores, and his basic endocrine research looms large in the history of medicine, as well as his studies on design of decompression chambers, on decompression sickness, on acceleration, and on the ways and means of protecting flying personnel from the deleterious effects of high *g* forces. For these and many other things Banting's place in the history of our time is lastingly assured.

JOHN F. FULTON, M.D.  
New Haven

*Dr. Fulton, formerly Sterling Professor of Physiology at Yale University and now Sterling Professor of the History of Medicine, was invited by Professor Eugene F. DuBois to prepare this tribute to Sir Frederick Banting to be read with his, when Dr. DuBois was presented with the Banting Medal of the American Diabetes Association at the Annual Meeting, June 1955.*

## THE FIRST CLINICAL USE OF INSULIN

The clinical application of the discovery which Fred Banting and I hoped to make was in our minds from the very start of our partnership. This was inevitable because a part of Banting's motivation stemmed from an interest in a schoolmate in Alliston, Ontario, who died of diabetes. Recently my wife and I went to Alliston and helped to dedicate a portrait of Fred Banting which is to hang in the entrance hall of the Banting Memorial High School. We saw again the farm where he was born; where I first met his fine parents; and where our friend, Fred's older brother Thompson Banting, now lives. We drove along the road where Fred Banting walked to school and passed the house in which, we were told, the little diabetic girl had lived.

My own interest in diabetes began when my father's sister, who had gone from Nova Scotia to train as a

nurse at the Massachusetts General Hospital, came to help my father in his small hospital on the Maine-New Brunswick border. She had developed diabetes some years previously and although her life was prolonged by the treatment administered by Dr. Joslin, she died a few years before insulin became available.

Every time one of our diabetic dogs responded to insulin we hoped that the effect on patients would be just as dramatic. When, in the autumn of 1921, we had demonstrated on 75 successive occasions in 10 completely depancreatized dogs, the invariably definite and frequently very impressive lowering of blood sugar after the administration of our pancreatic extracts, we considered that the phase of the discovery was complete. The clinical improvement in many of our animals was almost as convincing as the sweeping falls in blood sugar. We had concentrated on these main points: the lowering of blood sugar in completely depancreatized dogs and the improvement in their condition, but many other findings confirmed and supplemented these results.

It became necessary in the late autumn of 1921 in view of the intense experimental and clinical interest in our findings, to enlarge our team. Banting and I were forced to focus our interest on one series of problems and to make a very difficult selection. Banting decided that he would like to participate in the clinical application of our discovery. I chose the study of the effect of insulin on the respiratory quotient of completely depancreatized dogs for my M.A. thesis at that time because I thought that this was the central problem.

The records show that we had been making insulin by macerating whole beef pancreas, immediately after removal, in an equal volume of 95 per cent alcohol made acid by the addition of 0.2 per cent of concentrated hydrochloric acid. After thorough grinding of the mixture with mortar and pestle, the acid alcoholic extract was filtered and the clear filtrate evaporated to dryness, at first in a warm-air current, and later in an efficient laboratory vacuum-still which I had used during the previous year. In our second paper, which I have looked at again recently, it is noted that on Dec. 15, 1921, 200 mg. of the dried residue of ox pancreas extract were washed twice in toluol and then in 95 per cent alcohol and then dried again, and the resulting powder dissolved (or emulsified) in saline. At 10 a.m. this was given intravenously to a completely depancreatized dog. The blood sugar dropped from 0.37 per cent to .06 per cent in four hours. Our notes indicate that the improvement in the dog's condition was as dramatic as the fall in sugar.

In the extension of our research team, Professor Macleod assigned various problems to the members of his staff. The further purification of our insulin-containing extracts was entrusted to Prof. J. B. Collip in December 1921. Prof. Collip made rapid strides in the fractionation and concentration of the material, and contributed brilliantly in other ways to the development of the insulin researches.

Just after Christmas in 1921, Fred Banting came to me and suggested that I should make, as rapidly as possible, our best whole beef pancreas extract and that this should be the first insulin administered to a human case. This request came as a surprise but his sense of urgency was contagious and I immediately agreed. I suggested, however, that we should make an extract of foetal pancreas which was much easier to process than whole beef glands and was much more potent. We now know that foetal pancreas contains about seventeen times as much insulin per gram as the average whole beef pancreas does; we also know now that an extract of foetal pancreas made by the exact procedure which we used in 1921 provides an excellent potent solution of insulin. Banting was in favor, however, of using the beef gland, and I can remember his exact words: "If we use foetal calf pancreas they will say that the first extract used in patients was not made from a readily-available commercial source." Another argument in favour of normal beef pancreas was its availability. It might have taken us a week or more to collect sufficient foetal glands to make a good-sized lot of insulin.

Banting and I frequently went together to the abattoir to collect foetal pancreas or glands from adult animals. On this particular occasion I went alone and the abattoir authorities kindly immobilized a recently killed steer in a fairly convenient position so that I could remove the pancreas with aseptic precautions. This was taken back to the laboratory in a sterile container and worked up in the way I have described above. We had previously shown that it was possible to put the aqueous solution made from our acid alcoholic extract of normal beef pancreas through a Berkefeld filter. The final material in this particular case was a reasonably good looking product although of course it contained a very great deal of inert protein. Banting gave the first injection to himself and the second one to me. The next morning we had rather red arms but there was no other effect. We did not follow our own blood sugars. However, we did test the material on one of our diabetic dogs and obtained a fine fall similar to that which I have recorded above, and thus we established the potency of this extract. This was the solution which was sent over to the Toronto General Hospital and which was adminis-

tered to several of the patients under the supervision of Dr. W. R. Campbell and Dr. A. A. Fletcher in Prof. Duncan Graham's department. The first person to receive an injection was Leonard Thompson whose history has been recorded in the clinical reports (*vide infra*). The first clinical publication from Toronto, which has often been overlooked, was in the Canadian Medical Association Journal, March 1922: "Pancreatic extracts in the treatment of diabetes mellitus," by F. G. Banting and C. H. Best, Department of Physiology; J. B. Collip, Dept. of Path. Chem.; W. R. Campbell and A. A. Fletcher, Dept. of Medicine, University of Toronto and Toronto General Hospital. A useful description of the early work which Banting and I had done is given in that report. It is recorded that the extracts given on January 11 (these are the ones which I have described above) were not as concentrated as those used at a later date and other than a lowered sugar excretion and a 25 per cent fall in blood sugar level no clinical benefit was evidenced. Banting described the results with Leonard Thompson and in some of the other early cases in somewhat more detail in his Nobel Prize Lecture and that paper should be consulted by those who are particularly interested.

The first injection of insulin was actually given to Leonard Thompson by the Senior Houseman on that particular ward—Dr. Ed. Jeffrey. Dr. Jeffrey was a close friend of Fred Banting's and of mine, and he told us all the details surrounding this first clinical trial. During the early stages of our work, Banting and I had not planned that our partially purified insulin which was so effective in dogs, would be the first material used on patients. We had often discussed these matters and hoped that the burden of the production of insulin for clinical use would be assumed by experienced chemical engineers. We were extremely happy, however, that a fall in blood sugar and a diminution of sugar excretion had been produced in the human subject by our extracts. The more concentrated and purified material made from the early type of extract by Dr. Collip soon became available and a great deal of further and very convincing clinical evidence was rapidly secured. After a relatively short period, however, Dr. Collip encountered serious difficulties in the preparation of active material and the supply of insulin for the Clinic completely stopped. Several of the patients, including a young girl, in whom my wife and I were particularly interested, died from lack of insulin after having been dramatically improved by the first injections which they received.

This failure of the supply of insulin created a major crisis. Fred Banting insisted that I should give up my study of physiological problems and take up the large-

scale preparation of insulin. Dr. Collip had returned to his professorial duties and no one else was available for this work. The struggle to recover the secret of making insulin in sufficient quantities for clinical use, was for me the most difficult and trying part of the whole insulin investigations. There was no time to approach the problem systematically and the only thing that seemed worth-while was to wage a night and day struggle in the hope that we might hit upon success. It may have been that a return to the use of a 0.2 per cent of concentrated hydrochloric acid in the extractive, or the introduction of the very efficient wind tunnel for rapid evaporation of our extracts, or the substitution of the lower boiling point acetone for alcohol as the original extractive, was the secret of the success which we achieved after a few weeks. More than one of these factors may have been important. In any case a consistent production of reasonable amounts of insulin was again made possible and the clinical work was started over again. The supply was at first not large and indeed over the summer months of 1922 the records show that not very much insulin was actually produced. The following table of the amounts sent to Fred Banting each month from what we called The Insulin Division of the Connaught Laboratories may be of interest. Further small amounts were probably sent directly to the Toronto General Hospital and to the Military Hospital at Christie Street. Some insulin was also made available for experimental work. The total was, however, very small and the product was of low potency—I to 10 units per cc. as I remember it.

*Insulin Supplied to Dr. Banting*

June 1922 .....	122½	cc.
July 1922 .....	512	cc.
August 1922 .....	390	cc.
September 1922 .....	1,682	cc.

The recovery of the process for making insulin bridged the gap between the laboratory preparation and the large-scale commercial production. I have paid my tribute before to Dr. G. H. A. Clowes and the chemical engineers of Eli Lilly and Company and to my working partner in the Connaught Laboratories, Dr. D. A. Scott, who helped with further modifications and improvements in the large-scale preparation of insulin. There are many other names which should be mentioned and I can select only a few. The contributions of E. A. Doisy, M. Somogyi, and P. A. Shaffer, of the late Harold Ward Dudley, of P. J. Moloney and D. M. Findlay, will not be forgotten. Many different processes were soon developed for the further purification and concentration of the active material which we had found. This is not the place to review the many important steps by which

insulin has been made a more efficient therapeutic agent. When the active substance has been synthesized it is possible that modification can be introduced which will further improve the antidiabetic effects of the hormone.

CHARLES H. BEST, M.D.  
Toronto

*A PERSONAL IMPRESSION*

It is fitting to honor Leonard Thompson, the first patient to receive insulin, by placing his picture upon the cover of *DIABETES*. He had the courage to volunteer for an experiment. He was not like the dog, a passive participant, but an active member of the diabetic team. He stands out as an example of thousands of diabetics who have followed their doctors' advice, often bizarre, and have lived an honest diabetic day, not for themselves alone, but for the benefit of mankind. Would that they, especially those in the starving decade before insulin, could be immortalized as Rodin did those six emaciated burghers of Calais, who with halters around their necks, expecting death after its year-long siege, surrendered to Edward III to save their city.

For a quarter of a century I had been treating, or rather fighting, diabetes, when I heard a rumor of a surprising discovery by two young men in Toronto and went to New Haven in December 1921 to hear Banting speak about his experiment before the American Physiological Society. As we listened we physicians became so excited over what we learned and asked so many questions that the customary serenity of the meeting of that elite organization was upset and some of the members showed they regretted our presence. Banting spoke haltingly, Macleod beautifully. The possibility of mistakes in the work was fully exploited by those who discussed the paper in a skeptical but on the whole in a sympathetic way. A few months later Banting and Best and their clinical colleagues, Campbell and Fletcher, in Toronto showed us their early cases, but the full impact of the discovery did not fully dawn upon me until I learned I was to receive insulin for trial with my own patients. I remember well staying awake all night the day before it was to arrive. The first unit I gave to Miss Mudge, my severest patient, a nurse, on Aug. 7, 1922. She had obeyed the rigid regime. During her five years of diabetes her weight had fallen from 157 to 72 pounds, but she remained sugar free. She was nearly bedridden and, I recall, had gone over a flight of stairs in her home (oddly enough on the site of the New Hospital Teaching Clinic), but once in nine months. I watched her come back to life and go on in later years