new ones.

The true nature of diabetes mellitus with its protean manifestations, complications, and variations of occurrence from childhood to old age, still eludes us. Indeed the exact structure, role, and locus of action of insulin are still sources of much provocative research and even controversy. In these days of complicated research with large grantors often pursuing the grantees to "do research," it may be timely to reflect on what was done with minimal assistance and meager equipment by two young men without titles or staff but with an idea and careful labor.

Reminiscences of the Discovery of Insulin

SIR FREDERICK BANTING

1891-1941

Banting was no ordinary investigator; indeed, he was not an ordinary man. I first met him in the autumn of 1923 in the house of Lady Osler at Oxford, and the occasion deserves to be recorded because it so happened that the Regius Professor of Medicine from Cambridge, Sir Clifford Allbutt, was visiting Lady Osler at the time. She introduced him to the young Canadian investigator and suggested that they go for a walk in the parks. Sir Clifford, who had always been greatly interested in young men who were making their way in scientific medicine, was fascinated by Banting, and he questioned him closely about the steps which had led to the discovery of insulin. He also questioned him about much else—art and literature, among other things—and he found that his young Canadian colleague was not only a physiologist, but in the Baconian sense he was also a "full man," for his interests extended to literature and art, and also to music (he was the best baritone in his class). At that time Banting was young, unsure of himself, and almost uncouth in dress and general appearance, but Sir Clifford, with his unerring tact, brought out the best that Banting had to offer, and when they returned to 13 Norham Gardens, Banting's eyes were glittering with a new light, and it was clear that Allbutt had inspired him.

In appraising Banting's various contributions it can be said that his work on insulin and other endocrine extracts gave meaning and significance to classical scientific method as we now recognize it. I should like also to reiterate the tribute which Dr. DuBois* has paid to his practical contributions, not only in the field of aviation medicine but also in military medicine generally. Banting had a genius for making practical applications, be it in a penetrating study of protective clothing, his introduction of the "clo" unit, or a study of aircraft equipment. He agitated for redesign of cockpits, strengthening the moorings of pilot seats and seat belts, and for moving the pilot's seat back far enough so that in the event of a head-on collision, or a nose-over landing, the pilot's face would not be thrown against the instrument panel.

I always admired Banting for quite another reason, namely, his common-sense attitude toward security regulations. Many of his colleagues in Canada and England were inclined to be overconscientious in matters of security, a trait which generally took the form of an unwillingness to discuss anything with anyone, with the result that there was little in the way of free exchange of ideas, even in a small military establishment, and there was no exchange whatsoever for well-screened and qualified individuals from outside who might have been able to lend the greatest assistance in the solution of a given military problem. Banting was never that way, but gauged his audience and spoke freely about classified material, and especially about instruments that fell into the classified categories, if he felt his colleagues or visitors had something worth while to offer. It was a kind of common sense that was rare, particularly during the early phases of the war. Everything was so hush-hush that one scarcely dared breathe. But not Frederick Banting. And as far

*Remarks of Professor Eugene F. DuBois following presentation of the Banting Medal at the Annual Meeting of the American Diabetes Association, June 1955. Diabetes 4:426-27, Sept.-Oct. 1955.

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.
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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 fœtal pancreas which was much easier to process than whole beef glands and was much more potent. We now know that fœtal 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 fœtal 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 fœtal 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 fœtal glands to make a good-sized lot of insulin.

Banting and I frequently went together to the abattoir to collect fœtal 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 Berkfeld 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 administered 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—1 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

to care for her mother instead of her mother's taking care of her. After four weeks of insulin, she walked four miles, and in seven months she gained twenty pounds. She lived another twenty-five years happily until she died suddenly of coronary thrombosis.

By Christmas of 1922 I had witnessed so many other near resurrections that I realized I was seeing enacted before my very eyes Ezekiel's vision of the valley of dry bones—Ezekiel XXXVII, 2-10:

> ". . . and behold, there were very many in the open valley; and, lo, they were very dry.
>
> And he said unto me, Son of Man, can these bones live?
>
> And . . . lo, the sinews and the flesh came up upon them, and the skin covered them above: but there was no breath in them.
>
> . . . Thus saith the Lord God: Come from the four winds, O breath, and breathe upon these slain, that they may live.
>
> . . . and the breath came into them, and they lived, and stood up upon their feet, an exceeding great army."

Colonel Palmer, my standard Case Number 632, a most brilliant young officer in the Canadian Army whose career was shattered by diabetes just before the first World War, came back for insulin. When he saw the children, his first reaction was: "Now they make a noise." Formerly they sat with protruding bellies, silent for hours, resignedly consuming their washed 3 per cent vegetables. Yet today of those feeble creatures there is many a one alive, breathing and standing upon his own feet. Von Noorden shuddered and turned aside at the sight of one of them a quarter of a century ago, but now he has passed on, and little Ruth is now working in a doctor's office in Chicago. For Christmas in 1922 the group of my first insulin users, numbering 83, sent a "round-robin" letter of thanks to Mr. Lilly in Indianapolis. He replied with the present of a doll to the girls, which they promptly named "Lilly," and to the boys, an insulin syringe set.

There was almost a tinge of regret in several of us over the discovery of insulin, because it had come so soon. It was known that much was being learned about the disease and we feared intensive effort would stop. Children were living two years instead of one; adults six years instead of five; an occasional patient outlived a normal life expectancy and we were discovering day by day mistakes that we had made in dietetic treatment and learning how they could be corrected and the metabolism of the diabetic preserved and strengthened. We argued by analogy, if a similar improvement occurred in a group of cancer patients, how it would be acclaimed! We knew that progress was being made and that the whole field of the betterment of diabetes by existing methods had yet to be explored. Although it still was a Cyrano de Bergerac fight, the joy of working and fighting was uppermost, even though it was realized the cause might be lost. Never before had such a high pitch of endeavor been evident in all centers in diabetes.

Then came insulin and what a reaction followed. "Now, Dr. Joslin, you will have no more diabetics to treat," was the common saying. The relaxation was as great as that I saw Nov. 11, 1918, in France the day of the armistice. In the twinkling of an eye, the whole atmosphere changed. Instantly salutes, which before 11 o'clock were alert and snappy, by noon had become informal and sloppy. Only one thought possessed the thoughts of the American soldiers—namely, to get home.

The finding of insulin by Banting and Best was unusual in that it was an anticipatory discovery. Then there were comparatively few diabetics in the world, because the average age at death of people generally was around forty years, whereas the onset of two-thirds of all cases of diabetes occurs above the age of forty years. Future generations therefore will rise up and call them blessed even more than those in their own generation.

It is a great satisfaction today to sense that same old enthusiasm, zeal and endeavor to prevent and treat diabetes which existed just before insulin was discovered. But the attack upon the disease is now on a broader basis. Then we were fighting a battle, but now we are conducting a campaign. Then the object of the encounter was to defeat diabetic coma, which took the lives of two-thirds of all the patients; today our campaign is to prevent and overcome complications in the eyes, circulation and kidneys. The battle ended in a quick death in unconsciousness, the campaign involves a lingering illness often with pain and despair, yet now there is more hope because we are convinced and have found the proof that such a sad outcome can be avoided by meticulous control of the disease, particularly in its early years, temporarily utilizing undernutrition diets, supplemented by insulin.

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