

*The Man
With the compliments
of the writer
W.R.C.*

THE FIRST CLINICAL TRIALS OF INSULIN

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Tamen alte in memoriam sculptum

Mr. President, Mr. Premier, colleagues and cousins. You wonder perhaps how I can call you cousin. Actually there are many Canadians here today who can do so: eight generations ago our joint fore-fathers came to a New World seeking religious freedom. In our great-grand-fathers' time, those deprived of civil rights in the new United States drove their Conestogas or ox-drawn touring cars into the northern wilderness to help found in Canada a new democracy.

But besides a transfusion of United Empire Loyalists the American Revolution was destined to provide a further service to the development of democracy in Canada. Propaganda is not a new weapon, as many seem to think, but propaganda may have results, unexpected and unforeseen. The Continental Congress employed it on the French-Canadians who, under French rule, had never enjoyed any civil rights worth mentioning. Though it failed in its object it became, as Lanctot¹ has said, perhaps the greatest single factor in uniting us into the present Dominion of Canada since it brought French-speaking Canadians into contact with more modern ideas of the rights of man. In peace and amity Americans and Canadians have lived together; in war, fought side by side. As an experimentalist, I believe that we should never be joined closer, two nations with the greatest opportunity in all the world of working out for the good of all peoples the problems that beset mankind.

I am glad we have with us still most of those who so greatly assisted in the early clinical evaluation of insulin—Allen and Joslin, Woodyatt, Williams and Wilder. But alas, some of that little group have passed from the sight of men: Macleod—Geyelin—Banting.

We shall not see them more till that great day
When time shall meet eternity—
Methinks, in spirit they are with us still ;
Hush! Can you not hear them from beyond the stars?
They shall not be forgotten, they
Who sailed a course so true,
Nay, not in a thousand years.

“My days have been passed in pleasant places.” According to my recollection, the quotation should be from the Psalms of David, but I have been unable to verify the reference. Reminiscence is always boring to the recipient, but today reminiscence seems to be asked of me and what can I do but respond. For my training I have been indebted to many masters and, if that was their duty, it has been mine to endeavour to thank them by passing the torch to others. In 1915, under the guidance of Dr. William Goldie, I instituted a diabetic clinic in the Toronto General Hospital—the first in Canada so far as I am aware. At the close of the first World War my present chief, Professor Duncan Graham, invited me to return to help develop the chemical aspects of medicine in our University and Hospital. Under his system of allocating patients with certain conditions to those clinicians most interested, a maximum of the permutations and combinations of metabolic disease are soon encountered. I was agreeably astonished to learn that the old maxim: one patient—one disease, is untrue, among diabetics at least. The combinations which are possible furnish an unending field of interest for study and individualization of treatment. Probably for these reasons, with my dear friend and associate, Almon Fletcher—now happily restored to health after years of illness—I was assigned by Professor Graham to assist in the clinical evaluation of insulin.

Our Professor of Physiology, T. G. Brodie, died on service during the war. He was succeeded by an acknowledged master in carbohydrate metabolism, J. J. R. Macleod. To him in 1921 came a young man with an idea—Frederick Grant Banting, a recent graduate in medicine with a distinguished war record—asking for an opportunity to work.

University departments are chronically short of funds and someone who wants only to work is more than welcome. With a young graduate in Arts, newly appointed a demonstrator in Physiology—Charles Best, now the young but distinguished Professor Best who has just spoken—he set to work and, at a meeting with the Department of Medicine late in 1921*, they showed us results which made clinical trials imperative. Do not bemoan the fact that the work was done in an attic animal room. That is a standard formula for success. All the best painters have done their best work in an attic. After success the attic becomes an atelier, but still remains as hot in summer and as cold in winter. This attic was no exception as I have reason to know.

Banting's original idea: to ligate the pancreatic ducts, allow the acinar tissue to degenerate, then extract the islet cell contents, served its purpose as you have heard. Larger amounts of pancreatic extract were required to carry the problem further. Extracts of foetal calf pancreas and, later, adult beef pancreas were used to obtain them. Macleod used all the resources of his department to advance the knowledge of the physiology of insulin as rapidly as possible, while Collip undertook the preparation of more concentrated extracts. Banting and Best reported the early physiological results at a meeting of the Federation of American Societies for Experimental Biology, Christmas 1921, presided over by its Chairman, Professor Macleod.

The clinical investigation was begun early in 1922. Banting brought to us a flask of brownish-gray liquid and saw it injected into selected patients. One of these patients was a boy of fourteen weighing sixty-five pounds, referred to us by Dr. L. Skeeles of Toronto. At that time he had suffered from severe diabetes for more than a year, and you may remember that the average duration of life in such juvenile patients was then 1.3 years. I was unable to get him sugar free by starvation or other dietetic measures then available, and told his father that our one remaining hope lay in the trial of Banting's pancreatic extract to which he consented.

The earliest results would not have convinced anyone

*November 14, 1921.

familiar with the variations to be expected in diabetics under treatment. We were fortunate then to be constantly in touch with the physiological observations as they progressed. It is true though that the injection of pancreatic extract did produce a small reduction in blood sugar and in glycosuria, and provided some encouragement to continue. More concentrated extracts were provided and these yielded better results, but many delays and disappointments were still in store until a standardized process could be worked out. For example: Collip put a batch of potent extract through a Berkefeld filter and it entirely lost potency. This was controlled by suitable adjustment of the hydrogen ion concentration of the solution but, even when a process was shown to be effective in five-litre lots, the transfer of the process to a semi-manufacturing scale was impossible and new conditions had to be worked out.

As supplies permitted, the work was continued and commenced to yield more satisfying results. In March, 1922, a preliminary report² was published reviewing briefly the physiological background and relating the progress made in the clinical field. It was stated that: "Blood sugar can be markedly reduced even to the normal values. Glycosuria can be abolished. The acetone bodies can be made to disappear from the urine. The respiratory quotient shows evidence of increased utilization of carbohydrates. A definite improvement is observed in the general condition of these patients and in addition the patients themselves report a subjective sense of well being and increased vigor for a period following the administration of these preparations."

Among the tragedies of this early period was a little friend of Best from a nearby suburb, who came to hospital in acidosis and who was rescued from near-coma several times during the next few weeks. Collip gave us the last bit of partially completed extract at two o'clock one morning and then no more could be completed for days. It was not enough. Though a failure, this patient taught us much. As you know, the death of diabetic dogs cannot strictly be compared to the phenomena of acidosis and coma in human beings; so this was an experience not covered by physiological investigations. We saw the improvement after administration of pancreatic extract and the

lapse toward coma as the supply of extract waxed and waned. The dramatic is always more impressive than the routine. For us all it dispelled forever any doubt that Banting really had something of value for the human diabetic. Here we passed from the possible to the factual (*a posse ad esse*).

Early in May, 1922, the combined results of the investigations, both clinical and physiological, were presented by the group at the meeting of the Association of American Physicians in Washington. This brief communication contained sufficient evidence to indicate that a new era had dawned for the diabetic, and the Association recognized it in a thrilling and unprecedented manner by a rising vote of thanks. I remember Woodyatt's pleasure; I remember Joslin's joy. What others had tried many times before had now succeeded.

The situation created in the medical world by the discovery of insulin was, I think, unprecedented, and if unprecedented methods were adopted to deal with it which did not meet with immediate approval in some quarters, time has shown the wisdom of our seniors. Insulin was patented by Banting, Best and Collip and the patents were assigned to the Governors of the University of Toronto. And let me say here that none of the original investigators profited by one penny from the patent. The patent has been held by the University, a sacred trust for the benefit of humanity.

The necessity for expanded clinical facilities was immediate and pressing. With Professor Graham directing, a clinic was formed to carry further the clinical investigation, with Banting, Fletcher and I taking charge of the patients. We worked together literally night and day and Professor Graham was not the least tireless of the group. It was absorbing work and each day someone in the laboratory or the clinic had a new fact to add—a new hypothesis to test. The pooling of facts and ideas was an important element in the rapid progress in both laboratory and clinic. By this time others were working too, and confirmation from our associated American clinics was by no means the least factor in the crystallization of the evidence which was to place diabetic treatment on a new and sounder basis.

Less than a year after the initial decision to investigate the clinical merits of Banting's pancreatic extract we had fifty cases under observation, some of them for many months—a reasonable guarantee that no late effects would vitiate the earlier results. We decided to offer a paper to the *British Medical Journal* and it was accepted³. Probably few of you have read it, but I am still proud to have my name on it. For clear, careful and complete presentation and felicitous phrasing, necessarily condensed into a few pages, it is at least the equal of anything written on the subject subsequently. The hand that held the pen is unmistakably Fletcher's. *Litera scripta manet*, his father, the late Professor of Latin, might have said. Essentially the paper confirmed our preliminary observations and extended our clinical knowledge of the phenomena of diabetes under insulin. Coma was treated with success; the state of insulin-hypoglycaemia in man was described and treated and plans of diabetic treatment with insulin were discussed. Further estimations of the respiratory quotient before and after the administration of insulin confirmed our earlier conclusion that carbohydrate was utilized by severe diabetics under the influence of insulin.

Through the kindness of the editor, Dr. F. M. Allen, a whole number of the *Journal of Metabolic Research*⁴ was devoted to the investigations on insulin carried out in Toronto and in our associated clinics in the United States. In these papers a very considerable part, indeed the most, of our present clinical knowledge of insulin is presented by one group or another and, in general, confirmed by the others. In them the physiological aspects of the problem as it appears in man and the clinical aspects of the therapeutic application of insulin in the treatment of diabetes and its complications have been discussed in detail and illustrated by example. By this cooperative effort, there can be no doubt that the proper use of insulin in the treatment of diabetes was accelerated by years to the great and lasting benefit of many, many patients.

Since such diabetics no longer exist, you younger men must see the pictures of Buchenwald to gain an idea of the state of human misery attained by severe diabetics in pre-insulin days. All grades of severity existed then, of course, but the state of denutrition, depression and black

despair all too commonly attained before death relieved them must indeed be rare today. This, then, accounts for our joy in observing how soon the provision of adequate diet and suitable insulin dosage restored these patients to health and vigor in mind and body. Quite as important, however, is the protection afforded by insulin to less severe diabetics from ever developing such states.

The more obvious evidences of insulin action in the diabetic, first on the carbohydrate, then on the fat metabolism, are actually of lesser importance in the long run than its influence on protein metabolism. In particular and dramatic circumstances, the carbohydrate and fat aspects stand out more vividly it is true, but one cannot neglect the fact that correction of the abnormal protein metabolism is of more fundamental value to the patient over the years. The protein-sparing action of insulin treatment was early noted by us and confirmed by others. Indeed it was fortunate that the original insulins were impure products as, in some fashion, the impurities contributed to a longer action and better protein conservation which the later, purer insulins lost. Crystalline insulin requires a larger number of injections per day to obtain an equivalent effect: Hence, in part, the value of the later insulins of the protamine, globin and histone types first introduced by Hagedorn. Wilder has beautifully demonstrated the action of protamine zinc insulin in controlling protein destruction during the night.

While much has been gained by improvements in the original process of insulin manufacture, certain disadvantages are also apparent. With our present knowledge of protein chemistry it seems almost certain that insulin isolated from the pancreas is not the same substance as *insuline*, Schafer's hypothetical hormone, but a derivative largely identical in its properties. It is not untimely to suggest re-examination of our processes in the expectation of finding a superior product by newer physical and chemical methods.

As insulin production by the Connaught Laboratories and the Eli Lilly Company increased, additional physicians were associated with the work. An attempt was made to make it widely available across the continent by supplying it to those who had the requisite facilities. Special courses

of instruction for physicians were given in Toronto and elsewhere to ensure more thorough understanding of the properties of insulin and its application in treatment. The number of "first cases to receive insulin" in various quarters of the globe, which I have encountered, is very great. It is, however, of the greatest significance that so many of these early insulin patients are still living*.

With us, celebrating this day commemorating twenty-five years of insulin, is a young girl of eleven years—at least she was when first I knew her. A daughter of a woman physician, she had been stricken with severe diabetes a year previously. She had received the best of care; nevertheless, the condition had progressed. Fully familiar with the immediate dread prospect, her mother wrote to us and we decided that she was a case of considerable severity and invited them to come to Toronto. The severe cases were welcomed both because only such could provide unequivocal proof of the efficacy of treatment with insulin and because the supply of pancreatic extract still was small and the less severe could afford to wait. She came to us, not with pigtails flying down the wind, as is the right of childhood, but grave-faced and listless, tired and wan. "Mother, what are they going to do to me?" she asked without much interest. "They are going to make you better, dear." The hope in the eyes of patients was a challenge to us all.

Well, Geneva helped us with our proofs and we helped Geneva. Today she is attending our meeting, joyous, clear-eyed and vibrant. She has outlived by a hundred times her first prognosis and is now the busy and hard working auditor for a large midwestern institution. Do you marvel that we are proud? But let me say here that she illustrates the first principle of treatment in diabetes, which is not any particular type of diet or kind of insulin but Control and Control and Control. Call it discipline if you like—too many people hate that word—but it represents the foundation of that morale which makes great soldiers and is also the factor which makes the treatment of diabetes

*Our "first patient to receive insulin" died of bronchopneumonia in 1933, just prior to the introduction of sulphonamides. While this patient never developed any increase in carbohydrate tolerance, he was able to do his work acceptably as an assistant in a drug and chemical factory.

successful. Some of these people can add, Geneva, and I know it is not fair to give away a woman's age, but it is important that physicians and parents and patients should understand that the prognosis in juvenile diabetes has utterly changed and we now see no reason why children with diabetes should not live at least to a normal life expectancy. And why not to old age? The bogey of the inevitable degradation of tolerance for carbohydrate that once helped us to excuse our failures is now no more. Too many diabetic people in the insulin era, as Joslin has called it, have lived and disproved it. For those who fail, there is a cause: perhaps the patient, relative or doctor, self-indulgence, neglect or infection. Let us face it squarely.

One of the most important developments of this investigation is the psychological one. Diabetes has been changed from a metabolic *disease*, incapacitating and progressing slowly or more rapidly to an inevitable end, to a metabolic *defect* and this metabolic defect is controllable by suitable, though different, diet and the skilful application of crutches called insulin, thus enabling the patient and his family to live long, happy, and useful lives. The physician who cannot use this weapon for the strengthening of his patient's morale, who cannot make his patient see that science has discovered a way to train him to win the game is indeed to be pitied: he, and his patient also, for hope well founded is the most precious thing that we can offer to the suffering.

New problems await us and old problems remain yet unsolved. Earlier diagnosis, earlier and better treatment are important, but some of these problems are bound up with insulin, in that insulin now enables the diabetic to live long. I refer to the problems of ageing in the diabetic. Perhaps, too, in their solution some of the problems of ageing in the population as a whole may be solved. The problems of the intermediary metabolism of man are—now here, now there—yielding to the skill of men of vision and dogged perseverance. It is not too much to hope that we shall soon see the picture whole and in it the solutions we seek. Like Franz Urbach's "phosphor," insulin has been and still is converting the invisible infrared into visible light for the searchers in this field.

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