DIABETES BEFORE AND AFTER INSULIN*

by

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FIFTY YEARS AGO, a research project was under way at the University of Toronto that would soon revolutionize the treatment of diabetes. The first public announcement was made on 14 November 1921. The reports that an extract of pancreas had demonstrated life-saving effects were at first received with scepticism, incredulity, and faint hope. But soon the miracle of insulin was everywhere acclaimed.

THE STATUS OF A DIABETES TREATMENT BEFORE INSULIN

After five decades, it may be difficult for those who were unacquainted with diabetes in the pre-insulin days, to realize how much of a miracle was this discovery that transformed a disease, so often hopeless, to a disorder now subject to control or alleviation.

I find myself among the dwindling numbers of active physicians who can recall from direct observation what the management of diabetes was like in those days. Having been admitted to medical school as a teenager, I also had the good fortune to be an eyewitness of events at the University of Toronto.

My own boyhood memories bring to mind three examples of diabetic disasters, then not uncommon. First, a neighbour, a man in his late fifties, began to have severe pain in one of his toes, causing constant suffering and loss of sleep. Then to his horror it began to turn black. His family doctor called it gangrene and confirmed the diagnosis of diabetes which he himself had feared, since a brother and several members of his family had been diabetic. A surgeon, consulted in the hope that the gangrenous toe could be amputated, was unwilling to operate. He stated that, with diabetes, healing would fail to occur. The man was bedridden for months as the gangrene extended into his foot. Finally death came to end his suffering. Second, this man's daughter was found, years later, to have diabetes and tuberculosis. She died from so-called galloping consumption. Third, a young sister of one of my schoolmates, with diabetes in an early stage, was treated with the Allen 'starvation diet' then in vogue. Introduced by Dr. Frederick M. Allen, and promoted by Dr. Elliott P. Joslin, dietary restriction of extreme degree was then the chief hope for juvenile diabetics. The results for this girl at first appeared successful, but suddenly diabetic coma developed and she was gone. Cases such as these were known in every community.

When I became a medical student, I studied *The Principles and Practice of Medicine* written by Osler and McCrae,[1] a textbook universally used at that time by medical students in Toronto. I read with particular interest the section on diabetes. This book

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gave little encouragement in regard to the management of diabetes, except for persons over fifty, fat and subject to stress from 'worry, work, and excess in food and drink'. No hope was expressed for young patients or for those with complications such as tuberculosis and gangrene.

THE FIRST TREATMENT OF A HUMAN DIABETIC WITH INSULIN

It was with this experience and teaching about diabetes in mind that I witnessed, as a senior medical student, the treatment of Leonard Thompson, a fourteen-year-old boy who was admitted to Ward H of the Toronto General Hospital in December 1921. He had been diabetic for approximately two years and although dietary treatment had been attempted, he had been failing steadily in health. He was admitted to the hospital in a serious condition, emaciated and feeble. The dietary regimen employed in the hospital failed to check his downward course. He was a pathetic figure as he lay quietly in his bed or sat still in the chair at the bedside, too weak to show interest in the activities of the large, busy ward. All of us knew that he was doomed.

This was the patient selected for the first trial of the new pancreatic extract in the treatment of human diabetes. Drs. Banting and Best had already given themselves injections and decided it would be safe. But would it work in a human being as it had in a diabetic dog? On 11 January 1922, the almost moribund patient was given 15 cc. of the brownish fluid that had been prepared by Dr. Best with painstaking care. A drop in the blood sugar followed, but more extract had to be prepared for a decisive trial. Beginning twelve days later, on 23 January, daily injections were given until 4 February. Now the results were certain. The condition of the dying boy was dramatically changed; in fact, he came back to life. A few weeks later a report of the observations made in this case and in six others was published in the *Canadian Medical Association Journal.*[2] Effective treatment of the severest diabetes was now at hand.

Three years later, when I was an intern in the Toronto General Hospital, I saw Leonard Thompson when he came in regularly to secure his supply of insulin. He was now a sturdy young man, who showed little resemblance to the emaciated, dying boy who had been the subject of the most crucial clinical experiment in the field of diabetes.

After 1922 the chapter on diabetes in every textbook had to be rewritten to teach that early diagnosis and prompt treatment with insulin could restore health to both young and old, even in severe cases with complications. Knowledge of diabetes that had slowly accumulated for centuries, suddenly led to the crystallization of the ideas that quickly brought successful treatment to the rescue of victims of the disease.

THE EARLY HISTORY OF DIABETES

It is instructive to recall the earlier history of diabetes in order to picture the medical environment in which the researches of Drs. Banting and Best were carried on. May I first bring to your attention a paper published in the *Journal of the American Medical Association* in 1898 written by Dr. Elliott P. Joslin, in collaboration with Dr. Reginald H. Fitz,[3] in which they reported a study of the medical records of cases of 'Diabetes Mellitus at the Massachusetts General Hospital from 1824 to 1898'. During these

seventy-four years, the total number of cases of diabetes mellitus treated in the medical wards was 172. The mortality was twenty-seven per cent; eighty per cent of the fatalities were in coma. The closing paragraph of the paper included the following statement: 'The practical outcome of this examination of the records of cases of diabetes treated at the Massachusetts General Hospital during the past 74 years can be stated in a very few words. The average mortality of saccarin diabetes has not changed materially, for it was the same in the past 13 years as in the previous 61 years. The diabetic restrictions have undergone no essential alteration in this time. . . .'

It took courage for a physician to maintain a continuing and increasing interest in diabetes with such a hopeless outlook, but Dr. Joslin possessed the qualities of mind and heart that compelled him to continue his efforts to help the diabetics who flocked to him through the succeeding years. More than any other physician in any part of the world, Dr. Joslin successfully adapted and improved the techniques of medical management which became available to him, and within the limitation of his resources he was able to help a high percentage of his patients. He constantly emphasized the importance of teaching every diabetic patient how to live with the condition. Education of both patients and the medical profession in the management of diabetes was one of his major achievements.

Scientific dietary regulation had been developed with some measure of success before the insulin era, not only by Dr. Joslin in Boston, but by Frederick M. Allen in Boston and New York, Woodyatt in Chicago, Campbell and Fletcher in Toronto, Newburgh in Ann Arbor, and Wilder at the Mayo Clinic in Rochester, Minnesota. Their influence was just beginning to spread, but the majority of patients with severe diabetes received little help, The average doctor felt helpless.

It is of interest to note that Osler's textbook, while presenting information about dietary treatment, did not give it the emphasis that one would expect; in fact, he emphasized other factors: 'The personal hygiene of the diabetic patient is of the first importance . . ,' he said. 'Sources of worry should be avoided, and he should lead an even, quiet life, if possible in an equable climate [Impractical advice for most Canadians and New Englanders.] The heat waste should be prevented by wearing warm clothes and avoiding cold. A warm, or if tolerably robust, a cold bath should be taken every day. An occasional Turkish bath is useful. Systematic, moderate exercise should be taken. When this is not feasible, massage should be given. . . .' Diet, described next, seems to have been recommended in a half-hearted manner. The emphasis placed on personal hygiene before giving attention to the diet would give the impression that diet therapy was considered to be of relatively minor importance or ineffectual. One may conclude that Sir William Osler was not as well informed about diabetes, or did not have as much interest in this subject as in other matters which seemed to be of greater importance in the medical practice of the day. It is significant to note that his book contained thirteen pages on diabetes while devoting forty-six pages to typhoid fever, a disease that has now become almost obsolete.

Finally, in a section headed Medicinal Treatment, mention is made of a variety of drugs employed. It is surprising to read that opium is recommended! 'Opium alone stands the test of experience as a remedy capable of limiting the progress of the

disease.' Dr. Joslin also stressed the common usage of opium in his 1898 report, stating: 'Opium is the only drug which has been persistently used in the treatment throughout this entire period.' One suspects that opium was employed because it would make it easier for the hungry diabetic patient to tolerate his misery, but certainly it was never efficacious in actually overcoming the objective effects of the disease. Nowadays, any doctor prescribing opium for diabetes could be charged with malpractice, but, until the early years of this century the use of opium was traditional.

In the first publication on diabetes printed in English, Thomas Willis,[4] in 1675, recommended a number of drugs including a 'syrup of poppies', presumably an opium product. He also advised a 'thickening and moderately cooling diet', certainly a vague prescription. A textbook published in Boston nearly two centuries later gave similar recommendations.[5] This book which appeared in 1839, edited by Dr. Oliver Wendell Holmes, famous as author, poet, and medical teacher, recommended opium and, of all things, bichloride of mercury—fortunately in dose small enough to avoid poisoning. In addition to drugs, repeated blood-lettings were advised. Along with these measures, a 'strictly animal diet' was mentioned, a type of diet proposed by Rollo, an English physician, about fifty years before.

One may wonder why through the years credit has been given to many drugs and other measures, such as blood-letting and personal hygiene, which could have little actual benefit. There are three factors that may explain this. First, the institution of new treatment may give a psychological stimulus. Patients often think they feel better temporarily when given hope. Second, a physician who has not had scientific training or who lacks critical judgment may fail to compare accurately his observations in treated cases with untreated cases. Modern scientific medicine demands whenever possible 'double-blind controls', in which both patient and physician are protected against biased judgment. Third, anyone who is started on a new treatment is likely to take his dieting more seriously for a time at least. If he has mild diabetes, the limitation of his diet may cause glycosuria to disappear; he may give credit to the new drug he is taking when actually the credit should be given to the change in his eating habits.

Hurwitz and his associates at the Boston City Hospital have published observations indicating that physicians may have too readily accepted the extent of usefulness of current oral antidiabetic medication.[6] They found that one of six patients given chlorpropamide and one of three given tolbutamide appeared to manage just as well when given a placebo.

Oliver Wendell Holmes' book contained a statement that the morbid anatomy and cause of diabetics was 'still very imperfectly known'. A similar but even more dogmatic statement appeared in a textbook of physiological chemistry I used, as a student, eighty years later. In commenting on the cause of diabetes in human beings, the author, A. P. Matthews, stated: 'Nothing is known of this whatsoever.' Actually several facts had been demonstrated. The relation of the pancreas to diabetes was indicated in 1788 by Cawley, an English physician, who found at autopsy of a diabetic patient gross changes in this organ. Then, the experimental production of diabetes in dogs by removal of the pancreas, reported by von Mehring and Minkowski in Germany in 1889, clearly indicated its important role. It came to be generally accepted

that there must be an internal secretion of the pancreas essential for the metabolism of carbohydrate and that the lack of this hormone must be responsible for diabetes.

It should be recalled, however, that there was not agreement on the existence of such a hormone. Prior to 1921, numerous attempts had failed to demonstrate extractable internal secretion from the pancreas, or its presence in the blood. J. J. R. Macleod, an authority on the subject, who became professor of physiology at the University of Toronto in 1918, stated that the function of the pancreas in relation to diabetes might be of a different nature—that instead of supplying an internal secretion, the normal pancreas might remove from the blood flowing through it some enzyme or other agent which would otherwise interfere with the utilization of sugar. He concluded that the existence of an internal secretion had not been proven. Yet, because of Macleod's experience and prestige in research in the field of carbohydrate metabolism his laboratory became the scene of experiments that were soon to reverse his earlier conclusion. How did this come about?

THE DISCOVERY OF INSULIN

In an address given by Sir Henry Dale,[7] the famous British physiologist, at a special convocation at the University of Toronto on the occasion of the dedication of the Charles H. Best Institute, he said:

> When young Frederick Banting . . . came asking with a burning eagerness and a sense of mission for an opportunity to make a new attempt to obtain from the islands of the pancreas the hormone, insulin, the production of which speculation had long credited them, Macleod was well qualified to give him a discouraging account of the failure of many earlier attempts, most of them by workers of a much riper experience. It was a fair and proper warning and it is to be counted to Macleod's lasting credit that having given it he agreed, nevertheless, to give Banting the desired opportunity. . . . It was Macleod also who saw that if Banting's attempt was to give any intelligible result he must have the co-operation of somebody with recent biochemical training, and this recommendation was responsible for bringing Charles Best, recently graduated in science, trained in the necessary biochemical methods and himself rendered eager by a family contact with diabetes to do something for those whom it affected, into the historic collaboration. Frederick Banting supplied, on his part, the determined unquenchable initiative and an equipment with the necessary surgical technique. The collaboration was to be one of intimate understanding with no question between the two participants of any but an equal sharing of its success. . . .

In their first paper on The Internal Secretion of the Pancreas, published early in 1922, Banting and Best[8] cited the published work of certain investigators who had previously attempted to discover insulin and fell just short of the mark. There were others, too. Two deserve special mention. In December 1922 a curious announcement came from Paris. A French scientist, Professor E. Gley,[9] requested that a letter he had deposited in 1905 with the Société de Biologie be opened and read at the meeting of the Society held on 23 December 1922. In this communication he stated that he had prepared extracts from degenerated pancreas and had found that they decreased the sugar in the urine of diabetic dogs. He had not followed up on his observations; apparently he became too busy with other work. Thus his name was added to the list of those who came close but failed to discover insulin.

Last year, I received a letter from Professor I. Pavel of Bucharest, Romania, accompanied by documents supporting a claim that Dr. N. Paulesco of that city had

discovered insulin before the Toronto project was begun. Paulesco's report, submitted to the *International Archives of Physiology* in June 1921 and published on 31 August 1921, did indeed show that he had made a pancreatic extract that lowered the blood sugar of diabetic and normal dogs. Another paper by Paulesco quoted by Banting and Best was published in *Comptes Rendus de la Société de Biologie,* 23 July 1921. The documents sent to me included copies of correspondence between Professor Pavel and Professor Tiselius, President of the Nobel Institute. The latter expressed his personal opinion that there had been injustice in failing to recognize Paulesco's work. He thought that Paulesco should have been given at least a share of the Nobel award. Professor Pavel appealed to me, and also to other medical editors and teachers to try to set the matter straight in the record of medical history.

In reply, I agreed that Paulesco had earned a place of honour in the history of research in pancreatic physiology. I said further that 'this need not minimize the credit to a number of others who prepared active pancreatic extracts even earlier. These include Zuelzer[10] of Germany, Murlin and Kramer,[11] Kleiner,[12] and Scott[13] of the United States, and Gley[9] of France. The work of Banting and Best launched with the support of Macleod in Toronto, Canada, finally led not only to convincing evidence of the existence of the hypothetical islet hormone, but also to the practical application of its use in the treatment of diabetes. The award of the Nobel prize to the Canadian investigators came as recognition of the total significance of their work.' Best has received many additional honours.

Dr. Banting and Professor Macleod were named in the Nobel award. It was Banting's idea to make an extract of pancreas that had been caused to become atrophic by duct ligation. Although this procedure was found to be unnecessary, it was soon followed by demonstration of activity of extract of normal pancreas. The initial publication by Banting and Best describing the progress made up to 10 November 1921 was a landmark even though the authors stated '. . . it is very obvious that the results of our experimental work as reported in this paper do not justify the therapeutic administration of degenerated gland extracts to cases of diabetes in the clinic.' Achievement of the final therapeutic goal was reached a few weeks later through teamwork in which Macleod's experienced direction played a vital role. Without Macleod, the Toronto project might have been less convincing and its clinical application might have been long delayed as was the case with penicillin. Banting shared his half of the prize money with Best and Macleod shared his with Collip who contributed help in the method of extraction. Campbell and Fletcher, the clinicians, were awarded the Banting Medal of the American Diabetes Association thirty years later.

After the initial demonstrations of insulin in the laboratory and in the hospital, intensive work was begun to purify the pancreatic extract, to develop commercial production, and to study many phases of its physiological action and its clinical use. When a fellowship in physiology was offered me by Professor Macleod, you can imagine the enthusiasm with which I accepted the opportunity to join the group to work and study in this exciting environment.

The first project suggested to me by Professor Macleod was to investigate the quantitative effects of insulin and to explore the possibility of assaying it in terms of

the amount of sugar that it would enable the body to metabolize. I soon discovered that this was not feasible because of multiple variables. The rabbit unit based on hypoglycaemic convulsions had to suffice at the time; however, two important relationships of dosage and effect were revealed.[14,15] First, the glucose equivalent of a unit of insulin increases when the glucose intake is increased. This accounts for the ability of a diabetic to change from a low to a high carbohydrate diet with only a small increase in the units of insulin. Second, the glucose equivalent of each unit is decreased as the number of units administered is increased; doubling an insulin dose does not increase the total effect proportionately. This accounts for the relative rarity of severe hypoglycaemia from overdosage.

NEW CONCEPTS OF ETIOLOGY AND THERAPY

After the discovery of insulin, it seemed that the etiology of diabetes had been finally settled and that there would be agreement on standardization of therapy. It was thought that diabetes could be explained simply by lack of the production of insulin. It became evident, however, that in some cases much more insulin was needed to control the condition than could be accounted for by the loss of the usual supply; this is particularly true in cases of insulin resistance in which hundreds of units of insulin may be required for prolonged periods. There must be in some cases, at least, not merely lack of an insulin supply but interference with insulin action. Other factors which come into play include other endocrine glands, such as the thyroid, pituitary and adrenals, the liver and the central nervous system. It has become evident from clinical observations also that the development of complications affecting the arteries, eyes, nerves, and kidneys must be related not merely to a lack of insulin supply or to an increase in the blood sugar, but to other factors the nature of which has not yet been fully determined. Needless to say, much concerning the etiology of the total picture of diabetes remains to be explored.

In the field of therapeutics, any thought of uniform standard practice had to be modified. Wide differences of opinion soon appeared. Some authorities continued to recommend diets low in carbohydrate and calories; this made control of hyperglycaemia easier, and for the majority eliminated the need for daily injections. Others tried diets high in carbohydrate and found they could be employed without much more insulin. Many adopted a position between these extremes. Some abandoned dietary restrictions. The credits and debits are still debated.

The life-saving role of insulin in ketoacidosis is obvious, but otherwise there are still differing opinions regarding indications, appropriate relation to diet and oral antidiabetic medication, immediate objectives, and long-term goals of therapy.

CONCLUSION

The one factor of predominant importance in the management of diabetes is still insulin. In the crises of diabetic management, there is no substitute. After fifty years, nothing can take its place. It has not only restored health and protected the lives of persons who would otherwise have little hope of survival. It has opened the doors to avenues of research which promise to bring solutions to many of the mysteries of life.

This review of historical events in relation to insulin points to the importance of an open mind—an open mind in planning a scientific investigation and an open mind also in regard to concepts of physiology, pathology, and therapy of disease. This is the essential conclusion.

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