1.1 Introduction

In 1923 the Nobel Prize for Physiology or Medicine was awarded to Frederick Grant Banting (1891–1941) and John James Rickard Macleod (1876–1935) for the discovery of insulin and has been a source of controversy ever since. What is controversial is not the importance of the discovery but the identity of the Laureates and particularly whether Macleod had done enough to be included. These issues will be explored in this chapter but first it should be explained why people thought that the pancreas might produce an anti-diabetic substance or hormone.

1.2 The Pancreas and Diabetes

In his 1866 book, *Diabetes: Its Various Forms and Different Treatments*, the English physician George Harley (1829–1896) suggested that there were different types of diabetes. In one the sufferer was ‘fat and ruddy’ which Harley attributed to excessive formation of sugar by the liver. The other was due to ‘defective assimilation’ with emaciation one of the earliest and most prominent symptoms. These corresponded to what the French physician Etienne Lancereaux (1829–1910) later called *diabète gras* and *diabète maigre* and what we call Types 2 and 1. Their prognoses were succinctly summed up by the Toronto physician Walter Campbell (1891–1981) who wrote, ‘Before the First World War there were only two kinds of diabetics, those who died quickly and those who stuck around slowly deteriorating for a long time. For the first group there was little or nothing
one could do; the second type had certain inconveniences to put up with.\textsuperscript{22}

The first clue that the two types might have different causes came in 1889 when Oskar Minkowski (1858–1931), working in Strasbourg, discovered serendipitously that pancreatectomy in the dog caused a severe wasting type of diabetes.\textsuperscript{3,4} One possible explanation was that the pancreas destroyed a toxin which interfered with glucose metabolism but Minkowski and others believed that it produced an internal secretion. In 1894, Gustave Laguesse (1861–1927) suggested that this was produced by the ‘small irregularly polygonal cells, with brilliant cytoplasm, diffusely scattered in the pancreatic parenchyma’, which had been discovered in 1861 by a medical student Paul Langerhans (1847–1888). In 1905 Ernest Starling (1866–1927) coined the word hormone from the Greek ορµαω = to stir up. In 1909, a Belgian physiologist Jean de Meyer (1878–1934) named the hypothetical anti-diabetic hormone insulin.

One powerful piece of evidence for the existence and importance of internal secretions was the dramatic effects of (sheep) thyroid extract, which in 1891 had been shown, either subcutaneously or by mouth, to cure myxoedema in humans.\textsuperscript{5} It seemed likely that pancreatic extracts would have a similar effect on diabetes, and the decade after Minkowski’s pancreatectomy experiment was marked by attempts to cure diabetes by pancreas feeding and injecting. Most were done by physicians on an \textit{ad hoc} basis without any clear end points except whether the patient felt better and had less glycosuria. All were failures, but between 1900 and 1921 at least five investigators came close to discovering insulin.\textsuperscript{6}

In bony fish, such as the cod and haddock, the islets are separate from the exocrine pancreas and in 1903 in Aberdeen a zoologist, John Rennie (1865–1928), and a physician, Thomas Fraser (1872–1951), took advantage of this to prepare extracts of the islets. They treated several patients by mouth and one with hypodermic injections but gave up after the latter produced what seemed to be a toxic reaction. In 1922, the \textit{Lancet} suggested that they might have discovered insulin if they had a simple method of measuring blood sugar — the one they used needed 50 ml of blood and took about 3 hours!
In 1906, a Berlin physician Georg Zuelzer (1870–1949) produced a pancreatic extract which in eight patients eliminated glycosuria and ketonuria without any change in diet. This, patented in America as Acomatol, was tested in Minkowski’s department in Breslau (now Wroclaw in Poland) on three dogs and three patients, but, although confirming that it suppressed glycosuria, the side effects, especially fever, were so severe that it was concluded it would never be safe for therapeutic use. In 1928, Minkowski said, ‘In retrospect I blame myself that — considering the indubitable action of these extracts on the glycosuria — we did not make an effort to explore the causes of side effects, and that we resigned ourselves with the statement of the uselessness of the extract for the treatment of human diabetes.’

Another who nearly discovered insulin was Ernest Scott (1877–1966) at the University of Chicago. His extract produced a significant drop in glycosuria and in his thesis in 1911 he concluded that:

(i) There is an internal secretion from the pancreas controlling the sugar metabolism.
(ii) By proper methods this secretion may be extracted and still retain its activity.
(iii) This secretion is easily destroyed by oxidation or by the action of the digestive enzymes of the pancreas.
(iv) The secretion is insoluble, or nearly so, in strong alcohol but is readily soluble in acidulated water.
(v) The failure of previous workers to procure satisfactory results was due to their not preventing oxidation or the action of the digestive enzymes.

Unfortunately by the time his paper was published, a sentence had been inserted (by his professor AJ Carson who believed in the detoxification theory of pancreatic action) warning that, ‘It does not follow that these effects are due to the internal secretion of the pancreas in the extract’ [my italics]. After moving to Kansas, Scott maintained his interest in the internal secretion of the pancreas and in 1912 visited JJR Macleod, then Professor of Physiology in Cleveland, Ohio but, according to Scott, Macleod was ‘not interested, he just shrugged it off’.
In New York in 1912 John Raymond Murlin (1874–1960) put his idea of trying to find an active extract to his boss, Graham Lusk, whose response was, ‘Oh, but Minkowski tried that and failed.’ Nevertheless, Murlin went ahead with his idea of combining duodenal mucosa and pancreas in the hope that secretin might be an adjuvant. When the extract was given subcutaneously to a diabetic patient it did diminish the excretion of sugar. In March 1913, he made a new extract which completely eliminated glycosuria in a depancreatised dog but Lusk convinced him that this was because its kidneys had been damaged by too much alkali. Murlin later discovered and named glucagon.

In 1919, Israel Kleiner (1885–1966) at the Rockefeller Institute in New York published the results of intravenous injection of a pancreatic extract in 16 depancreatised dogs. In most there was a substantial reduction of blood sugar between 60 and 90 minutes after the injection. Kleiner thought the temporary effect of his extract in dogs might be duplicated in man and might be useful in emergencies. He also noted that it was simple to make and did not have any toxic effects. Kleiner never tried it in humans and his contract at the Rockefeller Institute was terminated by Frederick Allen in 1919 on the grounds that this sort of research was futile. Allen may be said to have had a conflict of interest since he was the inventor of the undernutrition treatment which kept those who had the fortitude to follow it half alive.

In 1920 there were still many who did not believe that there was an internal secretion of the pancreas and even believers were depressed about the possibility of isolating it, fearing that it might not be stored in the pancreas or that it might be species specific. It was also abundantly clear to clinicians and physiologists that attempts to cure severe diabetes by feeding or injecting pancreatic extracts had been an abject failure.

Given this background (of which he was ignorant) the chutzpah of Banting in approaching Macleod was amazing.

1.3 Banting and Macleod

Fred Banting was born on a farm in Ontario and began his medical studies in 1912 at the University of Toronto. In 1917 he was sent with
the Canadian Army Medical Corps to Europe where he was wounded at the battle of Cambrai and awarded the Military Cross. He hoped to become a surgeon at the Toronto Hospital for Sick Children but, after missing out on this prestigious position, set up practice in London, Ontario. This was not a success and to earn extra money he got a part-time job as a demonstrator at the University of Western Ontario. At the end of October 1920, he had to lecture to the students on carbohydrate metabolism of which he knew little. While preparing, he read an article, ‘The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis’ by Moses Barron (1884–1975), Professor of Pathology at the University of Minnesota. Barron reported a case in which a stone had blocked the pancreatic duct leading to atrophy of the acinar tissue but leaving the islets intact. This was not new since it was well known, at least to physiologists, that this was what happened when the duct was ligated in experimental animals. In his notebook, Banting wrote:

Diabetus [sic].
Ligate pancreatic ducts of dog. Keeping dogs alive until acini degenerate leaving Islets.
Try to isolate the internal secretion of these to relieve glycosurea [sic].

Banting mentioned his idea to a university colleague, who suggested he should consult JJR Macleod, the Professor of Physiology in Toronto (Fig. 1.1). Macleod, Jack to his friends, qualified in medicine at Aberdeen in 1889 and then spent a year studying physiological chemistry in Leipzig. He became a demonstrator in physiology at the London Hospital in 1900 and in 1903, when still only 27, was invited to apply for the Chair at Western Reserve University, Cleveland, US.10 In 1906 he contributed three chapters to a book *Recent Advances in Physiology and Biochemistry* edited by Leonard Hill, his former boss at the London Hospital. One chapter was 74 pages on carbohydrate metabolism, a subject on which he had not done any research. He soon rectified this with a series of papers entitled ‘Studies in experimental glycosuria I-XII’ published in the *American Journal of Physiology* between 1907 and 1917. His magnum opus was a textbook *Physiology and Biochemistry in Modern Medicine*, first published in 1918, in which he wrote all but 8 of the 101 chapters. In 1918 he moved to Toronto where his research was mainly

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concerned with acid base balance. In 1922, after the event, Macleod claimed that he had ‘devoted practically all my spare time during the past 18 years to the investigation of the problem of diabetes, and like every other worker in this field I have constantly had in mind the discovery of some “internal secretion” whose absence might be the cause of diabetes’. This was not true. He had gradually wound down his carbohydrate research although he did study the blood sugar of turtles with his research students Charles Best (1899–1978) and Clark Noble (1900–1978). Furthermore, like many other physiologists he shared the general pessimism about finding the internal secretion of the pancreas, even if it existed. As late as 1921, he wrote:

The removal of some hormone necessary for proper sugar metabolism is, however, by no means the only way in which the results [of pancreatectomy] can be explained, for we can assume that the pancreas owes its influence over sugar metabolism to some change occurring in the composition of the blood as this circulates through the gland — a change which is dependent on the integrity of the gland and not on any one enzyme or hormone which it produces.\textsuperscript{11}
The meeting between Macleod and Banting took place on 7 November 1920. As when Scott had asked his advice in 1912, Macleod did not seem particularly interested, writing afterwards, ‘I found that Dr Banting had only a superficial textbook knowledge of the work that had been done on the effects of pancreatic extracts in diabetes and that he had very little practical familiarity with the methods by which such a problem could be investigated in the laboratory’. For his part, Banting wrote that Macleod ‘put me off by saying that many men had worked for years in well-equipped laboratories and had not even proved that there was an internal secretion of the pancreas’. Finally, Macleod said that negative results would be of great physiological value. According to Banting, he repeated this three times, and when introducing the project to Best, Macleod opined that ‘It would likely all go up in smoke’. Nevertheless, he offered to help Banting who procrastinated about whether to leave his practice in London, Ontario but contacted Macleod again in April 1921 and was told that the offer still stood. He was given a small disused and dirty room in the physiology department. Macleod’s students Charles Best and Clark Noble were given the chance to make money by helping Banting and tossed a coin to decide who should do the first month. It was originally agreed that they should do a month each but, in Noble’s words, ‘When (Best’s) month was up, we agreed mutually that there was no reason to change horses in mid stream’.

Banting needed an assistant because he did not know how to measure blood sugar and Macleod had wisely insisted on this as the end point of the experiment. One crucial factor in their ultimate success was that, during his research with Macleod, Best learned the recently introduced Lewis–Benedict method which needed as little as 0.2 ml blood whereas Paulesco (vide infra) used Pflüger’s method, which needed 25 ml. Another stumbling block was that Banting had never done a pancreatectomy, an operation used only in animal research. On 14 May Macleod showed Banting how to do Hédon’s two-stage pancreatectomy and during the rest of the month Banting and Best did several more operations. In the middle of June Macleod went on holiday to Scotland although he could be (and was) contacted by letter, which took a month. How much advice Banting
obtained in this way was later disputed. Banting said that if he needed advice he went to the Professor of Pharmacology, Velyien Henderson (1877–1945), and never got any from Macleod. When Macleod returned from holiday at the end of September, Banting and Best already had some evidence that their pancreatic extracts lowered the blood sugar of dogs and Banting presented a list of demands including a salary and improved facilities. At first Macleod refused saying that Banting’s research was no more important than any other in the department. Eventually he did produce better facilities and Banting was given a salaried job in the department of pharmacology.

At a journal club on 14 November 1921 Banting and Best (Fig. 1.2) gave a preliminary presentation of their work to colleagues and students (Fig. 1.3). This caused further resentment because, according to Banting, Macleod in his introduction said everything Banting was going to say as well as using the pronoun ‘we’ throughout. One important suggestion at this meeting was that the best way of showing that the extract worked would be if regular administration could prolong the life of diabetic dogs. This was difficult because the duct-ligation method of obtaining dog insulin was slow, cumbersome and expensive. It involved delicate operations, many dogs and a four- to seven-week wait while the acinar tissue degenerated. Banting’s solution was to use foetal calf pancreas which Best got from the local abattoir. The rationale was that calf pancreas contained a high proportion of islets in relation to acinar tissue. An important breakthrough came on 6 December 1921 when Banting decided to use alcohol instead of saline in making their extract (an idea Macleod had suggested some months before). It worked well and led them to wonder whether fresh adult beef pancreas might be equally good. That it was must have been a surprise because the original rationale for duct ligation was that the internal secretion would be destroyed by proteolytic enzymes from the exocrine pancreas. In fact, although Macleod and many others believed this, the German physiologist Rudolf Heidenhain (1834–1897) had shown in 1875 that fresh pancreas did not have any proteolytic qualities. The intact gland contains an inactive
precursor, trypsinogen, which is only converted into trypsin by contact with duodenal juice.

At the same time Banting and Best were joined by the biochemist Bert Collip — it might be more accurate to say that he was foisted on them by Macleod who regarded him as a proper scientist in contrast to the volatile surgeon Banting. James Bertram Collip (1892–1965) had originally trained at the University of Toronto and by 1920 was Associate Professor of Biochemistry in Edmonton, Alberta. In 1921 he was working with Macleod on a Rockefeller travelling fellowship. Sometime in December 1921 Collip began making extracts from whole pancreas and found that they reduced the blood sugar of
normal rabbits, which was important in providing a cheap way of testing the potency of a batch. He also used his extract on a diabetic dog and showed that it restored liver glycogen. Banting presented his and Best’s results at the American Association of Biological Sciences on 30 December 1921. This was not a success, partly because of his extreme nervousness but also because he could not answer the critical questions of the assembled experts. Macleod was chairman of the meeting and intervened to help, again, according to Banting, talking about ‘we’. Later Banting commented that Macleod had not contributed one idea of value except to suggest measuring haemoglobin before and after injection of the extract (to prove that the fall in blood sugar was not due to dilution).

1.4 The First Clinical Test

The first use of insulin (a pancreatic extract made by Charles Best) in a human being was on 11 January 1922 when a house physician at Toronto General Hospital injected what he described as 15 cc of ‘thick brown muck’ (known to the clinical staff as Macleod’s serum) into the buttocks of the 14-year-old Leonard Thompson who had been on the Allen starvation regime since 1919 and weighed only 65 lbs. After the injection his blood sugar fell from 24.4 to 18.3 mmol/L (440 to 320 mg/dl) but no clinical benefit was seen and he developed a sterile abscess at one injection site. It was accepted that this test had been a failure but the experiment was resumed on 23 January when
he was given 5 cc of a pancreatic extract made by Collip and then 10 cc more over the next 24 hours. This time the results were spectacular. Thompson’s blood sugar fell from 29 mmol/L (520 mg/dl) on the morning of 29 January to 6.7 mmol/l (120 mg/dl) the next morning. He continued on Collip’s extract for the next ten days with marked clinical improvement and complete elimination of his glycosuria and ketonuria. Subsequently he lived a relatively normal life, working intermittently and even playing baseball. He died in 1935 of bronchopneumonia and at autopsy had marked atheroma of the aorta and coronary arteries.14

This test caused resentment in that Banting was excluded because he did not have treatment rights at Toronto General Hospital. Therefore it was supervised by Walter Campbell who chose Leonard Thompson because, ‘We thought it should be tried on the most severe cases we could find, for two reasons. If nothing happened their number was up anyway, and, more important, if effective in such patients, the results could not be gainsaid’.2

Banting asked Collip for details of how he had made the effective extract and Collip refused to tell him. This led to a confrontation in which Banting grabbed Collip by the collar. Clark Noble drew a cartoon which showed Banting sitting on and trying to choke Collip which he entitled ‘The discovery of insulin’. After peace had been restored the first clinical results were published in the March 1922 Canadian Medical Association Journal where the authors reported that up to 22 February they had treated seven cases, Leonard Thompson being the only one described in detail. Dramatically the paper concluded:

(i) Blood sugar can be markedly reduced, even to normal values.
(ii) Glycosuria can be abolished.
(iii) The acetone bodies can be made to disappear from the urine.
(iv) The respiratory quotient shows evidence of increased utilisation of carbohydrates.
(v) A definite improvement is observed in the general condition of these patients and, in addition, the patients themselves report a subjective sense of wellbeing and increased vigour for a period following the administration of these preparations.15
Given the 30-year history of false dawns since 1889, it is not surprising that the reports from Toronto were greeted with scepticism, especially in Europe. However the imprimateur of the North American scientific community was given at a meeting of the Association of American Physicians on 3 May 1922 when Macleod presented the clinical results. Nobody present seems to have doubted them and a standing vote of appreciation was given to Macleod and his associates, something which had never happened before in the history of the Association.

In Toronto, production was handed over to the Connaught Laboratories, a small industrial plant set up in 1914 to make vaccines and antitoxins, but its efforts were dogged by problems. Therefore, in May 1922 it was decided to call in Eli Lilly and Co. of Indianapolis, an ethical pharmaceutical company with experience in production and standardisation of glandular extracts.

The Dean of the University of Toronto set up an ‘insulin committee’ to manage the problems of the patent, finances and monitoring the quality of insulin. At the end of May the university gave Lilly exclusive rights to produce and sell insulin for one year. Lilly’s part of the bargain was to provide it free to selected clinicians (who Lilly’s research director later described as ‘the insulin aristocrats’), to have all batches tested in Toronto and to assign the patent for any improvements to the university. Insulin was first supplied to the aristocrats in August 1922 and their experiences were published in a special edition of Allen’s *Journal of Metabolic Research* which, although dated Nov–Dec 1922, did not come out until 1923 — the last contribution was received on 9 May 1923! The journal contained 10 papers and was 438 pages long. In his 1962 reminiscences Walter Campbell wrote that by the end of 1922,

> We had studied 50 patients for many months, including patients with coma, acidosis, gangrene and various infections. There is little doubt that we ourselves were over-impressed by the dramatic repair of patients in such dire extremity as we will never encounter again, and we even had visions of islet cell repair taking place, far beyond anything that has yet been seen. We saw such remarkable repair of malignantly progressing tuberculosis in a young diabetic, under adequate treatment with diet and insulin, as would still astonish the chest physician of today. Other infections, too, responded, far beyond our expectations. Acidosis was now no great problem.
Before and after photographs of children who had been resurrected offered dramatic evidence of the power of insulin. The most famous are those of Kansas Professor of Medicine Ralph Major’s patient Billy Leroy in his June 1923 paper in the *Journal of the American Medical Association*. This 3-year-old boy had diabetes for 2 years and weighed only 6.8 kg. After 3 months on a regimen of 55 g carbohydrate and 25 units of insulin daily his weight had doubled and his urine was sugar free.16

Even in a world without fax or e-mail, news of the discovery spread rapidly. One reason for this was the more international outlook of medical journals in those days; American, English, French and German journals all reported medical meetings in other countries and printed abstracts of papers from other journals. In *Index Medicus* in 1922 there were only 19 references to ‘insulin’ or an equivalent term (such as pancreatic extract): 7 each in the *Lancet* and *British Medical Journal* and 5 in the *Journal of the American Medical Association*. In 1923 there were 320: 108 in Britain, 88 in the *Journal of the American Medical Association*, 86 in the 3 main German journals and 41 in the French *Presse Medicale*. In just the first half of 1924 the number of references reached 317.17

In October 1922 the Danish Nobel Prize winner August Krogh (1874–1949) was lecturing in the US and contacted Macleod wondering ‘if it might be consistent with the plans of your collaborators and yourself to have experiments carried out also in Denmark’. Krogh’s wife Marie had been diagnosed with diabetes a year earlier so that he had a personal as well as professional interest. He suggested that his friend Dr Hagedorn would ‘be able to do very good work with the insulin’ and that pancreata and money would be easy to get. Production in Denmark began in December 1922 in Hagedorn’s home. Krogh played an important part in the award of the Nobel Prize.

1.5 The Nobel Prize

It is very unusual for Nobel Prizes to be awarded within two years of a discovery and to people being nominated for the first time. Banting and Macleod were nominated for the first time in 1923: Banting by George
W. Crile (Cleveland), Francis G. Benedict (Boston) and Krogh; and Macleod by George N. Stuart (Cleveland) and Krogh. Krogh considered nominating Collip as well but thought he had not done enough. Charles Best was never nominated and was thus ruled out because only nominated candidates can be considered.

Krogh’s reasons for proposing Banting and Macleod were that Banting (‘a young and apparently very talented man’) had the idea but that it could not have been progressed without the assistance of Macleod. Written evaluations of Banting’s and Macleod’s scientific contributions were provided by two members of the Nobel Committee, John Sjöqvist (Professor of Chemistry and Pharmacy) and Hans Christian Jacobaeus (Professor of Internal Medicine). Sjöqvist arrived at the same conclusion as Krogh, but Jacobaeus found the decision more difficult because Macleod’s contribution was ‘not apparent from the literature’.

There seems no doubt that the decision was made more hastily than usual and what must have swayed the committee is that by the time of their final decision in October 1923, there was already abundant evidence of the value of insulin, especially in the previously fatal diabetes of children and young people and the treatment of diabetic coma. Banting was furious at having to share the prize with Macleod and his first instinct was to refuse it. The Chairman of the Insulin Committee persuaded him that he must accept as this was the first Nobel ever awarded to a Canadian whereupon Banting decided to share his money with Best. Later Macleod did the same with Collip.

One controversy which will never be resolved is whether the Romanian, Nicholas Paulesco (1869–1931) should have shared the prize with Banting and Macleod. In contrast to the ‘amateurs’ Banting and Best, Paulesco was a professional physiologist of international renown. His interest in diabetes began in 1891 when he worked in Paris with Étienne Lancereaux. Paulesco left Paris in 1900 to take up the Chair of Physiology in Bucharest and never went back to France. In 1908 he invented a way of approaching the pituitary gland by the temporal route without causing cerebral injury and was thereby able to show that the pituitary was essential to life. His monograph *The Hypophysis of the Brain* was acknowledged by Harvey
Cushing as being a seminal work and one which stimulated and maintained Cushing’s interest in the pituitary.

As early as 1899 Paulesco wrote that, ‘Among others, together with Professor Dastre, I undertook a work whose scope was the isolation and study of the active product of the internal secretion of the pancreas. This work will be published soon.’ In fact no publication resulted and he probably did not return to his pancreatic research until 1916. In his *Textbook of Medical Physiology*, written in French and published in Bucharest in 1920, he included a 15 page chapter entitled ‘Personal Research’ in which he described an aqueous pancreatic extract, called pancreine, which resulted in ‘disappearance of the symptoms of diabetes’ in depancreatised dogs.

In the autumn and winter of 1920 he did a new set of experiments which were published in French journals in July and August 1921. One cannot but agree with Paulesco’s supporters that these papers report a beautifully conceived and executed series of experiments and in April 1922 he obtained a patent for ‘Pancréine and the Process of its Production’. His application included the sentence ‘In order that Pancréine be used in the treatment of human diabetes, it must be prepared in large quantities — which requires a lot of capital’.

When Paulesco heard of Banting and Macleod’s award he wrote to the President of the Nobel Foundation citing his paper in the *Archives Internationales de Physiologie* and saying, ‘I seek the opportunity to protest against the fact that this distinction was accorded to some people who did not deserve it. Indeed, the discovery of these physiologic and therapeutic effects belongs to me in their entirety.’ After summarising the results of his experiments, he continued, ‘Thus, the treatment of diabetes was already discovered and nothing remained but its application in man’. Unfortunately for Paulesco there is no appeal against Nobel Prize assignments and there the matter rested.

1.6 The Long-term Impact of the Discovery

Populist accounts of the discovery of insulin often imply that it revolutionised the treatment of diabetes overnight. In fact it was such a radically different treatment from any in the medical armamentarium of
the time that many doctors were frightened to use it. In 1923, Hugh Maclean, Professor of Medicine at St Thomas’ was hardly reassuring when he stated, ‘Every medical man employing insulin should be thoroughly impressed with the fact that he is using a powerful and dangerous, though easily controlled, remedy, and that any neglect on his part may end in disaster’. The editor of *The Medical Journal of Australia*, attacked insulin as a dangerous and unproven remedy claiming that, ‘No doubt hundreds of diabetics will be hastened to their graves (and that) it is too potent for safe use in advanced conditions.’

The most dramatic effects were seen in the previously universally fatal diabetic coma (ketoacidosis). The famous American diabetes specialist Elliott Joslin (1869–1962) and colleagues reviewed their first 33 cases treated with insulin between 1 January 1923 and 1 April 1925. The most important statistic was that 31 survived and these results were attributed to ‘promptly applied medical care. Rest in bed, special nursing attendance, warmth, evacuation of the bowels by enema, the introduction of liquids into the body, lavage of the stomach (and) cardiac stimulants’. They were at pains to play down the idea that since insulin had been available, coma no longer needed to be taken seriously, writing that, ‘Coma patients recover as the result of hard work by day and night of doctors, usually young, who apply the most modern methods of medical practice’.

At first insulin was very expensive and English physicians used it as a last resort. Newly diagnosed diabetics were admitted to hospital or a nursing home and put on a severely restricted diet. Only if they still had glycosuria on 40–50 g of carbohydrate per day was insulin started. How far patients were encouraged to be active participants in their own treatment probably depended on the views of their physician and many not only prescribed an excessively rigid routine but were also authoritarian. For example Jack Eastwood, a retired headmaster writing in 1986, remembered that when he developed diabetes in 1925 at the age of 13:

I was taken to a Harley Street specialist and spent three weeks in a nursing home, during which time my diet and insulin requirements were settled. I returned home to be looked after by my parents in accordance with the
detailed instructions given to them. My diet was strictly controlled, especially on the carbohydrate side: for two years all my food was weighed and no excesses at all were allowed.

In 1931 Eastwood won a scholarship to Oxford where he implemented a ‘not less intelligent method of treatment that had become normal in my case by the time I left university’. He ate lunch in an ordinary restaurant, played golf nearly every afternoon (such was university life in the 1930s!) and then had a normal four course dinner in hall, eating whatever was necessary to give himself carbohydrate 65 g, protein 35 g and fat 30 g. His basic regimen was two injections a day but he tested himself before every meal and often gave extra insulin after lunch. Eventually he decided to eat normal meals and have an injection before each of ‘the amount of insulin that I knew from experience would be needed to cope with the food about to be eaten, due allowance being made for what I expected to be doing during the next few hours’. In 1935 he visited a specialist for the last time and was told there was no need to go again since he knew more about controlling his own diabetes than the specialist.

Most authorities believed that the aim of treatment should be physiological normality and patients were told that their urine should not contain sugar at any time. Inevitably this led to hypoglycaemic attacks and in self defence many patients decided it was safer and more comfortable to run with ‘a little sugar in the urine’. In the mid-1930s some physicians realised that rigid treatment was acting as a psychological strait jacket, especially in the young, and advocated a free diet and no attempt to maintain sugar-free urine. This coincided with the introduction of long acting insulins — protamine insulinate in 1936 and protamine zinc insulin (PZI) in 1937 — and led to two decades in which many patients lived with permanently high blood sugars. Between 1935 and 1950 diabetes specialists were disturbed to find that so called juvenile diabetics whose lives had been saved by insulin were developing complications such as blindness and renal failure, which, before insulin, had only been seen in middle aged and elderly diabetics. As the Canadian physician, Israel Rabinowitch (1890–1983) put it in 1944, ‘There is nothing more disturbing than the diabetic
who acquires the disease in childhood, who apparently is a picture of robust health — who looks and feels perfectly well — but whose blood vessels have been degenerating insidiously for years; who, in the early 20s or 30s and probably married and with a family, is beginning to feel the effect of the degenerative changes, either because of a progressive hypertension, kidney failure, disturbance of sight due to retinitis or a sudden attack of coronary thrombosis.26 Ruth Reuting followed up 50 patients of Elliott Joslin who had originally been identified in 1929 when the only criteria were that they should be under 40 and have had diabetes for more than 5 years. By 1949 a third had died at an average age of 24.9 years with an average diabetes duration of 17.6 years. Of the 19 deaths, 8 were due to cardiovascular-renal disease, 4 to pulmonary TB and 4 to other infections. Among the survivors she reported that, ‘ominous signs of hypertension, azotemia and proteinuria are evident in significant numbers and 27 of the 29 living patients had X-ray evidence of vascular calcification’.27 These tragedies led to a long running debate about whether complications were due to poor glucose control or were an inevitable, possibly inherited, consequence of the disease. The issue was not resolved until 1993 when the results of the American Diabetes Control and Complications Trial (DCCT) clearly showed that near normoglycaemia prevented or delayed the onset of complications.28

References

27. Reuting RE. Progress notes on fifty diabetic patients followed 25 or more years.