ROBERT TATTERSALL

DIABETES

The Biography
List of illustrations

Prologue

1 The pissing evil: defining the disease
2 Unravelling the role of the pancreas
3 Insulin: a force of magical activity
4 The dark ages
5 Treating long-term complications
6 Adult-onset diabetes and tablets at last
7 At the laboratory bench
8 The pharmaceutical era
9 Diabetes becomes epidemic

Postscript

Glossary

Notes

Further reading

Index
You have either reached a page that is unavailable for viewing or reached your viewing limit for this book.
15. Stylized glucose tolerance test results from the *Edinburgh Medical Journal*, 1921

16. A typical Nauruan on a motor bike

17. 1829 drawing of a man with abdominal obesity

18. Doctor lecturing a patient about what not to eat
You have either reached a page that is unavailable for viewing or reached your viewing limit for this book.
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Identical twins with type 1 diabetes

In 1971, while doing research on diabetes in identical twins, I met Jane and Sandra, who were born in 1938. At age 5, when Jane developed diabetes, they were as alike as ‘two peas in a pod’. Sandra has remained unaffected, a not uncommon situation for type 1 diabetes in identical twins, indicating that it is not purely a genetic disease. Being a child with diabetes is often lonely and stigmatizing (Fig. 1). Jane’s glucose control was always poor and she had frequent hospital admissions as a teenager. This chronic ill health affected her development, so that her adult height was 2½ inches shorter than Sandra’s and she started her periods four years later—healthy identical twins are the same height and start their periods in the same week or month. In her late teens Jane had anorexia nervosa and told me that she deliberately underdosed herself with insulin to lose weight. She married in her 20s and, after three miscarriages, she had a stillborn child. The first signs of diabetic eye damage were noted when she was 26, and by the age of 35 she was blind. Protein in her urine, the earliest sign of kidney damage, appeared when she was 24, and she was about to start dialysis when she died of a heart attack aged 37.
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disease and kept her blood sugars high to avoid the inconvenience of hypoglycaemic (low-blood-sugar) attacks.

**A new kind of diabetes: MODY**

As John Malins pointed out, diabetes is so variable that one can never say that ‘this always occurs or that never happens’. When I was a medical student, it was axiomatic that normal-weight young people with diabetes needed insulin. Jennifer, whom I met in 1971, disproved that. She developed diabetes in 1943 at the age of 12, presenting with thirst and increased urination. She was put on insulin, but discontinued it on her own initiative between 1948 and 1951. When she returned to the clinic in 1951, she was relatively well but had a high blood sugar. She was given a stern telling-off and restarted on injections. In 1970 she insisted on being tried on anti-diabetic tablets, and, to the surprise of the doctors, they worked. I asked why she had been so certain she could manage without insulin; her answer was that her aunt and cousin had both developed diabetes in their teens and been put on insulin, but had been able to stop it after thirty years. I found two other patients in the clinic at King’s College Hospital with very similar histories. They also had family members with the same unusual form of diabetes. I described them in a paper entitled ‘Mild familial diabetes with dominant inheritance’ and in 1975, while working with Professor Fajans in Ann Arbor, Michigan, changed this to Maturity Onset Type Diabetes or MODY, a name that has stuck. In the 1990s it was found that diabetes in these families was caused by single gene mutations, and it is now clear that MODY (of which there are five separate types) accounts for 1–2 per cent of all diabetes.
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Aretaeus’ writings were unknown in Europe until 1552. His aim in treating what was clearly type 1 diabetes was to overcome the intense thirst, and to this end he began with a purge and followed it with a variety of mixtures to soothe the stomach.

Galen (AD 129–210), whose teachings dominated Western medicine for more than a thousand years, mentions diabetes only briefly and regarded it as a kidney disease or, as he put it, ‘diarrhoea of the urine’. He reported having seen only two sufferers, which, given that he had a large practice among the rich of Rome, seems odd. Perhaps most cases were among middle-aged epicureans whose symptoms were not striking? Physicians were expected to taste the urine to make a diagnosis, but screening those without symptoms in this way was perhaps beyond the call of duty. Galen’s view that diabetes was a disease of the kidneys remained dominant in Europe throughout the Renaissance and lasted well into the nineteenth century.

The Persian physician and philosopher Avicenna (980–1037) was very familiar with diabetes, which he thought could be primary or secondary to another disease. He gave a comprehensive list of the symptoms and noted that, when the urine evaporated, it left a residue like honey. He also listed gangrene, carbuncles, and phthisis (tuberculosis) as complications.

The work of Avicenna and other Arab physicians and philosophers was not known in Europe, where the Church decreed that, since all knowledge was found in the Bible, there was no excuse for experiment. The revival of scientific medicine is often attributed to Theoparastus Bombastus von Hohenheim (1493–1541), better known as Paracelsus, whose first public act when he became professor of medicine in
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Where the sugar in the urine came from was unclear, but an army surgeon John Rollo (d. 1809) thought it was formed in the stomach from vegetables. To him the obvious solution was to eliminate greens and to give a diet that consisted principally of animal food. The regimen published in his 1797 book *An Account of Two Cases of the Diabetes Mellitus* was:

First. The diet to consist of animal food principally, and to be thus regulated:

*Breakfast.* 1½ pints of milk and half a pint of lime water mixed together; bread and butter.

*Lunch.* Plain blood puddings, made of blood and suet only.

*Dinner.* Game or old meats which have been long kept; and as far as the stomach may bear, fat and rancid old meats, as pork. To eat in moderation.

*Supper.* The same as breakfast.

Secondly, a drachm of kali sulphuratum [potash] to be dissolved in four quarts of water which has been boiled, and to be used for daily drink. No other article whatever, either eatable or drinkable, to be allowed, than what has been stated.

Thirdly, the skin to be anointed with hog's lard every morning. Flannel to be worn next to the skin. The gentlest exercise only to be permitted: but confinement to be preferred.

Fourthly, a draught at bedtime of 20 drops of tartarized antimonial wine and 25 of tincture of
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(1806–79) invented the first test for glucose in 1841. Urine was heated with blue cupric (copper) sulphate, and in the presence of a reducing substance such as glucose, red cuprous oxide was formed. The copper test was improved by Herrmann von Fehling (1812–85), and, although it was ideal for detecting glucose, ordinary doctors found it too complicated for measuring the amount of glucose, it was a useful test of the progress or otherwise of treatment. In 1862 William Roberts (1830–99) of Manchester described a method in which two samples of diabetic urine were put in flasks and a piece of yeast added to one. After twenty-four hours on a warm mantelpiece, glucose in the flask with yeast had fermented so that the specific gravity fell. The amount of glucose was equal to the difference of the specific gravity before and after fermentation × 0.23. This was promoted as ideal for the doctor who wanted to treat his cases of diabetes ‘scientifically’. Its advantage was that everything necessary, except the urinometer for measuring specific gravity, could be found in an ordinary domestic kitchen. Measuring blood glucose was possible, but needed large volumes of blood, plenty of time and meticulous technique. It was hardly ever used in clinical practice until the development of micromethods after the First World War.

Being able to measure the amount of glucose in the urine enabled scientifically minded physicians to compare different diets. One of these was Frederick William Pavy (1829–1911), who spent his working life at Guy’s Hospital investigating what he called ‘one of the most inscrutable of diseases’. His colleague Sir William Gull asked satirically: ‘What sin has Pavy committed or his fathers before him, that he should be condemned to spend his whole life seeking the cure of an incurable disease?’ In 1861 Pavy’s patient Joseph North, aged 32, was in Guy’s Hospital for four months on a variety
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obesity cures. One was Vin Urane Pesqui, a small amount of uranium nitrate in old Bordeaux wine—uranium nitrate was widely used for diabetes and approved by mainstream physicians. According to the advertising blurb, it 'positively cures sugared diabetes, provided it is resorted to at an early stage and used during a sufficient length of time ... as soon as the patient has made use of this wine, his thirst is allayed almost instantaneously; his strength reappears, all his functions are gradually restored'. Another nostrum was Dill's Diabetic Mixture, advertised as 'The only known remedy for this deadly disease. No dieting is necessary.' One-third of it was alcohol, a common feature of secret remedies and one that presumably made the patient feel better. A preparation called 'Expurgo Anti-Diabetes' was described by the Journal of the American Medical Association (JAMA) as such an evident nostrum that even intelligent laymen could not be deceived by it. Nevertheless, some medical journals had accepted adverts for it, and physicians of what JAMA described as 'a certain type' supplied testimonials that appeared prominently in the adverts. Later in the twentieth century such physicians would be called drug company whores.

For sufferers who could be persuaded to diet, the outcome depended critically on their age and whether they were thin or fat. Camplin noted that, 'where the disease attacked the thin and delicate', there was little hope. He told of 'a thin, delicate, young lady, highly nervous and excitable, whose sister had died of a similar disease', who, in spite of strictly adhering to a meat diet, sank rapidly into a coma. Before they died, the breath and urine of these young people had a curious smell, which was variously compared to chloroform, rotting apples, or hay. It was assumed to be the result of some sort of fermentation and also thought to cause the coma in which
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recognized impotence as a common symptom, often the presenting one. Pavy described it in typically circumlocutory language: ‘What has been said in respect of muscular action will apply also in explanation of the loss of virility which accompanies the inveterate form of the disease. The condition which the blood presents may be considered as unsuited for the maintenance of functional activity in the organs in question.’¹³ A description of diabetic nerve damage, which would not be out of place in a modern textbook, was given by Pavy in 1885. He wrote:

The usual account given by these patients of their condition is that they cannot feel properly in their legs, that their feet are numb, that their legs seem too heavy—as one patient expressed it, ‘as if he had 20 lb weights on his legs and a feeling as if his boots were a great deal too large for his feet’. Darting or ‘lightning’ pains are often complained of. Or there may be hyperaesthesia, so that a mere pinching of the skin gives rise to great pain; or it may be the patient is unable to bear the contact of the seam of the dress against the skin on account of the suffering it causes. Not infrequently there is deep-seated pain, located, as the patient describes it, in the marrow of the bones which are tender on being grasped, and I have noticed that these pains are generally worse at night.¹⁴

As treatment, Pavy recommended opium or codeine and, if this did not work, ‘continuous galvanic current’. Where the main symptom was superficial pain, he suggested ‘cautious application of the linimentum aconiti’ (an alkaloid from the monk’s hood plant). Their modern equivalents are
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II

UNRAVELLING THE ROLE
OF THE PANCREAS

In the early nineteenth century the standard way of finding out which organ was involved with a group of symptoms was opening the body after death. Thus most people who had wasted away and coughed up blood were found to have characteristic lesions in the lungs—the tubercles of phthisis or pulmonary tuberculosis. In this condition, using a stethoscope or percussing the chest with the fingers could predict the presence of cavities or consolidation in the lung in life.

Another striking example of the value of correlating clinical and autopsy findings was the work of Thomas Addison of Guy’s Hospital, London, who in 1855 described a disease in which the sufferers became very tired and had a peculiar darkening of the skin. His first five patients with what became known as Addison’s disease all had changes in the adrenal glands, which had previously been thought to be vestigial structures.

Where diabetes was concerned, autopsies were unhelpful. In spite of the excessive urination, the kidneys looked normal, as did all other organs to the naked eye. Because knowledge of its cause was so sketchy, textbook writers had difficulty in knowing in which section to put diabetes. In the first edition of his textbook in 1892, Osler included it with gout under ‘constitutional diseases’. Others still put it in the section on kidney diseases, and in a 1901 book it was described as ‘a “general disease” which has no local seat, which is certainly not a disease of the kidney … We therefore place it by itself
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Bernard's research suggested that the liver was one organ involved in diabetes. Harley, who had suggested in 1866 that there were two types of diabetes, believed that in what he called ‘fat and ruddy’ patients the cause was overproduction of sugar by the liver. Pavy was sceptical but did record the case of a man who developed diabetes after being kicked over the liver by a horse.

Another organ that was thought to be involved was the brain. Prout had noted (wrongly) that animals did not get diabetes and asked, ‘Can the exception be referred to that fertile cause of bodily disorder in human beings, the influence of the mind?’ However, it was almost certainly Bernard’s *piqûre* experiment in 1849 that focused attention on the brain. This discovery came about because Bernard had found that cutting the vagus nerve abolished the secretion of glucose by the liver. He tried the process in reverse by stimulating the vagus, but found no effect. He therefore decided to prick the point in the fourth ventricle of the brain where the vagus arises and ‘I succeeded at the first attempt in making the animal diabetic. At the end of an hour, the blood and urine of the animal were full of sugar.’ This effect lasted only as long as glycogen remained in the liver. If the animal had been starved to exhaust liver glycogen, there was no glycosuria (glucose in the urine). The fact that *piqûre* diabetes was always temporary seems to have been ignored, and between 1860 and 1900 the nervous origin of diabetes was much discussed. Facts that were alleged to support it were cases that started soon after a nervous shock and, according to Robert Saundby, ‘the well known fact that the disease is much more common among the educated than the uneducated classes—that is it occurs chiefly among those whose nervous systems undergo more wear and tear’. It was also said that diabetes was more common among engine drivers than other
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He was an extraordinarily energetic man, who often worked 20 hours a day and published 577 papers during his career. He crossed the Atlantic more than sixty times and set up residence in America four times, France six times, England once, and Mauritius twice.

In 1869, during research on the adrenal gland, Brown-Séquard had suggested that all glands with (exocrine) or without ducts (endocrine) ‘supplied to the blood substances which are useful or essential and the lack of which may produce physiological signs’. In June 1889, three months before Minkowski’s presentation, he gave a lecture that, in the words of the *BMJ*, ‘caused the idea of internal secretion to take possession of the general imagination’. At the Société de Biologie in Paris the septuagenarian described how he had prepared testicular fluid from animals and injected himself with it every day for two weeks. As a result, he claimed to have been rejuvenated. The evidence was that he was much more vigorous, could lift heavy weights, and could run upstairs. Also the average length of his jet of urine had increased by 25 per cent. English doctors wrote to the *BMJ* complaining that the experiments were disgusting and unnatural. This was partly because Brown-Séquard had suggested that masturbation without ejaculation might have the same effect. One correspondent wrote that ‘vivisection may be an open question but self-abuse is not!’ Since Brown-Séquard was well known in England and America, his views, although greeted with some scepticism and lampooned by cartoonists, were taken seriously, and in 1893 the *BMJ* published two of his papers in which he stated that there was no doubt that the pancreas had an internal secretion that was even more important than its external one. He recommended the simultaneous use of orchitic (testicular) and pancreatic liquid in all cases of diabetes. Immodestly he concluded that
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success. In 1904 they gave the extract to another patient by hypodermic injection daily for six days but gave up because of side effects. Urine volume and glycosuria were unaffected, and they concluded either that they had not given enough extract or that a fish product would not work in mammals. (Fish insulin does work in man and was used in Japan during the Second World War when other types were not available.)

In 1906, in Berlin, Georg Zuelzer (1870–1949) tied the pancreatic ducts of animals and, after the organ had shrivelled, squeezed out the juice, precipitated the proteins with alcohol, and injected the extract. He treated eight patients and concluded that glycosuria and ketonuria (acetone or ketones in the urine) could be eliminated without any change in diet. His extract was tested in Minkowski’s unit on three dogs and three patients, but, although he was able to confirm that it suppressed glycosuria, the side effects were so severe that it was thought to be unsafe. After the discovery of insulin, Minkowski blamed himself for not investigating the side effects more thoroughly, since the drug obviously worked. Zuelzer continued his experiments and in 1913 persuaded the drug company Hoffman La Roche to make an extract, which was abandoned when it produced severe convulsions—almost certainly due to low blood sugar (hypoglycaemia).

Another who might have succeeded was Ernest Scott (1877–1966), who in 1908 went to the University of Chicago to work with the newly appointed Professor of Physiology, Anton J. Carlson. Rather than tying off the duct, Scott extracted fresh pancreas with alcohol. His extract produced a significant drop in urinary glucose in three of four dogs. The conclusions he drew in his thesis submitted to the University of Chicago in 1911 were that:
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an exhaustive review of the literature on metabolism in
general and diabetes in particular. Allen did animal
experiments in which he removed varying amounts of the
pancreas to produce the equivalents of severe or mild human
diabetes—what we would call types 1 and 2. Dogs left with
20 per cent of their pancreas or more did not develop diabetes.
The fate of those with 80–90 per cent of their pancreas
removed depended on what they ate. If fed a low-
carbohydrate diet, they remained relatively well, like middle-
aged humans with diabetes—since Eskimos lived on 52 grams
of carbohydrate daily, Allen called this an Eskimo diet. Large
amounts of carbohydrate (which Allen called a Hindu diet)
wore out the pancreatic remnant, and what had originally been
mild diabetes turned into the severe form. From this Allen
decreed that patients should order their lives ‘according to the
size of their pancreas’. Basically this meant reducing food
intake until the urine was sugar free. In 1914 he was given a
junior position at the Rockefeller Institute in New York,
where there was no shortage of clients, since physicians were
only too willing to send him their ‘hopeless’ diabetics. His
first findings on forty-four patients were published in 1915
under the title ‘Prolonged fasting in diabetes’. This article was
picked up by the Daily Mail, which announced that a cure for
diabetes had been found—such hyperbolic headlines continue
in the twenty-first century as shown below.

Diabetes is ancient and anything but mild (The
Times, 18 Nov. 1999, 44).

Twice-yearly diabetic jab (Daily Mail, 4 Apr. 2000,
9).

Diabetes defeated in 10 years (Scotsman, 27 Jan.
2001, 1).
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‘many cases unquestionably die because of lack of courage’. Allen also talked about ‘the habitually unfaithful type of patient’, but was sufficiently astute to point out that ‘fidelity’ (which would now be called compliance) could not be predicted from intelligence or social position. Allen also claimed that many patients died because ‘ignorant’ doctors did not understand his regimen.

Unfortunately for many faithful patients, the result was literal starvation and some died of inanition, not diabetes. In 1921 the most famous European diabetes specialist, Carl von Noorden, turned away in disapproval when he saw Joslin’s prize patient, 17-year-old Ruth A., who at just over 5 feet weighed only 54 lb (24.5 kg). Rawle Geyelin (1883–1942) of New York gave numbing descriptions of the pitiful state of such patients in a 1923 paper. A 15-year-old girl who had had diabetes for three years weighed 463/4 lb and went home on 6 grams of carbohydrate, 25 grams of protein, and 30 grams of fat per day. A 10-year-old boy who had had diabetes for 4½ years weighed only 27 lb (12.3 kg) and was so weak he could not lift his head from the pillow.

At a meeting in 1921 most London teaching-hospital consultants were enthusiastic about the fasting treatment; one dissenter was Frederick Poynton of Great Ormond Street Hospital, who described the disappointing results in children. Later he published the cases of five who all died within thirty months. In each case the parents went through three stages:

First, the thought that they were succeeding, then the uneasy feeling that they were losing, and finally the realisation that we protracted the illnesses, but nothing more, and the very partial success was so unsatisfactory from the children’s point of view that, had not there always been a hope that some new
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this was what happened when the duct was tied in animals, but 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*] ¹

Against the background of the fruitless attempts described in the previous chapter, it is not surprising that Macleod did not take Banting seriously. Macleod wrote: ‘I found that Dr Banting had only a superficial textbook knowledge of the work that had been done and no familiarity with the methods by which such a problem could be investigated in the laboratory.’ ² Quite apart from Banting’s ignorance, Macleod had lost interest in diabetes and was researching acid–base balance. Banting later said that during the first interview Macleod was so disinterested that he started reading letters on his desk. Nevertheless, he offered Banting a disused lab and two students, Charles Best (1899–1978) and Clark Noble (1900–78), who were to do alternate months. They tossed a coin to decide who should do the first month. Best ‘won’, but was so involved at the end of the month that Noble agreed that he should continue.

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 their experiments. During his research on the blood sugar of the turtle, Best had learned the new Lewis–Benedict method, which needed as little as 0.2 ml blood, whereas other methods needed 25 ml. Another stumbling block was that Banting had never done a pancreatectomy, an operation that at the time was used only in
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The first use of insulin (an extract made by Charles Best) on a human being was on 11 January 1922. The pancreatic extracts were relatively impure, and the house physician at Toronto General Hospital described what he injected into the buttocks of 14-year-old Leonard Thompson as ‘15 cc of thick brown muck’. Thompson had been on the Allen diet since 1919 and weighed only 65 lb (29.5 kg). After the injection, his blood sugar fell from 440 to 320 mg/dl (24.4 to 18.3 mmol/l), but no clinical benefit was seen. The experiment resumed on 23 January, when he was given Collip’s extract, and now his blood sugar fell during one day from 520 mg/dl (29 mmol/l) to 120 mg/dl (6.7 mmol/l). He continued treatment for ten days with marked clinical improvement and complete elimination of glucose and ketones from his urine. Subsequently he lived a relatively normal life, although reliant on insulin injections, before dying of pneumonia in 1935.

The first clinical results were published in the March 1922 Canadian Medical Association Journal, where the authors reported that 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 utilization of carbohydrates.
(v) A definite improvement is observed in the general condition of these patients and, in addition, the
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was life-saving. Paulescu’s scientific work was more impressive, but it was the Canadian group, with the commercial know-how of Eli Lilly, who had produced insulin in quantity.

Initial clinical experiences

Given the thirty-year history of false dawns since 1889, it is not surprising that the reports from Toronto were greeted with scepticism, especially in Europe. However, when Macleod presented the clinical results at the Association of American Physicians in May 1922, nobody seems to have doubted them, and he received a standing ovation. Insulin was supplied to American physicians in August 1922, and their experiences were published in ten papers in a special edition of Allen's *Journal of Metabolic Research* in 1923.

A picture is worth a thousand words, and the most impressive papers were those illustrated by ‘before and after’ photographs of children who had been resurrected by insulin. Best known is that of Ralph Major’s patient Billy Leroy. This 3-year-old boy had had diabetes for two years and weighed only 6.8 kilograms (15 lb). After three months on insulin his weight had doubled, and he was a normally active little boy.
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research into tuberculosis, was reluctant, but the clamour from physicians and the public meant that they had to do something, and their involvement offered the opportunity to ‘exercise a moral control of manufacturers and induce them to submit to a system of supervision, as regards this product, which the law does not enable the Council at present to enforce’. The reason for the MRC’s concern was that, in England until 1925, any drug could be advertised and marketed as a cure for any disease, even if it was completely ineffective.

One unforeseen consequence was that ‘enquiring, appealing, often heartrending letters arrived by the sack’ at the MRC offices. Approaches were made to drug companies, and the first British insulin was supplied to hospitals in April 1923.

Getting to grips with the new treatment

Insulin was totally different from existing medicines, its use raised as many questions as it answered, and every part of every answer raised more questions.

Newspapers led the public to believe that insulin was a cure and doctors did think it might rest the insulin-producing cells and allow them to regenerate. This was not irrational; the kidneys could recover after acute glomerulonephritis and the lungs after lobar pneumonia, so why not the pancreas? It therefore made sense to try to nurse the islets back to health by rest. Initial experience was encouraging; patients often needed large doses of insulin at first, but a month or two later these could be halved or quartered (what was later called the honeymoon effect—that is, something transient). By 1925 it
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The initial symptom may be a feeling of nervousness or tremulousness, sometimes a feeling of excessive hunger, at other times a feeling of weakness or a sense of goneness. The level at which a patient becomes aware of the fall in blood sugar is fairly constant for that individual, although this is not always the case ... [as the blood sugar falls further] ... the feeling of nervousness may become definite anxiety, excitement or even emotional upset. The feeling of tremulousness is possibly a form of incoordination. Patients have shown a loss of power to perform fine movements with their fingers ... Much more severe manifestations are observed with further lowering of the blood sugar. Marked excitement, emotional instability, sensory and motor aphasia, dysarthria, delirium, disorientation, confusion have all been seen.\(^{16}\)

Soon hypoglycaemia was being compared to drunkenness. Otto Leyton told of one of his patients who, during a meal, pressed his friends to help themselves to more pepper. Then in a loud voice, he insulted his wife, who, realising that he was hypoglycaemic, asked him to take some sugar. He replied that, of course she wanted him to take sugar, something the doctor had specifically forbidden, so that she could get rid of him and marry someone else. Eventually he was forced to take sugar, became normal within a few minutes, and had no recollection of what had happened.

Coma that was due to low blood sugar (hypoglycaemic coma) was a new disease, and what doctors understood by the term ‘diabetic coma’ was ketoacidosis. Some of the most dramatic effects of insulin were seen in these patients. In 1923 Nellis Foster (1875–1933) of Philadelphia treated fifteen
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boiling, other syringe problems were jamming of the plunger by residues from the methylated spirits in which it was kept and loosening of the plunger, leading to inaccuracies in dosing.

In England the first strength of insulin marketed was 20 units/ml (later called single strength), and syringes were made with 20 marks per millilitre, so that one mark equalled one unit. When 40- and 80-units/ml (double and quadruple strength) insulins were introduced in the 1930s, the old syringe was retained, so that marks on the syringe and units no longer corresponded. This caused confusion, because, depending on which strength of insulin was being used, a mark could be 1, 2, or 4 units, and some patients quoted their dose as 10 units when they meant 10 marks of 80 u/cc insulin—that is, 40 units. In the USA, and less commonly in Europe, syringes were made with dual scales for 40- and 80-strength insulin, which caused halving or doubling of the dose if the patient inadvertently used the wrong scale. These problems were not solved until a single strength of 100 units/ml was introduced in the 1980s, with a standard syringe in which units and marks again corresponded.
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evidence of vascular disease. They concluded that diabetes alone injured the small blood vessels of the retina. How this damage was caused they did not know, and what was confusing was that it was seen in cases of mild diabetes (those managed by diet alone) as frequently as in severe diabetes (those on insulin). Nobody yet realized that insulin had converted the acute fatal form of diabetes into something more like the chronic form.

Further evidence that diabetes alone could cause organ damage was the 1936 discovery by Paul Kimmelsteil (1900–70) and Clifford Wilson (1906–97) of a new type of kidney disease. Their eight middle-aged diabetic patients lost a large amount of protein in their urine and had gross oedema, a clinical picture known as the nephrotic syndrome. What was new was the microscopic appearance of the kidney, where there were large nodules in the glomeruli (intercapillary glomerulosclerosis). After the Second World War it became clear that this kidney disease could also affect the young, and there were increasingly frequent reports of diabetics who had been saved by insulin as children only to succumb to kidney failure in their 20s and 30s. Fifty of Joslin's child patients who had started insulin before 1929 were followed up in 1949, when a third had died at an average age of 25, after having had diabetes for an average of 17.6 years. One half had died of kidney failure and the other half of tuberculosis and other infections. Markers of early kidney disease were protein in the urine (albuminuria) and high blood pressure, and these harbingers of future trouble were found in most of the survivors. In the experience of the Joslin group, only 2 per cent of deaths of young diabetic patients before 1937 were due to kidney disease, but, of those who died between 1944 and 1950, more than half had advanced kidney disease.
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Tolstoi, who worked in New York, started using protamine insulin as a once-daily injection in the late 1930s, but his patients found that trying to keep the urine sugar free led to warningless hypoglycaemia. Two abandoned their diet and reported that, in spite of continuously having sugar in their urine, they felt well. During two months in hospital they passed up to 100 grams of sugar in twenty-four hours, but, according to Tolstoi, had a normal urinary volume and no diabetic symptoms. He therefore decided to let all his patients eat what they liked and see what happened. He described the result:

They are in good health, in a state of social and economic usefulness, and infections are no more frequent than in the average individual. All these patients enjoy their freedom as there appeared no necessity for careful dietary management, and it is not necessary for them to carry their insulin and syringe with them. They administer insulin to themselves in the morning and then put the equipment away until the following morning. These patients are not singled out as a group, apart from their fellow men, and their habits of living approximate the normal.  

To the criticism that they would develop complications, he pointed out that only 8 per cent of Joslin’s juvenile onset patients avoided retinopathy and kidney disease in spite of sermons about the importance of ‘chemical control’. To Tolstoi, quality of life was all-important, and, according to him, Joslin's patients ‘do not enjoy life nor have the freedom of people who live like normal human beings’. 
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old who developed ketoacidosis and labour at the same time and had a stillborn baby twelve hours later. Titus felt so badly about having lost a baby in front of his eyes, as it were, that he decided to deliver diabetic women by Caesarian section as soon as the baby was viable. He usually sterilized the women at the same time. A similar policy of early delivery was adopted at King’s College Hospital, London, where in 1942 there were fifty-four pregnancies with an overall foetal mortality of 33 per cent. Women who had attended the diabetic clinic irregularly or not at all during pregnancy had a foetal mortality between 50 and 70 per cent and their babies typically weighed 9–10 lb (4–4.5 kg). Waiting for such a large baby to be delivered normally risked it dying suddenly in the womb or the shoulders getting stuck during labour. Delivery between the 36th and 38th week by Caesarean section seemed safer but introduced the dangers of pre-maturity, especially if the woman’s dates were wrong.

The only place where a perinatal mortality ten times greater than in the general population was not replicated was in Boston, where Priscilla White (1900–89) managed the diabetes. She had not finished her internship when Joslin recruited her in 1924. Her recollection was that, ‘practically on my arrival, Dr Joslin assigned me to the study of diabetic children. He thought that, as the youngest member of the team, I would be close to them.’ She also took over the medical management of diabetic pregnancies. She was intensely involved in the lives of her patients, to whom she wrote a letter after each and every visit. She was also greatly affected by foetal deaths, which may have been what pushed her towards aggressive management, particularly hormone replacement. Her results in the 1930s were excellent, but in 1945 she introduced treatment with the female sex hormones, stilboestrol and progesterone; the results seemed miraculous.
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and it is hoped that they or related drugs may prevent proliferative retinopathy.

Back in the 1940s and 1950s oral drugs such as rutin (a glycoside from the rind of lemons that was supposed to strengthen blood vessels), vitamins C and K, and testosterone were tried, as was radiotherapy to the eye; all were ineffective, but continued to be used because there was nothing else to offer.

Faced with the rising tide of blindness in young diabetics, some doctors took desperate measures by removing the pituitary gland (hypophysectomy). The basis was a 1953 paper by a Danish physician, Jacob Poulsen (1907–88), ‘The Houssay phenomenon in man: recovery from retinopathy in a case of diabetes with Simmond’s disease’. Simmond's disease is atrophy of the anterior lobe of the pituitary gland (which produces growth hormone) as a result of uterine haemorrhage after childbirth. The Houssay phenomenon, discovered by the Argentinian Nobel prizewinner Bernardo Alberto Houssay (1887–1971), is a dramatic increase in insulin sensitivity after removal of the pituitary. In 1945 Poulsen's patient had a severe postpartum haemorrhage, after which her insulin dose fell from 80 units daily to 8 units every other day on which she had repeated severe hypoglycaemia. In the sixth month of pregnancy she had been noted to have (non-proliferative) retinopathy, but five years later this had disappeared. Poulsen wondered if the apparent cure of retinopathy might be a consequence of ‘metabolic hormonal disorder’ and suggested that removing the pituitary gland in young patients with severe retinopathy was worth trying.¹ This was first done in Sweden by the neurosurgeon Herbert Olivecrona (1891–1980) and the physician Rolf Luft (1914–2007). Luft was a friend of Poulsen and knew about the patient described above. Their
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preliminary results of a British trial showed that photococoagulation delayed the progression of maculopathy, the type of retinopathy most common in type 2 diabetes. The macula is the part of the retina used for sharp clear vision, such as in reading, and, when the blood vessels leak, as they do in diabetes, it leads to a build-up of fluid in the macula.

Photocoagulation was not a panacea but merely a way of stopping retinopathy getting worse. Even in the best hands there was still a 10 per cent or greater risk of progression of visual loss. It also had unavoidable side effects in the form of a reduction in visual field and night vision and, in the hands of careless or unlucky operators, excessive or misdirected burns, for example, on the macula.

Permanent blindness in people with proliferative retinopathy is caused by haemorrhage into the vitreous humour followed by scarring and retinal detachment. In 1972 a German eye surgeon Robert Machemer (b. 1933) made instruments with which it was possible to operate inside the eye. The vitreous humour could be sucked out and replaced with salt solution, bands of scar tissue could be cut, and detached retina stuck back on again. The technique was complex and the risk of complications high, especially in diabetic eyes. Nevertheless, a trial in 1985 showed that it was better than doing nothing. It is now widely used and leads to the return of useful, although never perfect, vision in people who have had massive haemorrhage in the eye.

Replacing the kidneys: dialysis and transplantation

Kidney failure (often referred to as uraemia) led to a particularly unpleasant death, with increasing anaemia and ill
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any were rehabilitated to the extent of being able to go back to work. During the 1980s results gradually improved, although diabetics still fared badly. For example, in a 1988 report, just over half of type 1 and 2 diabetics on dialysis died in the first four years.

An alternative to dialysis was transplantation. The first successful kidney transplant between (non-diabetic) identical twins had been done in Boston in 1954. Tissue transplanted between identical twins is not rejected, and the long-term success of this case showed that kidney transplantation would work if rejection could be suppressed. The first immunosuppressant drug, azathioprine, became available in 1961, and with steroids it produced good results with live, related donors and greatly encouraged the development of transplantation. The 1970s ended with two important innovations, the use of tissue typing, which made rejection less likely, and the introduction of cyclosporine as an immunosuppressive agent.

In the 1960s the Minnesota transplant surgeon Richard Lillehei (1928–81) described uraemic diabetics as ‘the pariahs of medicine’. According to him, diabetologists said, ‘I can’t take care of this patient, he/she has kidney failure,’ and kidney specialists said, ‘I can’t take care of this patient, he/she has diabetes.’ Hence by 1972 only 19 of 5,432 kidney transplants worldwide had been done for diabetic renal disease, when diabetics would have been expected to make up 20 per cent of those eligible. Surgeons were reluctant to ‘waste’ kidneys on diabetic patients because of high death rates, fear that the combination of diabetes and immunosupression would lead to rampant infection, and the theoretical possibility of the new kidney being damaged by diabetes. The pioneers were at the University of Minnesota, where the first five diabetic cases
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microalbuminuria—a misnomer, since what is being measured is not small albumin but small quantities of albumin. Surprisingly, microalbuminuria had already been discovered by the Ames Company. When they produced a tablet test for urine protein (Albutest) in the 1950s, clinicians complained that it gave ‘false positives’ in patients in whom the standard test for albumin was negative. In fact, Albutest was so sensitive that it was detecting microalbuminuria, but pressure from clinicians led to its replacement by a less-sensitive but more convenient dipstick, Albustix. By 1982 microalbuminuria was shown to be a marker of early nephropathy and later a more general indicator of bad blood vessels. It would become an important end point in trials of intensive treatment in diabetes.

Concurrently with research into microalbuminuria, a new class of drugs was introduced for hypertension, the angiotensinconverting enzyme (ACE) inhibitors. It was known from the early 1960s that ACE produced angiotensin II, which raised blood pressure. In the 1960s a Brazilian pharmacologist working in London found that a protein in Brazilian viper venom inhibited ACE, and his boss, the Nobel prize-winner John Vane (1927–2004), suggested that the Squibb company should try to make a synthetic ACE inhibitor. This was brave, since most experts did not believe that ACE had anything to do with ordinary symptomless (as opposed to the life-threatening malignant) hypertension. A chemist at the drug company Squibb did synthesize a nine-amino-acid compound (treprotide), which was effective but of no commercial interest, since it had to be injected and cost a million dollars per kilo to make. The project had effectively been scrapped, but in 1974 a biochemist, David Cushman, went back to the ACE inhibitor project, and within eighteen
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of a heart attack, diabetes was omitted from the death certificate in more than half the cases.

The most feared complication was gangrene of the foot or leg, which was between twenty and fifty times more common than in the non-diabetic. Any black areas on the feet of diabetic patients were called gangrene, and in the 1930s, before the discovery of antibiotics, surgeons advised prompt operation before infection became established. They also favoured above-knee amputations, since these were most likely to heal. A justification for high amputations was the maxim that the diabetic’s first amputation (on one limb) should be his last. This avoided the situation where the leg was removed in bits; a toe would be cut off and after a few weeks the amputation site would turn black. The foot would then be amputated through the ankle and again the wound would not heal. Eventually, after three or four operations, an above-knee amputation would finally heal. Early high amputation also made sense in people whose life expectancy was low—low because the hardening of the arteries that had caused gangrene in the leg was also present in the arteries of the heart, so that most died of heart attacks. In 1948 an American surgeon Samuel Silbert wrote that, ‘by the time a diabetic has reached the point where he requires amputation of a leg for gangrene, his life has nearly run its course, and he will be among the select few if he is alive five years later. If alive, it is probable that loss of the second leg will have been necessary.’ In the 1930s nearly 50 per cent of diabetics having an amputation died in the immediate post-operative period. One reason for the high mortality was that inexperienced surgeons did these ‘hopeless’ operations. Another factor was that what Joslin called ‘ward’ patients (that is, charity rather than private patients) initially refused amputation and gave consent only when extensive gangrene
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pressure of a relatively moderate degree on the ball of the foot. Ulcers could also be caused by a stone in the shoe, which, because of the lack of pain, would literally burrow into the sole. According to Brand, results with leprous ulcers in India were very poor until 1939, when immobilization in a walking plaster became the standard treatment and led to relatively rapid healing. In a 1966 pamphlet for the Leprosy Mission, Brand wrote that ‘the pathway to amputation of the leg is littered with bandages and dressings which have deceived both doctor and patient into thinking that by dressing an ulcer they were curing it … the whole problem is really one of mechanics not medicine’.

Transmission of his message about the vulnerability of the anaesthetic foot to the world of (American) diabetes came about by chance. In the late 1970s Brand read an article about diabetic bone disease illustrated with x-rays that looked identical to the changes in the feet in leprosy.

He contacted the authors and was invited to address the Sugar Club, which he explained was ‘a genteel group of diabetes specialists from the Southern states’. He described his work with leprous ulcers in India and his findings on repetitive stress. Most members of the audience were sceptical, pointing out that vascular disease was a complicating factor in diabetes but not in leprosy. However, John Davidson of Atlanta found that implementing Brand’s ideas on minimizing pressure dramatically reduced the frequency of ulcers and amputations. Brand also opened the foot clinic at Carville to patients with diabetes and found that ‘the notion of “non-healing wounds” proved as much a myth in diabetes as it had in leprosy. Our simple technique of keeping wounds in plaster casts for protection worked almost as well for diabetics. Ulcers chronic for years often healed within six weeks of the plaster cast routine.’
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2. **Insulin standard**: a fixed dose of Lente once daily according to the patient’s surface area. This group was included to distinguish between the blood-sugar-lowering and other possible effects of insulin.

3. **Tolbutamide**: a fixed dose of 1 gram before breakfast and 0.5 gram before the evening meal, chosen because it was the average dose used in clinical practice.

4. **Placebo**: Lactose tablets or capsules.

In 1962 a fixed-dose phenformin group was added. It was hoped to recruit 200 patients in each group, but this proved so difficult in the twelve university clinics that special screening procedures were used to find new diabetics. No attempt was made to exclude patients with vascular disease, and it later transpired that patients in one centre were recruited from the cardiac clinic. It was, of course, expected that the mortality would be lower in the insulin and tolbutamide groups than in those on diet alone. However, the tolbutamide arm of the study was stopped prematurely in 1969, because analysis by what the *Lancet* called ‘advanced, elaborate, and novel statistical techniques’ showed a significantly higher death rate in the tolbutamide group (12.7 per cent) than in the placebo group (4.9 per cent). Mortality in the two insulin-treated groups was nearly the same as for placebo patients. In 1970 an ad hoc committee of the American Diabetes Association commented that, apart from the apparent toxic effect of tolbutamide:

What is even more arresting is that neither of the insulin-treated groups had a lower mortality than the placebo-treated patients. This finding carries the broadest implications for the treatment of non-insulin-dependent adult onset diabetes. First, if
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12. Area of lipoatrophy at the top of the thigh where insulin injections have caused the fat to melt away.

That insulin was an antigen, or something that stimulated the production of antibodies, became the basis of a method for measuring insulin in the blood. The delicate bioassay in animals used by Bornstein (and others) was supplanted in the early 1950s by test-tube methods in which a patient’s serum was added to rat diaphragm or testicular fat, and glucose uptake or glycogen synthesis was measured. These lacked specificity, because other substances in the blood could produce insulin-like effects. Between 1956 and 1960 an exquisitely sensitive and specific method, the radioimmunoassay, was developed by Solomon Berson (1919–72) and Rosalyn Yalow (b. 1921). Berson, a physician whose research skills were self-taught, met Yalow, a physics PhD, in New York in 1947. Berson had not trained in endocrinology and why they became interested in insulin is not clear. Possibly it was because Yalow’s husband was an
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it was thought that, faced with a choice between human and animal insulins, customers would unhesitatingly choose the former. The first human insulin, the result of collaboration between the Genentech and Eli Lilly companies in the USA, was produced by genetic engineering in 1981. The human insulin gene was inserted into the *E. Coli* bacterium, which, after growing in a culture medium, produced insulin. The Novo Company soon did the same thing with yeast—in effect brewing insulin. The US Food and Drugs Administration, which was notorious for its tardiness in approving new drugs, took only five months to review and approve Lilly’s Humulin. Whether this haste was due to enthusiasm for the first product of genetic engineering or whether it owed something to a potential shortage of animal pancreata is uncertain.

Biosynthetic human insulin was a great scientific achievement, but the practical benefits were rather underwhelming, and in blind trials neither the investigators nor the subjects could distinguish between pork and human insulin. Nevertheless, Eli Lilly and Novo were desperate for human insulin to succeed to justify their investment and to free themselves from the abattoir, with its theoretical risk of contaminating insulin with prions such as bovine spongiform encephalopathy (BSE). The result was an advertising campaign (to doctors) promoting the benefits of human insulin, which was described as ‘identical to the body’s own insulin and therefore the logical choice’ (Novo) or ‘outstandingly pure and less immunogenic than that which comes from the pancreas of pigs or cattle’ (Eli Lilly). Marketing was so successful that between 1984 and 1988 more than 80 per cent of patients in the UK had been switched to human insulin, which cost twice as much as the products it replaced. The switch was often made autocratically by doctors, who justified it by claiming that the ‘old-fashioned
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process which has been going on for an indefinite time, perhaps from birth. One of Gepts’s subjects also had lymphocytic infiltration of the thyroid gland, and he suggested that the infiltrates in the islets and thyroid might be due to the newly discovered pathological process called autoimmunity. He was referring to the discovery by Deborah Doniach (1912–2004) of the Middlesex Hospital, London, of antibodies that destroyed the thyroid gland, causing myxoedema, and others that attacked parietal cells in the stomach, causing pernicious anaemia. Another glandular disease with lymphocytic infiltration was (non-tuberculous) Addison’s disease, and again the blood contained antibodies against the adrenal gland. By the late 1960s it was clear that glandular diseases involving autoantibodies and lymphocytic infiltration—Addison’s, myxoedema, and pernicious anaemia—were more common in people with type 1 diabetes but not in those with type 2. It therefore seemed likely that type 1 was caused by autoantibodies against the islets. In the event, islet cell autoanti-bodies (ICA) were not discovered until 1974. The main reason for the delay was that, unlike those in thyroid and adrenal disease, which persist indefinitely, ICA disappear in most people with type 1 diabetes during the year after diagnosis.

The (apparently) acute clinical onset of type 1 diabetes and the fact that it more commonly started in the winter had long suggested an infectious cause. One possibility was mumps, which had been known since the nineteenth century to cause pancreatitis and rarely to be followed by diabetes. However, since most children had mumps and very few children became diabetic, it was obvious that the relationship could not be very strong. In the late 1960s interest in an infection was rekindled by the finding of higher titres of antibodies to the Coxsackie B4 virus in newly diagnosed
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14. Ames Reflectance Meter (1970), the first device for measuring blood glucose outside the laboratory. On the left is one of the many meters available in 2000.

The relationship of diabetes and HbA1c was discovered in 1968 by an Iranian doctor, Samuel Rahbar, who described what he thought was a new haemoglobin (the protein in red blood cells that carries oxygen). Rahbar analysed blood samples, which contained a variant that accounted for between 9 and 15 per cent of total haemoglobin. This was odd, because genetic variants (of which there are many) always constitute a fixed proportion. Rahbar found that people with this variant all had diabetes and later learned that it had been identified ten years earlier as HbA1c. In 1976 it was found that when diabetic patients had their blood-glucose levels kept normal in hospital, raised HbA1c concentrations returned to normal in four to six weeks. It was later shown that HbA1c was formed when glucose attached itself to haemoglobin and that the amount formed was proportional to the average blood glucose concentration over the 120-day life of the red cell. In other words, HbA1c could be used as a measure of the average blood glucose level over the previous six weeks.

**The Diabetes Control and Complications Trial (DCCT)**

The person who gave an enormous push to diabetes research in the USA was a TV producer, Lee Ducat, who founded the Juvenile Diabetes Foundation (JDF) in 1970 after her son developed diabetes. Frustrated by what she saw as the limited aims of the (doctor-dominated) ADA, she decided to raise
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You have either reached a page that is unavailable for viewing or reached your viewing limit for this book.
INDEX

Abel, John Jacob 139
ACCORD trial 168
Addison’s disease 31, 67, 155
albuminuria 26
aldose reductase 173
Allen, Frederick Madison 46–50, 61, 79, 88–9, 197
American Diabetes Association, foundation 159
amputation 28, 76, 84, 116–17, 120–2, 186
Aretaeus 11
aspirin 171
Assal, Jean-Phillipe 199
atherosclerosis 27, 82, 112–13, 115, 171, 193
Avicenna 12

Bang, Ivar Christian 180, 183
Beaser, Samuel 89–90
Beetham, William 102
Benedict’s solution 74–5, 90 see also urine testing
Berger, Michael 146, 199
Bernard, Claude 33–6
Berson, Solomon 137–9
Bertram, Ferdinand 86
biguanides 129–30, 135 see also metformin and phenformin
Biostator 151
blood glucose, measurement of 161–4, 180
Lewis-Benedict method 54
Bloom, Arnold 134–5
Bloom, Stephen 144
Bohringer Mannheim 128, 162
Bornstein, Joseph 124
Bouchardat, Appollinaire 22
Brindley, Giles 173
brittle diabetes 91–2, 100
Brown-Séquard, Charles-Édouard 38–40, 70

Campbell, Walter 68
Camplin, John 18
carbutamide 127–9
Carrasco-Formiguera, Rosend 63, 68
chlorpropamide 129–30, 169
cholesterol 81, 171–2, 182, 185 see also statins
Clinitest 89 see also urine testing
Collip, Bertram 53, 57–8, 60, 126
Cudworth, Andrew 157
Cullen, William 15
Cushing's syndrome 125

DAFNE 199
Darwin, Erasmus 26
Darwinism 192
Dawber, Thomas 184
Diabetes Control and Complications Trial (DCCT) 165–6
Diabetes Prevention Program (DPP) 194–5
diabetes specialist nurses 149–50
diabetes surveys 183–5
diabetic coma 24–5, 92–4
    effect of insulin 69
    hypokalaemia as a complication of 93–4
    see also ketoacidosis
dialysis 104–8
diet
    animal 16
    failure to chew 45–6
    free 86–8
    high carbohydrate 86
    low protein 104
Dobson, Matthew 14
Doniach, Deborah 155

Eastwood, Jack 199–200
Eli Lilly 61, 64, 128–9, 144, 148, 175–6
employment of diabetics 74–6
Ellenberg, Max 113–14
Elliotson, John 32
erectile dysfunction, see impotence
European Association for the Study of Diabetes, foundation 159
exanatide 170

Falta, Wilhelm 124
Farquhar, Jim 96
Fehling, Herrmann von 19
Feudtner, Chris 84
Fletcher, Andrew Almon 68
Fletcher, Charles 81, 199
Foster, Nellis 69
Framingham study 184–6
Fraser, Thomas 42

Galen 12
gangrene 116–18
Garrod, Archibald 45
Gepts, Willy 154
Geyelin, Rawle 50
Gley, Eugène 43
glibenclamide 127
glucagon like peptide 1 (GLP 1) 170–1
glucose tolerance test 180–3
Graham, George 49, 77, 181–2
Guelpa, Guglielmo 22

haemoglobin A1c 164
Hagedorn, Hans Christian 80
Harley, George 34–5
Harris, Harry 191
heredity 32, 189–93
Himsworth, Harold 122, 124
Hippocrates 10
Hirschberg, Julius 26
Hodgkin, Dorothy 141
Holler, Jacob 93–4
Home, Francis 15
Houssay, Bernardo 99
hypertension 26, 84, 109, 111, 167, 171, 185, 189, 192–3
hypoglycaemia 6, 7, 43, 67–71, 76, 80–1, 87, 90, 99–100, 124, 127, 142, 146, 149, 161, 163, 166, 168, 175–6
hypokalaemia 94

impotence 27, 85, 173–4

insulin
  amino acid structure 140–1
  antigenicity of 143
  coma treatment 70–1, 139
  commercial production 64–5
  continuous subcutaneous infusion of 152–3
  discovery of 53–60
  fast acting analogues 174–6
  human 147–9
  inhaled 177
  initial clinical experiences 61–3
  injection equipment 72–3
  long acting preparations 80–2, 175–6
  measurement of 124, 137–9
  purification of 143–5
  regimens 145–7
  resistance 124, 143, 147, 167, 169, 193
  strength of solutions 72–3
  three dimensional structure of 141

insulitis 154
islet cell transplantation 153–4
International Diabetes Federation, foundation 159
lipoatrophy 136–7, 144
Loubatières, August 127
Luft, Rolf 100
Lukens, Francis 145

Macleod J. J. R. 44, 52–67
Malins, John 93, 109
Mehring, Josef von 36
Mendel, Gregor 189
metformin 130, 168–9, 195
Meyer-Schwickerath, Gerd 100–1
microalbuminuria 110, 172
Minkowski, Oskar 36–7, 126
Mirsky, Arthur 138
Mogensen, Carl Erik 110
Moss, James 134–5
mumps 155
Murray, George Redmayne 46
myxoedema 41, 155

Nauru 186
Neel, Jim 192

nephropathy 83–4, 103–9
  dialysis for 103–7
  kidney transplantation for 107
  prevention 109–12
  see also albuminuria and microalbuminuria
  neuropathy 27–8, 84–5, 112–4
Nobel prize 60–1, 99, 139, 141
Noble, Clark 54, 67
NOD mouse 156, 158
Noorden, Carl H. von 21, 50, 126
Nordisk Insulinlaboratorium 80, 144–5
    see also Novo-Nordisk
Novo 82, 143–8
Novo-Nordisk 147

Oakley, Wilfred 97, 118
Obesity 10, 26, 167, 179–80, 186–9, 193
    treatment 23, 195–6
Opie, Eugene 43
oral hypoglycaemic agents 126–31, 169–70
overweight see obesity
Osler, William 21, 32, 46

Paracelsus 12
pancreas 2, 36, 45, 54–7, 81, 127
pancreas, transplantation 153
Parving, Henrik 110
patient education 74, 90–1, 122–3, 150, 199
Paulescu, Nicholai 58, 60–1
Pavy, Frederick William 20, 27–8, 32–5
Pedersen, Jørgen 96
phenformin 129–30, 132–3
photocoagulation 100–3
Pickup, John 152
Pima indians 185–6
Pincus, Gregory 189
pioglitazone 169
Piorry, Pierre 20
Poulsen, Jacob 99
Poynton, Frederick 51
pregnancy 94–7, 162, 181
protamine zinc insulin 80–1

Reaven, Gerald 193
renal glycosuria 181
renal threshold for glucose 34, 90, 181
  retinopathy 26, 82–7, 98–103, 144–5, 160, 172
  treatment 99–103
Rennie, John 42
Rollo, John 15–17
Root, Howard 93
roziglitazone 169–70
Rundles, Wayne 112–14

Sanger, Frederick 140–1
Saundby, Robert 35, 178
Schäfer, Edward 40–1
Scott, Ernest 43–4
Scribner, Belding 103
self monitoring of blood glucose 161–4
Seltzer, Holbrooke 133
Siperstein, Marvin 132, 160–1
Slama, Gérard 152
Sobolev, Leonid V. 41–2, 55
Sönksen, Peter 93
Starling, Ernest 41
starvation treatment 46–51
statins 171–2
Steinberg, Arthur 191
Steiner, Donald 142
Sterne, Jean 130
Stolte, Karl 86
sulphonylureas 127–30, 135, 168
   see also tolbutamide, carbutamide, chlorpropamide and glibenclamide
Sushrut 10
synthalin 126

Tchobroutsky, Georges 145
Titus, Raymond 94
Thompson, Leonard 57
tolbutamide 129, 130–4
Tolstoi, Edward 87–8
transplantation kidney 107
troglitazone 169
Trommer, Karl August 19
tropical diabetes 179
Turner, Robert 167
secret remedies 23–4

ulcers, neuropathic 118–22
United Kingdom Prospective Diabetes Study (UKPDS)  
  167–8, 170–1
University Group Diabetes Program (UGDP) 131–5, 162
urine
tasting 13
tests for sugar 19, 74–5, 89–90, 180

Vague, Jean 193
vascular endothelial growth factor (VGEF) 99
vitrectomy 103

Walker, Joan 122, 149
weight loss 167, 194–6
West, Kelly 182
Westernization 187–8
White, Priscilla 95, 189
Wilder, Russell 80, 82
Williams John R. 50
Willis, Thomas 14
Wilson, Clifford 85
Woodyatt, Rollin 91

Yale–Luer Lok 72
Yalow, Rosalyn 137–9
Ying–lai, Wang 142
Young, Frank 125

Zahn, Helmut 142
Zuelzer, 43