1 The History of Diabetes Mellitus

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Key points

- Polyuric diseases have been described for over 3500 years. The name *diabetes* comes from the Greek word for a syphon; the sweet taste of diabetic urine was recognized at the beginning of the first millennium, but the adjective *mellitus* (honeyed) was added by Rollo only in the late eighteenth century.
- The sugar in diabetic urine was identified as glucose by Chevreul in 1815. In the 1840s, Bernard showed that glucose was normally present in blood, and that it was stored in the liver (as glycogen) for secretion into the bloodstream during fasting.
- In 1889, Minkowski and von Mering reported that pancreatectomy caused severe diabetes in the dog. In 1893, Laguesse suggested that the pancreatic *islets* described by Langerhans in 1869 produced an internal secretion that regulated glucose metabolism.
- Insulin was discovered in 1921 by Banting, Best, Macleod, and Collip in acid-ethanol extracts of pancreas. It was first used for treatment in January 1922.
- Diabetes was subdivided on clinical grounds into *diabète maigre* (lean people) and *diabète gras* (obese people) by Lancereaux in 1880, and during the 1930s by Falta and Himsworth into insulin-sensitive and insulin-insensitive types. These classifications were the forerunners of the aetiological classification into type 1 (insulin-dependent) diabetes and type 2 (non-insulin-dependent) diabetes.
- Insulin resistance and β-cell failure, the fundamental characteristics of type 2 diabetes, have been investigated by many researchers. The *insulin clamp* method devised by Andres and DeFronzo was the first accurate technique for measuring insulin action.
- Maturity-onset diabetes of the young was described as a distinct variant of type 2 diabetes by Tattersall in 1974.
- Lymphocytic infiltration of the islets (insulitis) was described as early as 1901 and highlighted in 1965 by Gepts, who suggested that it might be a marker of autoimmunity. Islet cell antibodies were discovered by Doniach and Bottazzo in 1979.
- The primary sequence of insulin was reported in 1955 by Sanger and the three-dimensional structure by Hodgkin in 1969. Proinsulin was discovered by Steiner in 1967, and the sequence of the human insulin gene by Bell in 1980. Yalow and Berson invented the radioimmunoassay for insulin in 1956. The presence of insulin receptors was deduced in 1971 by Freychet, and the receptor protein was isolated in 1972 by Cuatrecasas.
- The various types of diabetic retinopathy were described in the second half of the nineteenth century, as were the symptoms of neuropathy. Albuminuria was noted as a common abnormality in people with diabetes in the nineteenth century and a unique type of kidney disease was described in 1936 by Kimmelstiel and Wilson. The concept of a specific diabetic angiopathy was developed by Lundbæk in the early 1950s.
- Milestones in insulin pharmacology have included the invention of delayed-action preparations in the 1930s and 1940s, synthetic human insulin in 1979, and in the 1990s novel insulin analogues by recombinant DNA technology.
- The first sulfonylurea carbutamide was introduced in 1955, followed by tolbutamide in 1957 and chlorpropamide in 1960. The biguanide phenformin became available in 1959 and metformin in 1960.
- That improved glucose management in both type 1 diabetes and type 2 diabetes was beneficial was proved by the Diabetes Control and Complications Trial (DCCT) in 1993 and the UK Prospective Diabetes Study (UKPDS) in 1998.
- Landmarks in the treatment of complications include photocoagulation for retinopathy, first described by Meyer-Schwickerath; the importance of blood pressure management to slow the progression of nephropathy, demonstrated by Mogensen and Parving; the introduction of low-dose insulin in the treatment of diabetic ketoacidosis in the 1970s; improvements in the care of pregnant women with diabetes pioneered by White and Pedersen; and the emergence of heart failure as a common and treatable pathology.
- The understanding of the complex physiology of type 2 diabetes improved at the beginning of the twenty-first century with clarification of the roles of fat metabolism and signalling; the gut as an endocrine organ; the signals of satiety to the brain; and the role of glucagon as an important homeostatic signal.
- The many therapeutic breakthroughs of the twenty-first century include the discovery of peroxisome proliferator-activated receptor γ (PPAR-γ) activation as a therapy for insulin resistance; the activation of the incretin axis by glucagon-like peptide 1 (GLP-1) receptor agonists and the dipeptidyl peptidase 4 (DPP-4) inhibitors; and the blocking of the renal glucose transporter channels by sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

Professor Robert Tattersall died on 23 November 2020. This historical text is largely his work. Professor David R. Matthews has updated and revised the chapter.

Textbook of Diabetes, Sixth Edition. Edited by Richard I.G. Holt and Allan Flyvbjerg.

Ancient times

Diseases with the cardinal features of diabetes mellitus were recognized in antiquity (Table 1.1). A polyuric state was described in an Egyptian papyrus dating from c. 1550 BCE, discovered by Georg Ebers (Figure 1.1), and a clearly recognizable description of what would now be called type 1 diabetes was given by Aretaeus of Cappadocia in the second century CE (Figure 1.2a). Aretaeus was the first to use the term *diabetes*, from the Greek word for a syphon, 'because the fluid does not remain in the body, but uses the man's body as a channel whereby to leave it'. His graphic account of the disease highlighted the incessant flow of urine, unquenchable thirst, the 'melting down of the flesh and limbs into urine', and short survival.

The Hindu physicians Charak and Sushrut, who wrote between 400 and 500 BCE, were probably the first to recognize the sweetness of diabetic urine (Figure 1.2b). Indeed, the diagnosis was made by tasting the urine or seeing that ants congregated round it. Charak and Sushrut noted that the disease was most prevalent in those who were indolent, overweight, and gluttonous, and who indulged in sweet and fatty foods. Physical exercise and liberal quantities of vegetables were the mainstays of treatment in people with obesity, while lean people, in whom the disease was regarded as more serious, were given a nourishing diet. The crucial fact that diabetic urine tasted sweet was also emphasized by Arabic medical texts from the ninth to eleventh centuries CE, notably in the medical encyclopaedia written by Avicenna (980–1037).

Table 1.1 Milestones in the clinical descriptions of diabetes and its complications.

Clinical features of diabetes	
Ebers papyrus (Egypt, 1500 BCE)	Polyuric state
Sushrut and Charak (India, fifth century BCE)	Sugary urine; thin individuals and those with obesity distinguished
Aretaeus (Cappadocia, second century CE)	Polyuric state named *diabetes*
Chen Chuan (China, seventh century CE)	Sugary urine
Avicenna (Arabia, tenth century CE)	Sugary urine; gangrene and impotence as complications
Diabetic ketoacidosis	
William Prout (England, 1810–1820)	Diabetic coma
Adolf Kussmaul (Germany, 1874)	Acidotic breathing
Hyperlipidaemia	
Albert Heyl (Philadelphia, 1880)	Lipaemia retinalis
Retinopathy	
Eduard von Jaeger (Germany, 1855)	General features
Stephen Mackenzie and Edward Nettleship (England, 1879)	Microaneurysms
Edward Nettleship (England, 1888)	New vessels, beading of retinal veins
Julius Hirschberg (Germany, 1890)	Classification of lesions; specific to diabetes
Neuropathy and foot disease	
John Rollo (England, 1797)	Neuropathic symptoms
Marchal de Calvi (France, 1864)	Neuropathy is a complication of diabetes
William Ogle (England, 1866)	Ocular nerve palsies in diabetes
Frederick Pavy (England, 1885)	Peripheral neuropathy
Julius Althaus (Germany, 1890)	Mononeuropathy
Thomas Davies Pryce (England, 1887)	Perforating foot ulcers
Nephropathy	
Wilhelm Griesinger (Germany, 1859)	Renal disease in people with diabetes
Paul Kimmelstiel and Clifford Wilson (USA, 1936)	Glomerulosclerosis associated with heavy proteinuria

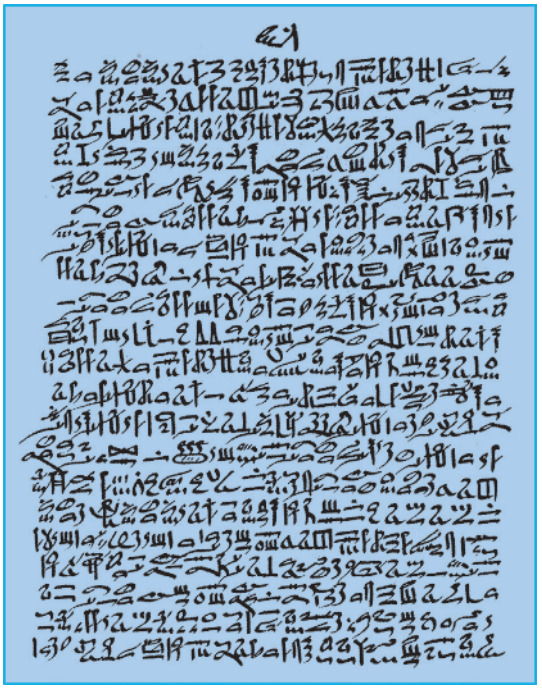


Figure 1.1 The Ebers papyrus. Source: Courtesy of the Wellcome Library, London.

Seventeenth and eighteenth centuries

In Europe, diabetes was neglected until Thomas Willis (1621–1675) wrote *Diabetes, or the Pissing Evil* [1]. According to him, 'diabetes was a disease so rare among the ancients that many famous physicians made no mention of it . . . but in our age, given to good fellowship and guzzling down of unallayed wine, we meet with examples and instances enough, I may say daily, of this disease'. He described the urine as being 'wonderfully sweet like sugar or honey', but did not consider that this might be because it contained sugar.

The first description of hyperglycaemia was in a paper published in 1776 by Matthew Dobson (1735–1784) of Liverpool (Figure 1.3 and Table 1.2) [2]. He found that the serum as well as the urine of his patient Peter Dickonson (who passed 28 pints of urine a day) tasted sweet. Moreover, he evaporated the urine to 'a white cake [which] smelled sweet like brown sugar, neither could it by the taste be distinguished from sugar'. Dobson concluded that the kidneys excreted sugar and that it was not 'formed in the secretory organ but previously existed in the serum of the blood'.

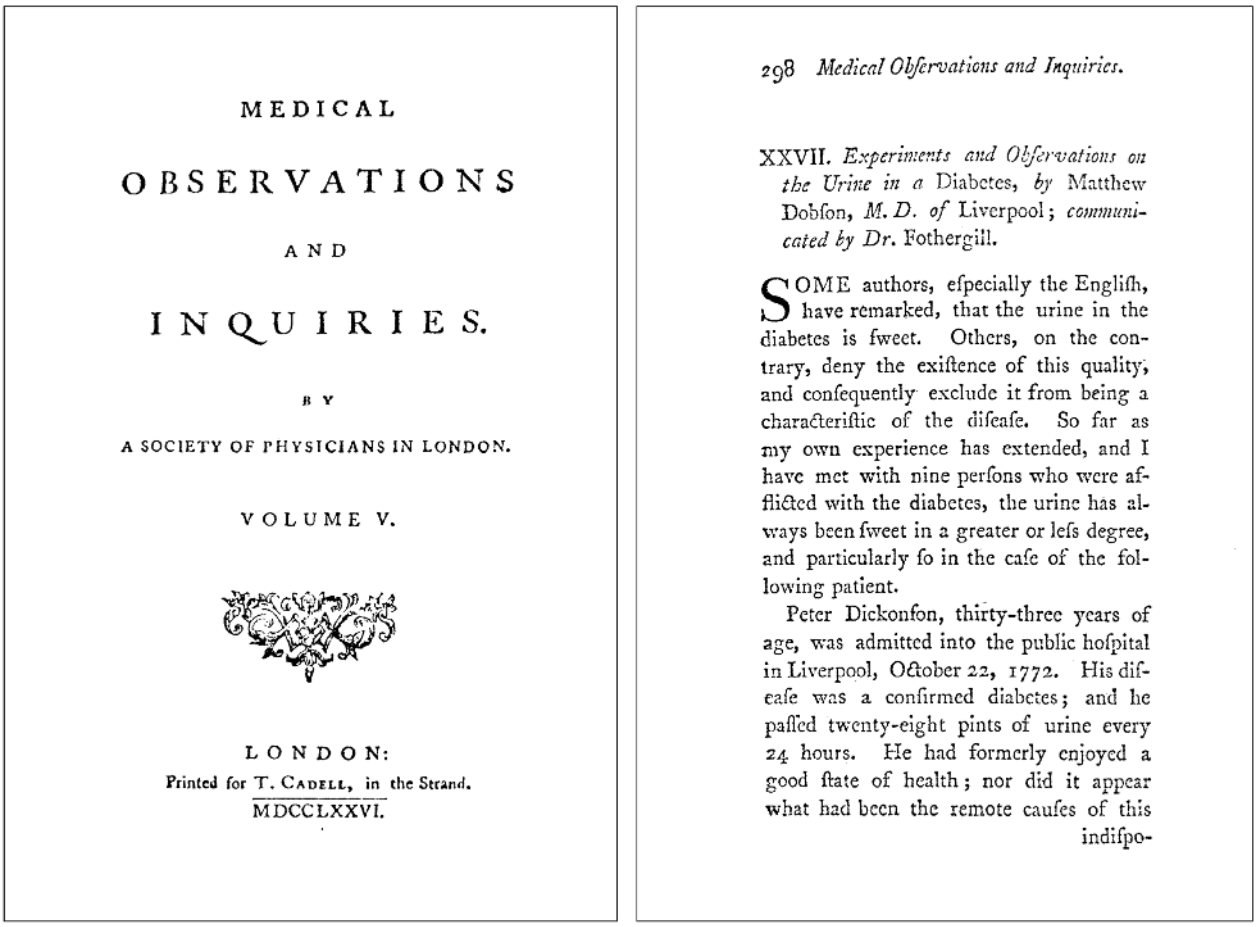
The Edinburgh-trained surgeon, John Rollo (*d.* 1809) was the first to apply the adjective *mellitus* (from the Latin word meaning *honey*). He also achieved fame with his *animal diet*, which became the standard treatment for most of the nineteenth century.

(a)

Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive, and disproportionate to the large quantity of urine, for yet more urine is passed. One cannot stop them either from drinking or making water. If for a while they abstain from drinking, their mouths become parched and their bodies dry; the viscera seem scorched up, the patients are affected by nausea, restlessness and a burning thirst, and within a short time, they expire.

(b)

Figure 1.2 (a) Clinical description of diabetes by Aretaeus of Cappadocia (second century CE). Source: Adapted from Papaspyros, N.S. (1952) *The History of Diabetes Mellitus*. (b) Sushrut (Susrata), an Indian physician who wrote medical texts with Charak (Charuka) between 500 BCE and 400 BCE.



MEDICAL

OBSERVATIONS

AND

INQUIRIES.

BY

A SOCIETY OF PHYSICIANS IN LONDON.

VOLUME V.

LONDON:
Printed for T. CADELL, in the Strand.
MDCCLXXVI.

298 *Medical Observations and Inquiries.*

XXVII. *Experiments and Observations on the Urine in a* Diabetes, *by* Matthew Dobſon, *M. D. of* Liverpool; *communicated by Dr.* Fothergill.

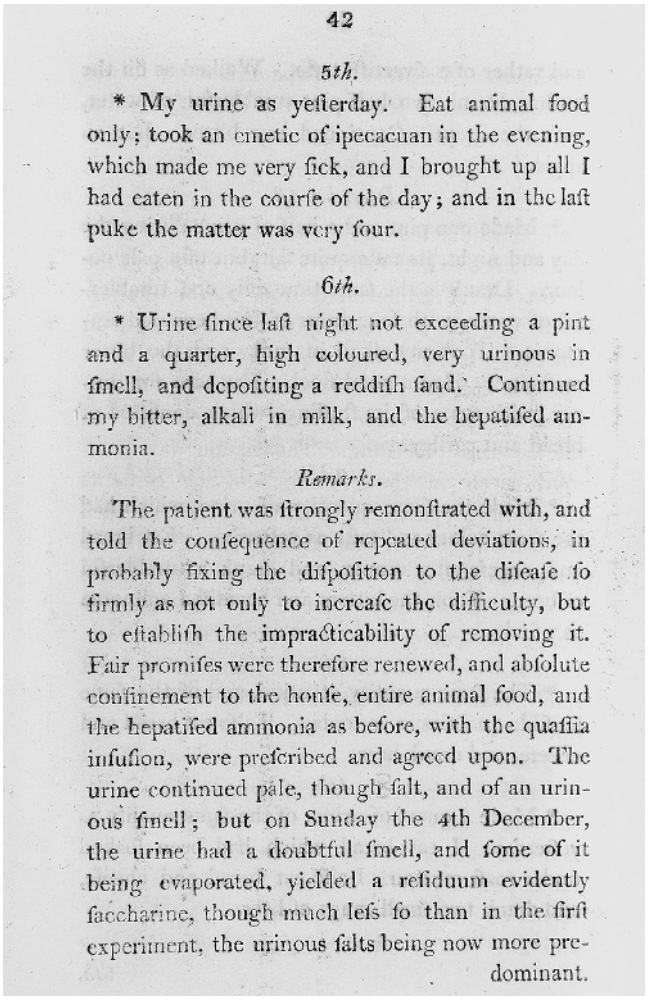
SOME authors, eſpecially the Engliſh, have remarked, that the urine in the diabetes is ſweet. Others, on the contrary, deny the exiſtence of this quality, and conſequently exclude it from being a characteriſtic of the diſeaſe. So far as my own experience has extended, and I have met with nine perſons who were afflicted with the diabetes, the urine has always been ſweet in a greater or leſs degree, and particularly ſo in the caſe of the following patient.

Peter Dickonſon, thirty-three years of age, was admitted into the public hoſpital in Liverpool, October 22, 1772. His diſeaſe was a confirmed diabetes; and he paſſed twenty-eight pints of urine every 24 hours. He had formerly enjoyed a good ſtate of health; nor did it appear what had been the remote cauſes of this indiſpo-

Figure 1.3 Frontispiece and opening page of the paper by Matthew Dobson (1776) in which he described the sweet taste of both urine and serum from a person with diabetes [2].

Table 1.2 Milestones in the scientific understanding of diabetes and its complications.

Matthew Dobson (England, 1776)	Diabetic serum contains sugar
Michel Chevreul (France, 1815)	The sugar in diabetic urine is glucose
Claude Bernard (France, 1850s)	Glucose stored in liver glycogen and secreted during fasting
Wilhelm Petters (Germany, 1857)	Diabetic urine contains acetone
Paul Langerhans (Germany, 1869)	Pancreatic islets described
Adolf Kussmaul (Germany, 1874)	Describes ketoacidosis
Oskar Minkowski and Josef von Mering (Germany, 1889)	Pancreatectomy causes diabetes in the dog
Gustave Edouard Laguesse (France, 1893)	Glucose-lowering pancreatic secretion produced by islets
M.A. Lane (USA, 1907)	Distinguished A and B islet cells
Jean de Meyer (Belgium, 1909)	Hypothetical islet secretion named *insuline*
Frederick Banting, Charles Best, J.J.R. Macleod, James Collip (Canada, 1922)	Isolation of insulin
Richard Murlin (USA, 1923)	Discovered and named glucagon
Bernado Houssay (Argentina, 1924)	Hypophysectomy enhances insulin sensitivity
Frederick Sanger (England, 1955)	Determined primary sequence of insulin
W.W. Bromer (USA, 1956)	Determined primary sequence of glucagon
Rosalyn Yalow and Solomon Berson (USA, 1959)	Invented radioimmunoassay for insulin
Donald Steiner (USA, 1967)	Discovered proinsulin
Dorothy Hodgkin (England, 1969)	Determined three-dimensional structure of insulin
Pierre Freychet (USA, 1971)	Characterized insulin receptors
Pedro Cuatrecasas (USA, 1972)	Isolated insulin receptor protein
Axel Ullrich (USA, 1977)	Reported sequence of rat insulin
Ralph DeFronzo and Reuben Andres (USA, 1979)	Invented insulin clamp technique
Graham Bell (USA, 1980)	Reported sequence of human insulin gene
Joel Habener (USA), Jens Juel Holst (Denmark) (1986)	Determined primary sequence of glucagon-like peptide 1 (GLP-1)



42

5*th*.

* My urine as yeſterday. Eat animal food only; took an emetic of ipecacuan in the evening, which made me very ſick, and I brought up all I had eaten in the courſe of the day; and in the laſt puke the matter was very ſour.

6*th*.

* Urine ſince laſt night not exceeding a pint and a quarter, high coloured, very urinous in ſmell, and depoſiting a reddiſh ſand. Continued my bitter, alkali in milk, and the hepatiſed ammonia.

Remarks.

The patient was ſtrongly remonſtrated with, and told the conſequence of repeated deviations, in probably fixing the diſpoſition to the diſeaſe ſo firmly as not only to increaſe the difficulty, but to eſtabliſh the impracticability of removing it. Fair promiſes were therefore renewed, and abſolute confinement to the houſe, entire animal food, and the hepatiſed ammonia as before, with the quaſſia infuſion, were preſcribed and agreed upon. The urine continued pale, though ſalt, and of an urinous ſmell; but on Sunday the 4th December, the urine had a doubtful ſmell, and ſome of it being evaporated, yielded a reſiduum evidently ſaccharine, though much leſs ſo than in the firſt experiment, the urinous ſalts being now more predominant.

Figure 1.4 Extract from John Rollo's account of two cases of diabetes (1797). Rollo was well aware of the problem of not following a treatment regimen. Note that 'the patient was strongly remonstrated with, and told of the consequences of repeated deviations'. Source: Courtesy of the Wellcome Library, London.

Rollo thought that sugar was formed in the stomach from vegetables and concluded that the obvious solution was a diet of animal food. Thus, the regimen described in his 1797 book, *An Account of Two Cases of the Diabetes Mellitus* [3], allowed his patient Captain Meredith to have for 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'. Rollo was probably the first to note the difficulty that some people with diabetes find in following a treatment regimen, a difficulty he blamed for the death of his second patient (Figure 1.4).

Nineteenth century

In 1815, the French chemist Michel Chevreul (1786–1889) proved that the sugar in diabetic urine was glucose [4]. In the middle of the century, tasting the urine to make the diagnosis was superseded by chemical tests for reducing agents such as glucose, as introduced by Trommer in 1841, Moore in 1844, and – the best known – Fehling in 1848. Measurement of blood glucose could only be done by skilled chemists, but needed so much blood that it was rarely used in either clinical care or research. It only became practicable with the introduction in 1913 of a micromethod by the Norwegian-born physician Ivar Christian Bang (1869–1918), and it was the ability to measure glucose repeatedly that led to development of the glucose tolerance test between 1913 and 1915.

Glucose metabolism was clarified by the work of Claude Bernard (1813–1878) [5], the Frenchman whose numerous discoveries have given him a special place in the history of physiology (Figure 1.5). When Bernard began work in 1843, the prevailing theory was that sugar could only be synthesized by plants, and that animal metabolism broke down substances originally made in plants. It was also thought that the blood only contained sugar after meals, or in pathological states such as diabetes. Between 1846 and 1848, Bernard reported that glucose was present in the blood of normal animals, even when starved. He also found higher concentrations of glucose in the hepatic than in the portal vein, and 'enormous quantities' of a starch-like substance in the liver that could be readily converted into sugar. He called this *glycogen* (i.e. sugar-forming) and regarded it as analogous to starch in plants. His hypothesis – the *glycogenic* theory – was that sugar absorbed from the intestine was

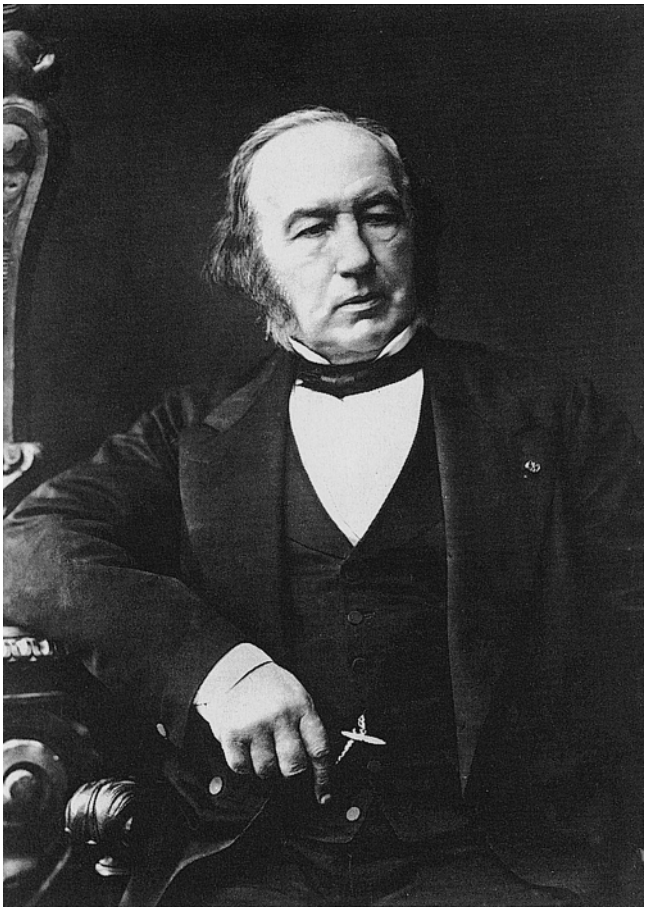


Figure 1.5 Claude Bernard (1813–1878). Source: Courtesy of the Wellcome Library, London.

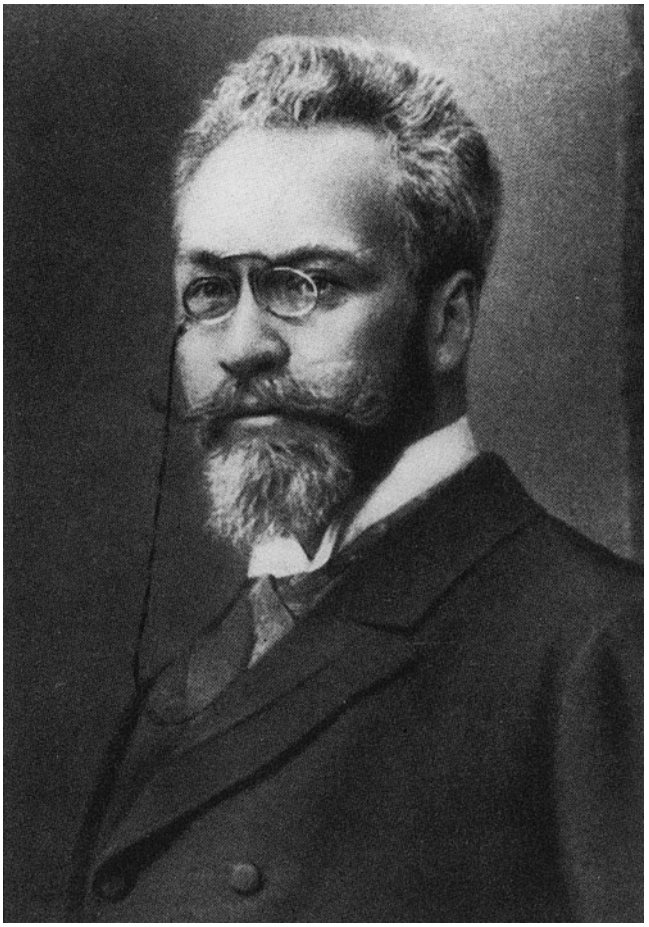


Figure 1.6 Oskar Minkowski (1858–1931).

converted in the liver into glycogen and then constantly released into the blood during fasting.

Another discovery by Bernard made a great impression in an era when the nervous control of bodily functions was a scientifically fashionable concept. He found that a lesion in the floor of the fourth ventricle produced temporary hyperglycaemia (*piqûre* diabetes) [6]. This finding spawned a long period in which nervous influences were thought to be important causes of diabetes; indeed, one piece of 'evidence' – cited by J.J.R. Macleod as late as 1914 – was that diabetes was more common among engine drivers than other railway workers because of the mental strain involved [7].

In the first part of the nineteenth century the cause of diabetes was a mystery, because autopsy usually did not show any specific lesions. A breakthrough came in 1889 when Oskar Minkowski (Figure 1.6) and Josef von Mering (1849–1908) reported that pancreatectomy in the dog caused severe diabetes [8]. This was serendipitous, because they were investigating fat metabolism; it is said that the laboratory technician mentioned to Minkowski that the dog, previously house-trained, was now incontinent of urine. Minkowski realized the significance of the polyuria, and tested the dog's urine (Table 1.3).

Possible explanations for the role of the pancreas were that it removed a diabetogenic toxin, or produced an internal secretion that regulated carbohydrate metabolism. The concept of *internal*

Table 1.3 Milestones in the understanding of the causes of diabetes.

Thomas Willis (England, seventeenth century)	Overindulgence in food and drink
Thomas Cawley (England, 1788)	Pancreatic stones cause diabetes
Oskar Minkowski and Josef von Mering (Germany, 1889)	Pancreatectomy causes diabetes in the dog
Etienne Lancereaux (France, 1880)	Lean and obese subtypes of diabetes distinguished
Eugene Opie (USA, 1900)	Hyaline degeneration (amyloidosis) of islets (type 2 diabetes)
Eugene Opie (USA, 1910)	Lymphocytic infiltration of islets (*insulitis*; type 1 diabetes)
Wilhelm Falta (Vienna) and Harold Himsworth (England, early 1930s)	Distinguished insulin-resistant and insulin-sensitive forms of diabetes
Willy Gepts (Belgium, 1965)	Suggested that insulitis caused β-cell destruction (type 1 diabetes)
Deborah Doniach and GianFranco Bottazzo (England, 1979)	Suggested that insulin-dependent diabetes is an autoimmune disease
Andrew Cudworth and John Woodrow (England, 1975)	Insulin-dependent diabetes associated with specific human leucocyte antigens

Figure 1.7 Paul Langerhans (1847–1888). Source: Courtesy of the Wellcome Library, London.

secretions had been publicized in June 1889 by the well-known physiologist Charles-Édouard Brown-Séquard (1817–1894), who claimed to have rejuvenated himself by injections of testicular extract [9]. It was given further credence in 1891, when Murray reported that myxoedema could be cured by sheep thyroid extract by injection or orally.

In 1893, Gustave Laguesse suggested that the putative internal secretion of the pancreas was produced by the *islands* of cells scattered through the gland's parenchyma [10], which had been discovered in 1869 by the 22-year-old Paul Langerhans (1847–1888) (Figure 1.7). Langerhans had described these clusters of cells, having teased them out from the general pancreatic tissue, but had not speculated about their possible function [11]; it was Laguesse who named them the *islets of Langerhans*. At this time the glucose-lowering internal secretion of the islets was still hypothetical, but in 1909 the Belgian Jean de Meyer named it *insuline* (from the Latin for *island*) [12].

It would be wrong to give the impression that Minkowski's experiments immediately established the pancreatic origin of diabetes. In fact, during the next two decades it was widely agreed that diabetes was a heterogeneous disorder with various subtypes, and that its pathogenesis involved at least three organs: brain, pancreas, and liver [13]. The discovery by Blum in 1901 that injection of an adrenal extract caused glycosuria implicated other glands, and led to the *polyglandular theory* of Carl von Noorden (Vienna), who proposed that the thyroid, pancreas, adrenals, and parathyroids controlled carbohydrate metabolism.

Clinical diabetes in the nineteenth century

Doctors in the nineteenth century were therapeutically impotent; their main role was as taxonomists who described symptom complexes and the natural history of disease. As a result, most of the major complications of diabetes were well described before 1900. Eduard von Jaeger (1818–1884) is credited with the first description of diabetic retinopathy, in his beautiful *Atlas of Diseases of the Ocular Fundus*, published in 1869 [14]. In fact, the features illustrated (Figure 1.8), from a 22-year-old man, look more like hypertensive retinopathy. In 1879, Stephen Mackenzie (1844–1909) and Sir Edward Nettleship (1845–1913) found microaneurysms in flat preparations of the retina and, in 1888, Nettleship described new vessels and the beaded appearance of retinal veins [15]. The full picture of diabetic retinopathy was described in 1890 by Julius Hirschberg (1843–1925), who was the first to claim that it was specific to diabetes [16].

Neuropathic symptoms in people with diabetes had been mentioned by Rollo at the end of the eighteenth century, and in 1864 Charles Marchal de Calvi (1815–1873) concluded that nerve damage was a specific complication of diabetes. In 1885, the Guy's Hospital physician Frederick Pavy (1829–1911) gave a description of neuropathic symptoms that could grace any modern textbook [17]:

> *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 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.*

Pavy also recorded unusual presentations, including a 67-year-old who complained of 'lightning pains on the right side of the waist' and cases in which the third nerve was affected with 'dropped lid and external squint' [18].

Kidney disease was known to be relatively common in diabetes. In 1859, Wilhelm Griesinger (1817–1868) reported 64 autopsies in adults, half of whom had renal changes that he attributed to hypertension and atherosclerosis [19]; however, the histological features of diabetic kidney disease and the importance of renal complications were not reported until the 1930s.

In the latter part of the nineteenth century it was becoming apparent that there were at least two clinically distinct forms of diabetes. In 1880, the French physician Etienne Lancereaux (1829–1910) identified individuals who were lean and those with obesity as having *diabète maigre* and *diabète gras*, respectively [20], and this observation laid the foundations for subsequent aetiological classifications of the disease.

Twentieth century

Murray's cure of myxoedema in 1891 led to a belief that pancreatic extract would soon result in a cure for diabetes, but, in the face of repeated failures over the next 30 years, even believers in an anti-diabetes internal secretion were depressed about the likelihood of isolating it, and diverted their attention to diet as a treatment for the disease.

Best known was the starvation regimen of Frederick Madison Allen (1876–1964), which Joslin (Figure 1.9) described in 1915 as the greatest advance since Rollo's time [22]. This approach was an

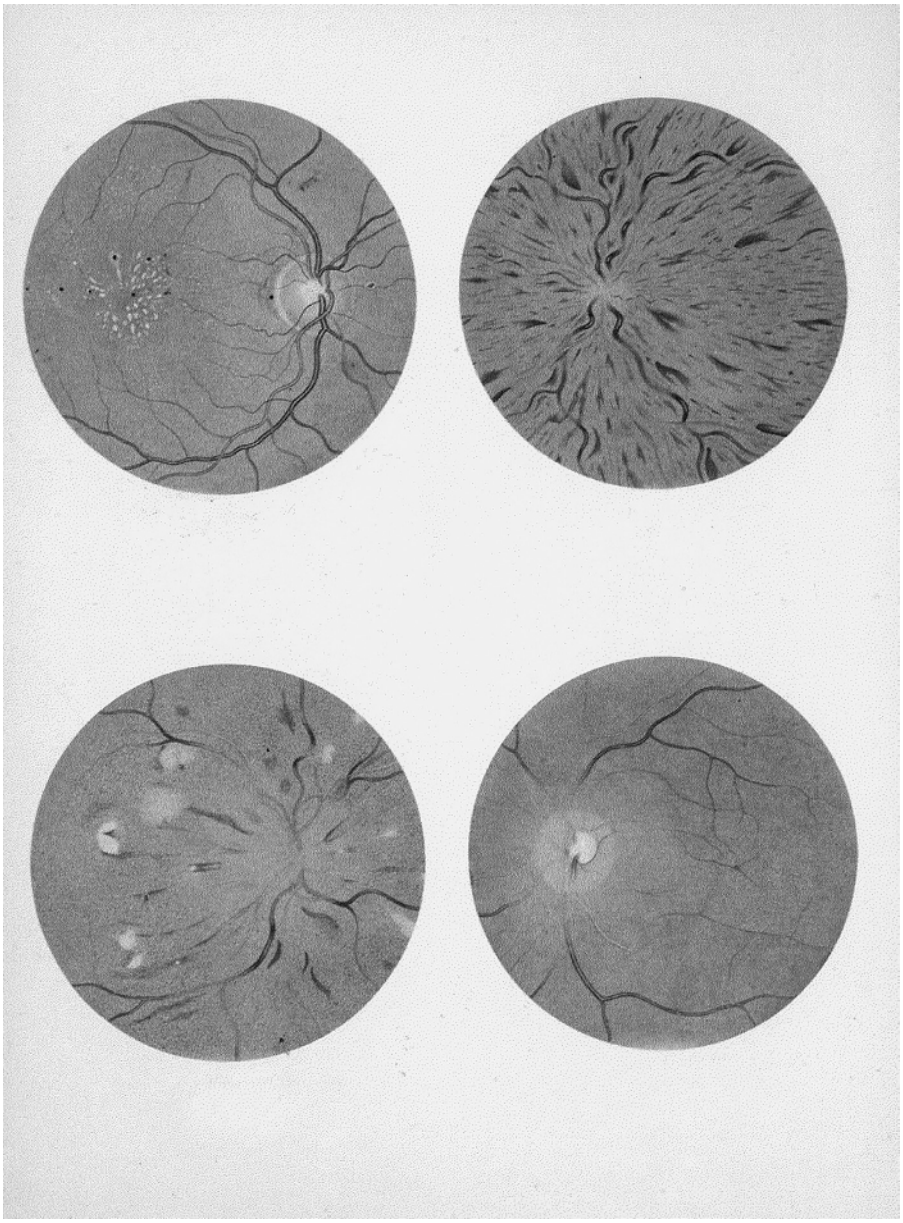


Figure 1.8 Pictures from *Jaeger's Atlas of the Optic Fundus*, 1869 [14]. Top left: Bright's disease. Top right: Jaeger's retinitis haemorrhagica is now recognized as central retinal vein occlusion. Bottom left: A 22-year-old man with suspected diabetes. Bottom right: Central retinal artery occlusion. Source: Courtesy of W.B. Saunders.

extreme application of one that had been proposed as early as 1875 by Apollinaire Bouchardat (1806–1886), who advocated intensive exercise and '*manger le moins possible*'. Starvation treatment did work in a limited sense, in that some people could survive for many months or even years, instead of a few weeks or months with untreated type 1 diabetes. The quality of life, however, was very poor, and some died of malnutrition rather than diabetes. In 1921, Carl von Noorden (1858–1944), proponent of the *oatmeal cure,* turned away in disapproval when he saw Joslin's prize patient, 17-year-old Ruth A, who at just over 1.52 m in height weighed only 24.5 kg (a body mass index of 10.6 kg/m^2).

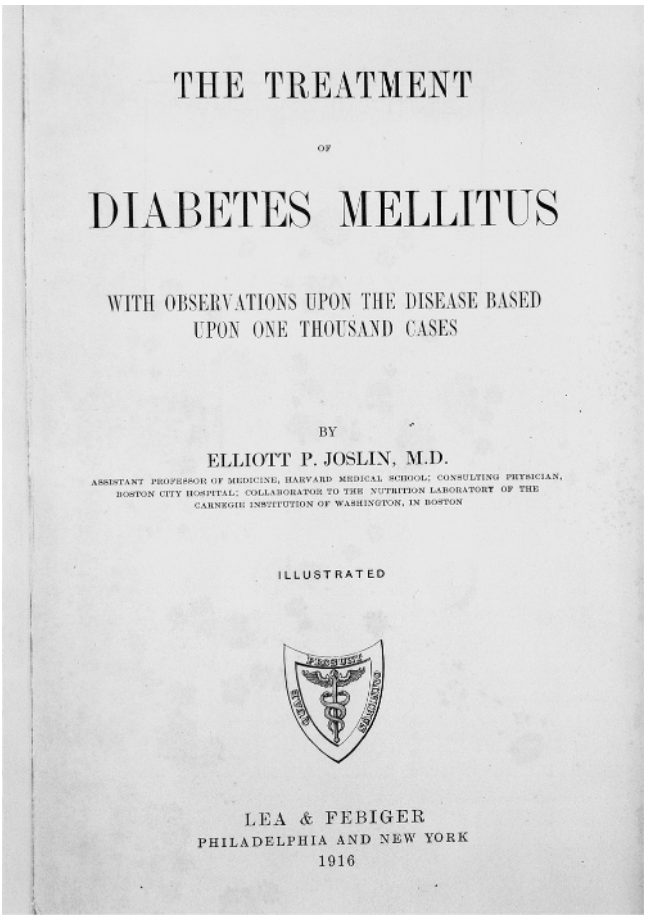
Discovery of insulin

Many attempts were made between 1889 and 1921 to isolate the elusive internal secretion of the pancreas. These largely failed because the extracts were inactive or had unacceptable side effects; some preparations may have had limited biological activity, but this was not recognized, either because hypoglycaemia was misinterpreted as a toxic reaction or because blood glucose was not measured. Those who came closest were the Berlin physician Georg Zuelzer (1840–1949) in 1907 [23], Ernest Scott (1877–1966) in Chicago in 1911 [24], and Nicolas Paulesco (1869–1931) in Romania in 1920–1921 [25] (Figure 1.10).

The story of how insulin was discovered in Toronto in 1921 is well known, at least superficially (Figure 1.11). A young orthopaedic surgeon, Frederick Banting, inspired after reading an article by the pathologist Moses Barron (1884–1975), wondered whether the anti-diabetes pancreatic principle was digested by trypsin during extraction, and decided to prevent this loss by ligating the pancreatic duct, thus causing the exocrine tissue to degenerate. He approached the professor of physiology in Toronto, J.J.R. Macleod, an authority on carbohydrate metabolism, who poured scorn on the idea and suggested that the only likely outcome would be 'a negative result of great physiological importance'.

(a)

(b)



THE TREATMENT

OF

DIABETES MELLITUS

WITH OBSERVATIONS UPON THE DISEASE BASED UPON ONE THOUSAND CASES

BY

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ILLUSTRATED

LEA & FEBIGER

PHILADELPHIA AND NEW YORK

1916

Figure 1.9 (a) Elliott P. Joslin (1869–1962), arguably the most famous diabetes specialist of the twentieth century, and (b) the frontispiece to his 1916 textbook [21]. Source: Courtesy of the Wellcome Library, London.

Eventually, Macleod relented and installed Banting in a rundown laboratory, later leaving for Scotland and a fishing holiday. A student, Charles Best, was chosen by the toss of a coin to help Banting. Within six months of this unpromising start, Banting and Best (referred to in Toronto academic circles as B^2) had discovered the most important new therapy since the anti-syphilitic agent salvarsan. These events are described in detail in the excellent book by Michael Bliss [26].

Their approach began with the injection of extracts of atrophied pancreas (prepared according to Macleod's suggestions) into dogs rendered diabetic by pancreatectomy. Subsequently, they discovered that active extracts could be obtained from beef pancreas, which Best obtained from the abattoir. The extraction procedure (using ice-cold acid-ethanol) was greatly refined by James B. (Bert) Collip, a biochemist who was visiting Toronto on sabbatical leave.

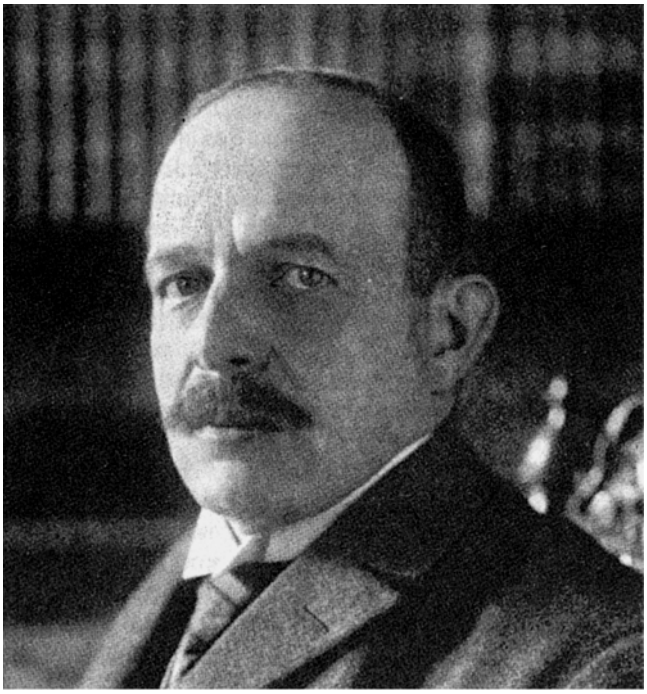
The first clinical trial of insulin (using an extract made by Best) took place on 11 January 1922, on 14-year-old Leonard Thompson, who had been on the Allen starvation regimen since 1919 and weighed only 30 kg (Figure 1.12). After the first injection, his blood glucose level fell slightly, but his symptoms were unchanged and he developed a sterile abscess. On 23 January, he was given another extract prepared by Collip, and this normalized his blood glucose by the next morning; further injections over the next 10 days led to marked clinical improvement and complete elimination of glycosuria and ketonuria. Initial clinical results in seven cases were published in the March 1922 issue of the *Canadian Medical Association Journal* [27], which had the following dramatic conclusions:

- Blood sugar can be markedly reduced, even to normal values.
- Glycosuria can be abolished.
- The acetone bodies can be made to disappear from the urine.
- The respiratory quotient shows evidence of increased utilization of carbohydrates.
- A definite improvement is observed in the general condition of these patients and, in addition, the patients themselves report a subjective sense of well-being and increased vigour for a period following the administration of these preparations.

The term *insulin* was coined by Macleod, who was unaware of de Meyer's earlier suggestion of *insuline*. News of its miraculous effects spread astonishingly rapidly [28]. In 1922, there were only 19 references in the world literature to *insulin* or equivalent terms such as *pancreatic extract*; by the end of 1923, there were 320 new reports, and a further 317 were published during the first six months of 1924.

By October 1923, insulin was available widely throughout North America and Europe. International recognition followed rapidly for its discoverers, and the 1923 Nobel Prize for Physiology or Medicine was awarded jointly to Banting and Macleod. Banting

(a)



(b)

Experimentelle Untersuchungen über den Diabetes.[1])

Kurze Mitteilung.[2])

Von

G. Zuelzer.

F. Blum hat vor einigen Jahren gezeigt, dass subkutane oder intravenöse Injektion von Nebennierensaft bei den verschiedensten Tieren Glykosurie hervorruft, die 48 bis 74 Stunden anhalten kann. Ich, und kurze Zeit darauf Metzger wiesen nach, dass gleichzeitig eine Hyperglykämie besteht, dass es sich beim Nebennierendiabetes also nicht etwa um ein Analogon des Phloridzindiabetes, um einen sogenannten Nierendiabetes handeln könne. Während ich mich dahin aussprach, dass dieser Diabetes seiner ganzen Natur nach dem richtigen Diabetes ähnele, nur durch die Dauer seines Bestehens von ihm unterschieden sei und naturgemäss auch keine Tendenz zum Fortschreiten zeigen, i. e. niemals das Endstadium des gewöhnlichen schweren menschlichen Diabetes darbieten könne, wurde die in Frage stehende Glykosurie von den meisten anderen Autoren als eine ziemlich belanglose toxische Glykosurie aufgefasst.

Es schien mir nicht sehr wahrscheinlich, dass ein Körper, der anscheinend unverändert, wie er normalerweise produziert und dauernd[3]) dem Säftestrom des Organismus zugeführt wird, dass ein solcher, quasi physiologischer Körper eine vollkommen unphysiologische Wirkung sollte hervorbringen können. Ich habe also versucht, den Ort des Angriffs des Nebennierensaftes[4]), sowie die Ursachen seiner toxischen Wirkung näher zu erforschen. Ich folgte dabei, wie gesagt, stets dem Gedanken, in dem Nebennierendiabetes ein, wenn auch nur flüchtiges Bild gewisser menschlicher Diabetesformen zu finden.

So untersuchte ich zuerst, welchen Einfluss hat der Nebennierensaft auf die Leber als dasjenige Organ, welches, allgemein ausgedrückt, mit der Zuckerregulierung im Körper in erster

1) Die Untersuchungen wurden zum Teil mit Unterstützung der Gräfin Bose-Stiftung im physiologischen Institut der Berliner Universität, und zwar noch unter Mithilfe der verstorbenen Proff. I. Munk und Paul Schultz ausgeführt.

2) Diese kurze Mitteilung wurde der Redaktion bereits vor ca. 3 Jahren eingereicht. Die Drucklegung unterblieb auf Wunsch des Verf. in der bisher nicht erfüllten Erwartung, dass es gelingen würde, aus den theoretischen Untersuchungen praktisch-therapeutische Resultate zu erzielen.

3) Durch Versuche von Ehrmann, Archiv f. experim. Pathol. u. Pharmakol., Bd. 55, ist inzwischen der Nachweis erbracht worden, dass die Adrenalinsekretion konstant vor sich geht.

4) In meinen ersten Versuchen bediente ich mich des von mir selbst hergestellten Nebennierensaftes. In den zahlreichen späteren Versuchen habe ich inzwischen genau die gleichen Wirkungen mit den verschiedenartig hergestellten käuflichen Adrenalinpräparaten feststellen können.

(c)

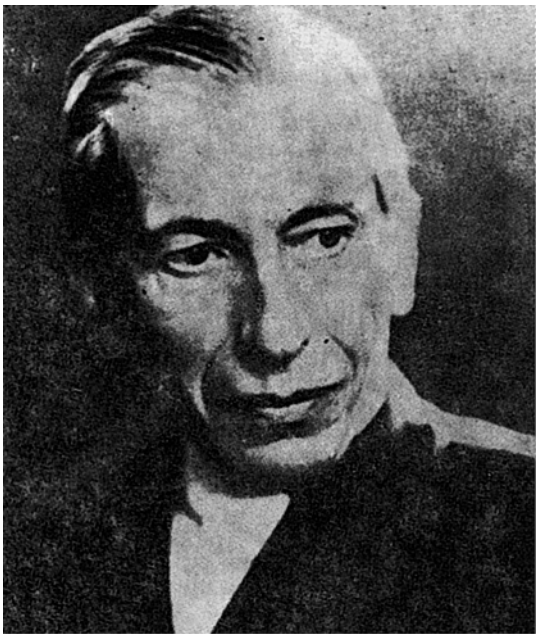


Figure 1.10 (a) Georg Zuelzer (1840–1949) and (b) the title page from his paper (1907) reporting that a pancreatic extract reduced glycosuria in pancreatectomized dogs [23]. (c) Nicolas Paulesco (1869–1931).

was angered by the decision, and announced publicly that he would share his prize with Best, whereupon Macleod decided to do the same with Collip.

The post-insulin era

It was confidently anticipated that insulin would do for diabetes in the young what thyroid extract had done for myxoedema, but it soon became obvious that insulin was a very different type of treatment. Thyroid was given once a day by mouth and at a fixed dosage. Insulin had to be injected in measured amounts that varied from day to day, and carried the ever-present danger of hypoglycaemia. One often reads that insulin 'revolutionized' the treatment of diabetes; it did so in the sense that it saved the lives of many who would otherwise have died, but its unforeseen effect was to transform an acute, rapidly fatal illness into a chronic disease with serious long-term complications. For example, only 2% of deaths among Joslin's young patients with diabetes before 1937 were caused by kidney disease, while over 50% dying between 1944 and

Figure 1.11 The discoverers of insulin. (a) Frederick G. Banting (1891–1941); (b) James B. Collip (1892–1965); (c) J.J.R. Macleod (1876–1935); and (d) Charles H. Best (1899–1978). Source: Courtesy of the Fisher Rare Book Library, University of Toronto.

Figure 1.12 Leonard Thompson, the first person to receive insulin, in January 1922. Source: Courtesy of the Fisher Rare Book Library, University of Toronto.

1950 had advanced renal failure. Strategies to avoid and prevent the chronic complications of diabetes remain important scientific and clinical priorities today.

The rest of this chapter highlights some developments that can be regarded as landmarks in the understanding and management of the disease; to some extent this is a personal choice, and it is obvious from the other chapters in this book that the *history* of diabetes is being rewritten all the time.

Causes and natural history of diabetes

The recognition that diabetes was not a single disease was important in initiating research that has helped to unravel the causes of hyperglycaemia.

The broad aetiological subdivision into type 1 (juvenile-onset, or insulin-dependent) diabetes and type 2 diabetes (maturity-onset, or non-insulin-dependent) stemmed ultimately from Lancereaux's *diabète maigre* and *diabète gras* distinction, as well as observations soon after the discovery of insulin that some individuals did not react *normally* to insulin. In the 1930s, Wilhelm Falta (1875–1950) in Vienna [29] and Harold Himsworth (1905–1993) in London [30] proposed that some individuals with diabetes were more sensitive to the glucose-lowering effects of insulin, whereas others were

insulin insensitive, or insulin resistant. The former were usually thin and required insulin to prevent ketoacidosis, while the latter were older, had obesity, and were ketosis resistant.

The *insulin clamp* technique developed in the 1970s by Ralph DeFronzo and colleagues [31] in the USA was the first to measure rigorously the hypoglycaemic action of insulin, and has led to countless studies of insulin resistance and its relationship to type 2 diabetes and vascular disease. Various groups, including DeFronzo's, have helped to clarify the role of β-cell failure in type 2 diabetes, and how it relates to insulin resistance. Maturity-onset diabetes of the young (MODY) was recognized in 1974 by Robert Tattersall (1943–2020) as a distinct, dominantly inherited subset of type 2 diabetes [32]; since 1993 many different molecular defects have been identified in this condition.

The causes of the profound β-cell loss that led to the severe insulin deficiency of type 1 diabetes remained a mystery for a long time. *Insulitis*, predominantly lymphocytic infiltration of the islets, was noted as early as 1901 by Eugene L. Opie (1873–1971) and colleagues [33], but because it was apparently very rare, found in only 6 of 189 cases studied by Anton Weichselbaum (1845–1920) in 1910, its importance was not appreciated. The possible role of insulitis in β-cell destruction was not suggested until 1965, by the Belgian Willy Gepts (1922–1991) [34]. The theory that type 1 diabetes results from autoimmune destruction of the β cells was first made in 1979 by Deborah Doniach (1912–2004) and GianFranco Bottazzo (1946–2017) [35]. Unlike other autoimmune endocrine diseases where the autoantibody persists, islet cell antibodies turned out to be transient and disappeared within a year of the onset of diabetes. An unexpected finding from the Barts–Windsor prospective study of the epidemiology of diabetes in childhood started by Andrew Cudworth (1939–1982) was that islet cell antibodies could be detected in siblings of young people with diabetes up to 10 years before they developed apparently acute-onset diabetes. This long lead-in period raised the possibility of an intervention to prevent continuing β-cell destruction. Cyclosporine in people with newly diagnosed type 1 diabetes prolonged the honeymoon period, but without permanent benefit once the drug was stopped [36]. Nicotinamide and small doses of insulin (together with many other interventions) prevented diabetes in the non-obese diabetic (NOD) mouse, but were without effect in relatives of people with type 1 diabetes with high titres of islet cell antibodies [37, 38].

From 1967, when Paul Lacy (1924–2005) showed that it was possible to *cure* diabetes in inbred rats with an islet cell transplant, it always seemed that the problem of islet cell transplantation in humans was about to be solved. Hope was rekindled in 2000 by a team in Edmonton, Canada. After five years 80% of those who had received a transplant were producing some endogenous insulin, but only 10% could manage without any injected insulin [39].

Chronic diabetic complications

It had been assumed that arteriosclerosis caused chronic diabetic complications, but this notion was challenged by two papers published in the mid-1930s, which pointed to specific associations of diabetes with retinal and renal disease (Table 1.2). In 1934, Henry Wagener (1890–1961) and Russell Wilder (1885–1959) from the Mayo Clinic reported people who had retinal haemorrhages but no other clinical evidence of vascular disease [40], and concluded that 'The very existence of retinitis in cases in which patients have no other signs of vascular disease must mean that diabetes alone does something to injure the finer arterioles or venules of the retina, probably the latter'.

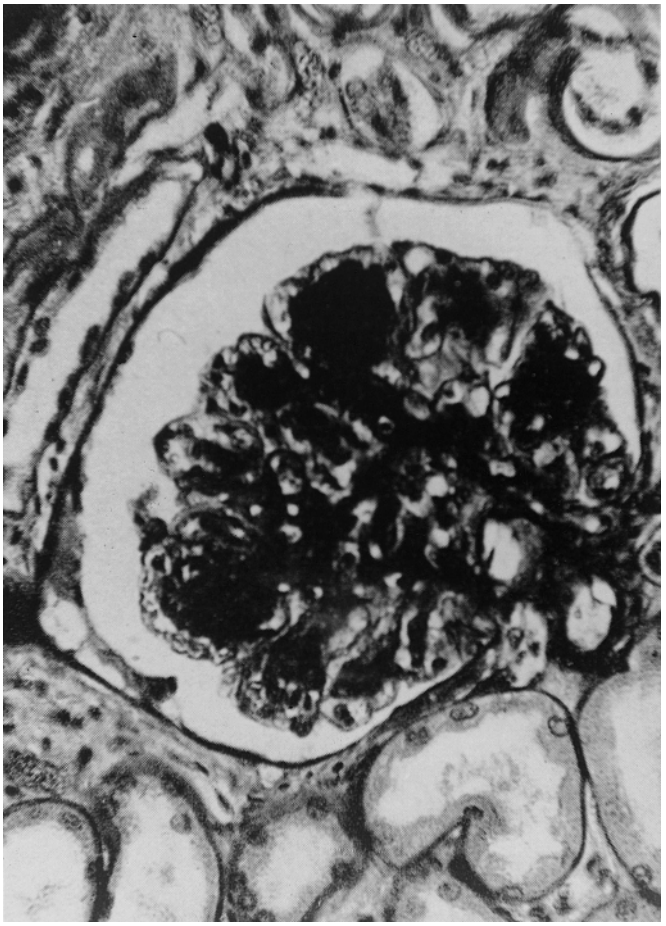


Figure 1.13 Nodular glomerulosclerosis. Figure from the paper by Kimmelstiel and Wilson, 1936 [41]. Source: Courtesy of the British Medical Association Library.

In 1936, Paul Kimmelstiel (1900–1970) and Clifford Wilson (1906–1997) described the striking histological finding of *intercapillary glomerulosclerosis,* large hyaline nodules in the glomeruli in the kidneys of eight people at autopsy (Figure 1.13) [41]. Seven of the eight individuals had a known history of diabetes, and Kimmelstiel and Wilson noted the common features of hypertension, heavy albuminuria with 'oedema of the nephrotic type', and renal failure. In fact, this paper led to considerable confusion during the next 15 years: according to one writer, the *Kimmelstiel–Wilson syndrome* came to mean all things to all people [42]. Nonetheless, it was significant because it drew attention to a specific diabetic renal disease.

Acceptance of the concept that diabetic angiopathy was specific to the disease owed much to the work of Knud Lundbæk from Aarhus, Denmark (Figure 1.14), who published his findings in a book in 1953–1954 and a paper in the *Lancet* in 1954 [43, 44]. His key arguments were that long-standing diabetic vascular disease differed fundamentally from atherosclerosis, in that both sexes were equally affected, and that microaneurysms, ocular phlebopathy, and Kimmelstiel–Wilson nodules were unique to diabetes and usually occurred together.

The molecular and cellular mechanisms underlying diabetic tissue damage remain controversial after decades of intensive research.

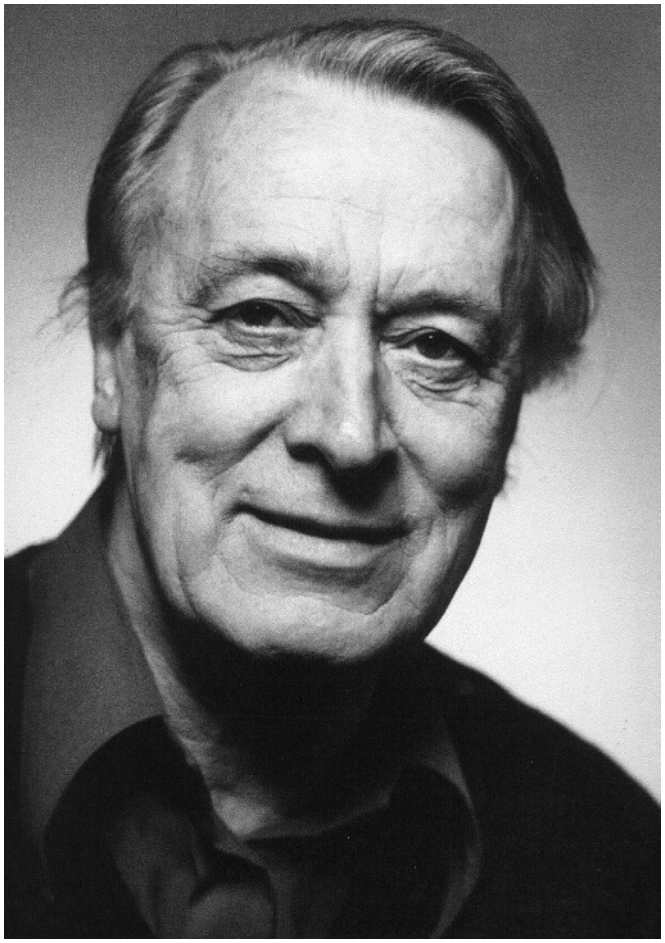


Figure 1.14 Knud Lundbæk (1912–1995). Source: Courtesy of Dr Carl Erik Mogensen.

One of the early landmarks in this field was the work of J.H. Kinoshita (*b.* 1922) during the early 1970s, which pointed to the involvement of the polyol pathway in the formation of diabetic cataracts [45].

Physiology

In 1907, M.A. Lane, a student of Robert Bensley (1867–1956), professor of anatomy in Chicago, used conventional histological techniques to distinguish two different cell types in the islet of Langerhans, which he termed A and B [46]. The hormones secreted by these respective cell types were not identified until much later (Table 1.2). Frank Young (1908–1988) and colleagues reported in 1938 that injections of anterior pituitary extract could induce permanent diabetes in the dog, and that this was accompanied by selective degranulation and loss of the β cells [47]; it was surmised that these cells produced insulin, and this was finally confirmed using immuno-histochemistry by Paul Lacy in 1959 [48]. Glucagon was similarly localized to the α cells in 1962 by John Baum and colleagues [49].

The amino acid sequence of insulin was reported in 1955 by Frederick Sanger in Cambridge, UK [50], and the three-dimensional structure of the molecule in 1969 by Dorothy Hodgkin in Oxford [51]; both discoveries were recognized by the award of Nobel Prizes (Figure 1.15). The complete insulin molecule was synthesized from amino acids by Wang Ying-lai (1908–2001) and colleagues in Shanghai in 1965 [52]. The insulin precursor, proinsulin, was described in 1967 by Donald Steiner (1930–2014) in Chicago [53]. The first bioassay for insulin, based on the hormone's ability to lower blood glucose in the alloxan-diabetic rat, was reported in 1950 by the Australian Joseph Bornstein (1918–1994), working in London with Robin D. Lawrence [54]. This method was superseded in 1956 by Rosalyn Yalow and Solomon Berson in the

(a)

(b)

Figure 1.15 (a) Frederick Sanger (1918–2013) and (b) Dorothy Hodgkin, née Crowfoot (1910–1994). Source: Courtesy of Godfrey Argent Studio, London.

Figure 1.16 Solomon Berson and Rosalyn Yalow.

USA, who discovered that insulin was antigenic; they exploited the binding of the hormone to anti-insulin antibodies to develop the first radioimmunoassay [55]. This assay method revolutionized endocrinology – and, indeed, many areas of physiology and medicine – and was also rewarded with a Nobel Prize (Figure 1.16).

The sequence of rat insulin genes was described in 1977 by Axel Ullrich (*b*. 1945) and colleagues [56], and the human sequence by Graham Bell (*b*. 1948) and his group in 1980 [57]. The existence of insulin receptors was inferred from the insulin-binding characteristics of liver-cell membranes by Pierre Freychet (*b*. 1935) and colleagues in 1971 [58], and the receptor protein was isolated by Pedro Cuatrecasas (*b*. 1936) in the following year [59]. The gene encoding the insulin receptor was cloned and sequenced in 1985 by two groups [60, 61]. In recent years, numerous advances have helped to clarify how insulin exerts its biological actions. Among these was the discovery in 1985 of the first of the glucose transporter (GLUT) proteins by Mueckler and colleagues in the USA [62].

Management of diabetes

An objective observer surveying clinical diabetes during the half-century after the discovery of insulin and the 'resurrection' (a word used by Joslin) of young people with diabetes would have been dismayed by what they saw (Table 1.4). In particular, young people were dying of complications that had previously been assumed to be the preserve of older people. Two particularly depressing papers were published in 1947 and 1950. First, Henry Dolger (1909–1997) in New York described 20 people who fulfilled the then-accepted criteria for excellent *diabetic control*, but who all developed severe retinopathy after 6–22 years [72]; among these was the first person ever to receive insulin at Mount Sinai Hospital, New York, who also had heavy albuminuria and hypertension by the age of 32. Second, Ruth Reuting reported a cohort of 50 young individuals with diabetes originally identified in 1929 [73]. By 1949, one-third had died (mostly from cardiovascular and renal disease) at an average age of 25 years, after only 18 years of diabetes, and the survivors showed 'ominous signs of hypertension, azotemia, and proteinuria in significant numbers'. This had occurred despite the introduction of more versatile insulin preparations; the situation was so hopeless that it inaugurated 20 years of treatment with 'heroic' measures such as adrenalectomy and hypophysectomy.

Table 1.4 Selected milestones in the management of diabetes.

Lifestyle modification	
Li Hsuan (China, seventh century)	Avoid wine, sex, and salty cereals
Thomas Willis (England, seventeenth century)	Food restriction
John Rollo (England, 1797)	Animal diet
Apollinaire Bouchardat (France, 1875)	Food restriction and increased exercise
Carl von Noorden (Germany, 1903)	Oatmeal cure
Frederick Allen (USA, 1913)	Starvation diet for early-onset diabetes
Karl Petrén (Sweden, 1915)	High-fat, low-carbohydrate diet
Roy Taylor (England, 2015) [63]	Very low-calorie diet – remission of diabetes
Insulin treatment	
Georg Zuelzer (Germany, 1907) and Nicolas Paulesco (Romania, 1921)	Isolated pancreatic extracts with hypoglycaemic activity
Frederick Banting, Charles Best, J.J.R. Macleod, and James Collip (Canada, 1922–1923)	Isolation and first clinical use of insulin
Hans Christian Hagedorn (Denmark, 1936)	Protamine insulin, the first long-acting insulin
David Goeddel (USA, 1979)	Synthetic human-sequence insulin produced by recombinant DNA technology
John Pickup (London, 1978)	Described continuous subcutaneous insulin infusion
John Ireland (Scotland, 1981)	Invented pen-injection device
Oral anti-diabetes agents	
Avicenna (Arabia, tenth century)	Recommended lupin, fenugreek, and zedoary seeds
Willhelm Ebstein (Germany, 1876)	Recommended sodium salicylate
E. Frank (Germany, 1926)	Biguanide derivative (Synthalin) introduced, but withdrawn because of toxicity
Celestino Ruiz (Argentina, 1930)	Noted hypoglycaemic action of some sulfonamides
Auguste Loubatières (France, 1942)	Discovered hypoglycaemic action of prototype sulfonylurea
H. Franke and J. Fuchs (Germany, 1955)	Carbutamide introduced
G. Ungar (USA, 1957)	Phenformin introduced
Parke-Davis (1997)	Troglitazone, first thiazolidinesione introduced
Eli Lilly (2005)	Exenatide, first GLP-1 receptor agonist introduced
MSD (2007)	Sitagliptin, first DPP-4 inhibitor introduced
Janssen (2013)	Canagliflozin, first SGLT2 inhibitors
Diabetic monitoring and treatment targets	
University Group Diabetes Program (USA, 1969)	First randomized trial in diabetes
Peter Sönksen and Robert Tattersall (1978)	Introduction of self-blood glucose monitoring
R. Flückiger and K.H. Winterhalter (Germany, 1975)	Showed that HbA_{1c} was glycated haemoglobin
World Health Organization (1991)	St. Vincent Declaration identified targets for diabetes care
James Scott; Exactech (England, 1991)	First direct electronic glucose testing [64]

(*continued*)

Table 1.4 (*Continued*)

Diabetes Control and Complications Trial (USA, 1993)	Proved that improved glycaemic management prevents and slows progression of microvascular complication in type 1 diabetes
UK Prospective Diabetes Study (UK, 1998)	Proved that improved glycaemic and blood pressure management improve microvascular and macrovascular outcomes in type 2 diabetes
Steno-2 study (Denmark, 1999)	Multiple risk factor interventions improve outcomes [65]
UK Prospective study 10-year follow-up (UK, 2008)	Early treatment legacy effects [66]
Complications	
Wilhelm Manz (Germany, 1876)	Described *Retinitis proliferans*
Gerd Meyer-Schwickerath (Germany, 1964)	First use of Xenon photocoagulation
University of Minnesota Team (USA, 1966)	First combined kidney–pancreas transplants
John A. Hartford Foundation (USA, 1968)	Argon laser therapy [67]
Carl Erik Mogensen and Hans-Henrik Parving (Denmark, 1980s)	Strict blood pressure controls slows progression of diabetic neuropathy
EMPA-REG trial (2015)	SGLT-2 inhibitors ameliorate heart failure and cardiovascular disease [68]
LEADER trial	GLP-1 receptor agonists ameliorate cardiovascular disease [69]
CREDENCE trial	SGLT-2 inhibitors ameliorate chronic kidney disease [70]
Surgical approaches	
SOS study (Sweden, 2013)	Demonstrated resolution of diabetes with gastric by-pass surgery [71]

DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT, sodium-dependent glucose cotransporters.

These and other studies raised questions about whether lowering blood glucose levels to normal could prevent diabetes-related complications or reverse them once they had appeared. The hypothesis remained untestable for four more decades, until the means to achieve optimal glycaemic levels and measure them had been devised.

Insulin

For the first decade after its discovery, insulin was available only in its soluble (regular) formulation, whose short-action profile required multiple daily injections. The first delayed-action preparation, protamine insulinate, was introduced in 1936 by Hans Christian Hagedorn at Steno Diabetes Center in Denmark (Figure 1.17) [74]. This was followed by protamine zinc insulin later the same year, then globin insulin in 1939, NPH (neutral protamine Hagedorn, or isophane) in 1946, and the lente series in 1952. Long-acting insulins were welcomed by diabetes specialists and people with diabetes, but their use as a single daily injection probably produced worse glycaemic levels than three or four

Figure 1.17 Hans Christian Hagedorn (1888–1971) from the Hagedorn Medal. Source: Courtesy of C. Binder, Steno Diabetes Center Copenhagen, Denmark.

injections of soluble insulin. Indeed, delayed-action preparations were initially condemned by some diabetes specialists, such as Russell Wilder of the Mayo Clinic, because the person with diabetes could slip without apparent warning into hypoglycaemia.

The number and variety of insulin preparations proliferated, but the main advances were in methods to produce highly purified preparations from porcine or bovine pancreas, which remained the source for therapeutic insulin until the early 1980s. Insulin was the first therapeutic protein to be produced by recombinant DNA technology, initially by David Goeddel (*b.* 1951), who expressed synthetic genes encoding the A and B chains separately in *Escherichia coli* and then combined these chemically to produce human-sequence insulin [75]. From there, genetic engineering has been used to produce *designer* insulins such as the fast-acting insulin analogues lispro and aspart and the *peakless* basal insulins such as glargine, detemir, and degludec. These insulins are more expensive than NPH but the evidence suggests that there is less clinical hypoglycaemia with their use [76].

Most people with diabetes still inject insulin subcutaneously. Major milestones in its administration were the replacement of glass and steel syringes by disposable plastic syringes with fine-gauge needles, and then by *pen*-injection devices invented by John Ireland (1933–1988) in Glasgow in 1981 [77]. Portable insulin infusion pumps were developed by John Pickup (*b.* 1947) and colleagues in London during the late 1970s [78], and have become progressively smaller and more sophisticated. Both people with diabetes and manufacturers hope that there will eventually be an insulin that can be given without injection. The first inhaled insulin was marketed in 2006, although withdrawn a year later because of lack of demand and concerns about safety [79], but other products have reached the market more recently.

Other anti-diabetes agents

The first orally active glucose-lowering drug, synthalin, a guanidine derivative, was developed by Frank and colleagues in Breslau in 1926 [80], but had to be withdrawn because of toxicity (a recurrent problem for oral anti-diabetes drugs). The sulfonylureas originated from the work of Auguste Loubatières (1912–1977) in France

Figure 1.18 Dan Drucker, Joel Habener, and Jens Juel Holst – recipients of the Warren Alpert Prize (2020) and Canada Gairdiner Award (2021).

during the early 1940s on the glucose-lowering action of a sulfonamide derivative, 2254RP. Loubatières made the crucial observations that proved that these drugs act as insulin secretagogues and that they were effective in intact, but not in pancreatectomized, animals [81]. In 1955 carbutamide was the first sulfonylurea to enter clinical practice and tolbutamide followed in 1957. Phenformin, the first biguanide, was introduced in 1959 following research into the metabolic effects of guanidine derivatives that had built on Frank's initial studies [82]. Metformin appeared on the European market in 1960, but was not marketed in the USA until 1994. Troglitazone, the first of a class of anti-diabetes drugs – the glitazones or thiazolidinediones – was marketed in 1997 but withdrawn because of liver damage. It was followed by rosiglitazone and pioglitazone.

Another class of drugs, acting on the incretin system, was introduced in 2005. In 1986, Joel Habener (*b*. 1937) and Jens Juel Holst (*b*. 1945) simultaneously identified the amino acid sequence of biologically active, truncated glucagon-like peptide 1 (GLP-1), while Dan Drucker (*b*. 1956) described the first direct actions of GLP-1 on the β cell, specifically the glucose-dependent stimulation of insulin secretion and biosynthesis (Figure 1.18) [83]. Holst discovered the glucagon-suppressing and appetite-regulating effect of GLP-1 in humans. Importantly, the islet actions of GLP-1 are glucose dependent, making GLP-1 a safer treatment than sulfonylureas or insulin.

Today, long-acting GLP-1 receptor agonists are very effective treatments for hyperglycaemia in type 2 diabetes and highly efficacious for inducing weight loss. Inhibitors of the enzyme dipeptidylpeptidase-4 (DPP-4), which breaks down GLP-1 (gliptins), are also widely used. Oral versions of GLP-1 receptor agonists are now on the market.

In the 2010s another class of agents, the sodium-glucose cotransporter 2 (SGLT-2) inhibitors – the gliflozins – became widely available with action blocking the renal sodium-glucose cotransporters and thereby causing glycosuria; their effects were to lower plasma glucose, reduce blood pressure, and cause weight loss. A landmark trial using empagliflozin in high-risk people with existing cardiovascular disease showed a marked reduction in mortality [68].

Tolbutamide, phenformin, and insulin were compared in the treatment of *maturity-onset* diabetes in the first randomized controlled trial, the University Group Diabetes Program (UGDP) [84–86]. This much-criticized study concluded that the death rate was higher for both oral agents than for placebo, and that insulin (whether given in a fixed or variable dose) was no better than placebo [85]. The UGDP study, however, did not have correct randomization for pre-existing conditions such as myocardial infarction and its conclusions were uninterpretable and unsafe. Nevertheless, these findings were considered by some as suggesting that treatment of maturity-onset diabetes was a waste of time, a myth that was only laid finally to rest by the UK Prospective Diabetes Study (UKPDS) [87]. Beyond the UKPDS, there have been many cardiovascular outcome trials addressing separate issues relating to individual pharmacological agents.

Glucose management and treatment targets

During the 1920s, opinion leaders advocated normalizing blood glucose in young people with diabetes, the rationale being to *rest* the pancreas, in the hope that it might regenerate. The only way of monitoring the diabetes was by testing the urine for glucose, and attempts to keep the urine free from sugar inevitably resulted in severe hypoglycaemia and often psychological damage. This led to the so-called *free diet* movement – linked particularly with Adolf Lichtenstein (Stockholm) and Edward Tolstoi (New York) – which encouraged people with diabetes to eat whatever they liked and not to worry about glycosuria, however heavy. Tolstoi's view [88] was that a life saved by insulin should be worth living, and that people with diabetes should be able to forget that they had diabetes after each morning's injection; it seems likely that many physicians followed this policy for the next 40 years.

Adult physicians were similarly ambivalent about the importance of optimal glycaemic management. Only one-third of diabetes physicians questioned in England in 1953 thought that normoglycaemia would prevent diabetes-related complications, and only one-half advised urine testing at home [89].

Practical monitoring of diabetes management became feasible in the late 1970s with the introduction into clinical practice of test strips for measuring blood glucose in a fingerprick sample and the demonstration that most people with diabetes could use them at home [90, 91]. The discovery of haemoglobin A_{1c} by Samuel Rahbar (1929–2012) paved the way for glycated haemoglobin (HbA_{1c}) assays that gave an objective measure of overall glucose levels [92]. These methods in turn made possible the North American Diabetes Control and Complications Trial (DCCT), which in 1993 finally established that optimal glycaemic management prevents and delays the progression of microvascular complications in type 1 diabetes [93]. For type 2 diabetes, the importance of optimal glycaemic management was definitively proved by another landmark study, the UKPDS, masterminded in Oxford by Robert Turner (Figure 1.19). The UKPDS, which reported in 1998, not only showed a beneficial effect of improved glycaemic levels on microvascular complications [87], but also established the importance of treating hypertension [94]. By the late 1990s it was clear that lowering glucose levels, high blood pressure, or cholesterol separately would reduce the frequency of heart disease and death, and it was

Figure 1.19 Robert Turner (1939–1999), instigator of the UK Prospective Diabetes Study, the first study to show that optimal management of blood glucose and blood pressure was beneficial in type 2 diabetes. Source: Courtesy of the British Diabetic Association.

natural to wonder whether tackling them simultaneously (multiple risk factor intervention) would be even better. The Steno-2 study, which began at the Steno Diabetes Center in Copenhagen in 1992, enrolled people with type 2 diabetes with microalbuminuria, and after 13 years of follow-up showed that multiple risk factor intervention reduced the risk of death by 20% and the risk of developing nephropathy, retinopathy, and neuropathy by 50% [95].

Diabetes-related complications

Apart from the general benefits of improving blood glucose, some specific treatments have emerged for certain chronic complications. Well-conducted clinical trials during the late 1970s showed the effectiveness of laser photocoagulation in preventing visual loss from both maculopathy and proliferative retinopathy [96]. This technique was derived from the xenon arc lamp originally described in the late 1950s by Gerd Meyer-Schwickerath (1921–1992) of Essen, Germany [97].

The importance of blood pressure management in preventing the progression of nephropathy is now fully recognized, and blockade of the renin-angiotensin system may be particularly beneficial; Carl Erik Mogensen (*b*. 1938) and Hans-Henrik Parving (*b*. 1943) published studies in the early 1980s demonstrating that lowering blood pressure slowed the progression of nephropathy [98]. The detection of very low albumin concentrations in urine (microalbuminuria), now used throughout the world to screen for and monitor the course of diabetic nephropathy, is derived from a radioimmunoassay developed in 1969 by Harry Keen (1925–2013) and Costas Chlouverakis, at Guy's Hospital in London [99].

Diabetic ketoacidosis

The introduction of insulin was only one aspect of the management of this acute and previously fatal complication of diabetes. Of the first 33 cases treated by Joslin and his colleagues between 1 January 1923 and 1 April 1925, 31 survived – an excellent outcome, even by modern standards, which Joslin [100] 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, cardiac stimulants, and above all the exclusion of alkalis'.

Sadly, other centres did not pay so much attention to detail. In 1933, the death rate from ketoacidosis in Boston was only 5%, but elsewhere in North America and Europe it averaged 30% and could be as high as 75%. An important advance in management was the acceptance of relatively low-dose insulin replacement, following the example of Ruth Menzel and colleagues in Karlsburg, Germany [101]. This broke with the tradition of high-dose regimens such as that proposed by Howard Root in the USA, which had recommended an average of 1200 units of insulin during the first 24 hours of treatment [102]. Another step forward was the recognition by Jacob Holler in 1946 of the danger of hypokalaemia [103]. Holler's observation helped to establish the need for monitoring plasma potassium levels, which became feasible with the introduction of the flame photometer and replacing potassium accordingly.

Diabetes in pregnancy

As late as 1950, the outcome of pregnancy in women with diabetes was still very poor in most units, with perinatal fetal losses of 45–65%, some 10 times higher than in the general population. Exceptions to this depressing rule were the units run by Priscilla White at the Joslin Clinic in Boston, who had published excellent results as early as 1935 [104], and by Jørgen Pedersen in Copenhagen (Figure 1.20). Pedersen identified the common features underpinning success as optimal glucose management and care provided by an experienced and dedicated team comprising a physician, obstetrician, and paediatrician [105]. Pedersen's target of a fetal mortality rate of 6% was not achieved in most European or US units until the 1980s.

Delivery of care for people with diabetes

From the earliest days of insulin injection and urine testing, it was apparent that people with diabetes needed knowledge and practical skills to manage their disease effectively. Lip service

(a)

(b)

Figure 1.20 (a) Jørgen Pedersen (1914–1978) and (b) Ivo Drury (1905–1988), pioneers, with Priscilla White (1900–1989), in the management of pregnancy in women with type 1 diabetes. Source: Courtesy of Dr Carl Erik Mogensen and the Royal College of Physicians of Ireland.

was often paid to the importance of diabetes education, but most individuals with diabetes were badly informed. In 1952, Samuel Beaser (1910–2005) questioned 128 people with diabetes attending the Boston Diabetes Fair, and found that 'all were distinctly deficient in knowledge of their disease' [106]; he felt that responsibility lay with both doctors and administrators. Further studies during the 1960s by Donnell Etzwiler (1927–2003) in Minneapolis showed that many doctors and nurses were also ignorant about managing diabetes. Since the 1980s, diabetes specialist nurses and nurse educators have been appointed in increasingly large numbers, thus fulfilling a suggestion originally made by Joslin in 1916.

National and international diabetes associations have also played an important part by supporting scientific and clinical research, providing practical and moral help for people with diabetes, and lobbying governments on their behalf. The first of these organizations was the Portuguese Association for the Protection of Poor Diabetics, founded in 1926 by Ernesto Roma of Lisbon after an inspiring visit to Joslin's clinic in Boston (Figure 1.21). The Association's aim was to provide free insulin and education for people with diabetes and their families. In the UK, the Diabetic Association (later the British Diabetic Association, and now Diabetes UK) was established in 1934 by Robin Lawrence of King's College Hospital, London, helped by the novelist H.G. Wells (Figure 1.21). Similar organizations were later founded in France (1938), the USA (1940), and Belgium (1942), and now exist in most countries.

On a wider scale, the American Diabetes Association (ADA) was founded in 1939, the International Diabetes Federation was established in 1950, and the European Association for the Study of Diabetes (EASD) in 1964. These organizations are devoted to the practice of diabetes care as well as the basic and clinical science of the disease, and have been valuable in coordinating treatment targets and strategies at international level; an important example was the St. Vincent Declaration, issued jointly in 1990 by the EASD and the World Health Organization [107].

(a)

(b)

Figure 1.21 (a) Ernesto Roma (1887–1978) and (b) Robin D. Lawrence (1892–1968). Source: Photograph of Dr Roma by courtesy of Manuel Machado Sá Marques and the Associação Protectura das Diabéticos de Portugal.

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