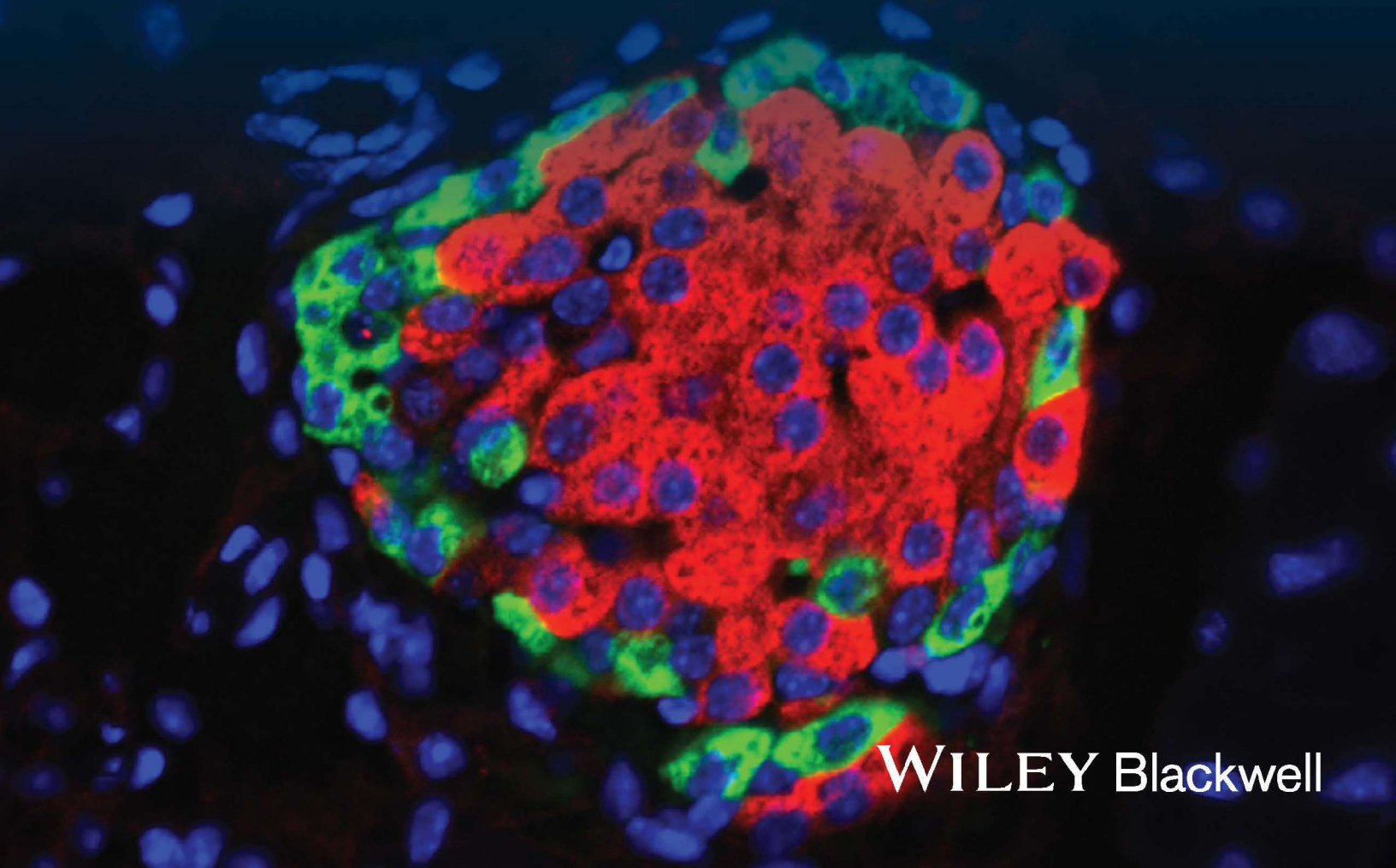
Sixth Edition

Textbook of Diabetes

Edited by Richard I.G. Holt • Allan Flyvbjerg



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We dedicate this book to all people living with diabetes and the healthcare professionals who look after them. We would also like to dedicate this book to our families, without whose support and encouragement the book would never have been finished.

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SIXTH EDITION

WILEY Blackwell

This sixth edition first published 2024

Edition History
Blackwell Publishing Ltd (1e, 1991; 2e, 1997; 3e, 2003); John Wiley & Sons, Ltd (4e, 2010; 5e 2017)

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data

Names: Holt, Richard I. G., editor. |Flyvbjerg, Allan, editor.
Title: Textbook of diabetes / edited by Richard I.G. Holt, Allan Flyvbjerg.
Other titles: Textbook of diabetes (Pickup)
Description: Sixth edition. | Hoboken, NJ : Wiley-Blackwell 2024. |
Includes bibliographical references and index.
Identifiers: LCCN 2022049550 (print) | LCCN 2022049551 (ebook) | ISBN 9781119697428 (hardback) | ISBN 9781119697435 (adobe pdf) | ISBN 9781119697411 (epub)
Subjects: MESH: Diabetes Mellitus
Classification: LCC RC660.4 (print) | LCC RC660.4 (ebook) | NLM WK 810 |
DDC 616.4/62–dc23/eng/20230125
LC record available at https://lccn.loc.gov/2022049550
LC ebook record available at https://lccn.loc.gov/2022049551

Cover Design: Wiley
Cover Images: Courtesy of Olaniru, Jones & Persaud, King's College London

Set in 9.25/11pt MinionPro by Straive, Pondicherry, India

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Preface

It is nearly seven years since the last edition of the *Textbook of Diabetes* was published, during which time there have been many exciting developments in our understanding of diabetes and novel treatments that have improved the lives of those living with diabetes. Despite our ability to alleviate the risk of its long-term complications, the global burden of diabetes continues to rise as the prevalence inexorably increases. According to the International Diabetes Federation, diabetes now affects 537 million adults, compared with 415 million when the last edition was published. Over three-quarters of people with diabetes live in low- and middle-income countries and diabetes causes 6.7 million deaths a year, approximately one every five seconds. The cost of treating diabetes has reached almost US$1 trillion per annum, a threefold increase over the last 15 years. The need for accurate and up-to-date information to help healthcare professionals support people with diabetes has never been greater.

Ironically, as the volume of information and diversity of digital resources have increased, many are finding it overwhelming to keep abreast of the new advances. It is particularly challenging to determine the validity of many source materials. In this textbook we aim to bring together a series of chapters from internationally leading diabetes experts who provide accurate and clinically relevant information to both academic and practising diabetes healthcare professionals.

We have retained the structure from the previous edition, with a similar length and number of chapters. The centenary of the discovery of insulin has just passed and the book begins with a history of diabetes that provides many valuable insights from the past. We then move through the epidemiology of diabetes, the physiology of glucose metabolism, and the pathogenesis of diabetes, before sections on clinical management. A discussion of the microvascular and macrovascular complications then follows, after which there are sections on the psychosocial aspects of diabetes, the management of diabetes in special groups, and models of care, before a final section to glimpse into the future. New chapters include an overview of glucose homeostasis and the central control of glucose metabolism, as well as chapters on the genetics and management of obesity to recognize the close relationship between obesity and type 2 diabetes. There is a new chapter on the emerging topic of biomarkers and precision medicine, while the rapid advance in diabetes technology has necessitated a split into separate chapters on glucose monitoring and insulin delivery. Transplantation has moved from future treatments to current management to acknowledge its current place in clinical care. In the macrovascular section, we have added a new chapter on heart failure, which has come to the fore as a result of the sodium–glucose cotransporter 2 (SGLT-2) inhibitor cardiovascular outcome trials. Oral health and sleep are added to the list of other areas of diabetes complications, while the importance of social determinants of health and ethnicity, culture, and religion is now included in the psychosocial aspects of diabetes section. The final new chapter describes managing diabetes in low- to middle-income countries, where the majority of people with diabetes live.

As editors, we are only too aware of the hard work that goes into the production of a comprehensive and up-to-date book such as this. For this edition the pressures of the Covid-19 pandemic added to the challenges of bringing the book to fruition. Our thanks go to each and every chapter author who, despite busy academic, clinical, and professional lives, was prepared to devote the time, energy, and expertise to provide their essential contributions to the text. Thank you for your forbearance of our nagging e-mails!

We are also grateful for the support we have received from our publisher, Wiley-Blackwell. Our commissioning editor Jennifer Seward, who took over from Priyanka Gibbons during the book's development, has provided guidance and encouragement. Our thanks also go to Rajalaxmi Rajendrasingh, Sally Osborn, and the rest of the Wiley-Blackwell team. The book looks even better than the last edition! We would like to pay tribute to Clive Cockram and Barry Goldstein, our editing colleagues for the fourth and fifth editions. You were missed this time round.

We hope you enjoy reading the book, whether it be dipping in or reading from cover to cover, as much as we did editing it. We have taken away useful, novel information that will aid in our daily professional lives and hope that this book will help you to support the people with diabetes you know in the widest sense of this meaning.

Richard I.G. Holt
Allan Flyvbjerg
February 2023

List of Abbreviations

AACE	American Association of Clinical Endocrinologists
AAV	adeno-associated vectors
ABP	ankle blood pressure
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ACR	albumin : creatinine ratio
ADA	American Diabetes Association
ADP	adenosine diphosphate
AICAR	5-aminoimidazole-4-carboxamide-1β-D-ribofuranoside
AMDCC	Animal Models for Diabetes Complications Consortium
AMP	adenosine monophosphate
Apo	apolipoprotein
aPWV	aortic pulse wave velocity
Arx	aristaless-related homeobox
ATP	adenosine triphosphate
AUC	area under the curve
BCAA	branched-chain amino acid
BMD	bone mineral density
BMI	body mass index
BM-MNC	mononuclear bone marrow-derived stem cell
BPH	benign prostatic hyperplasia
bpm	beats per minute
BTX-A	botulinum toxin type A
CABG	coronary artery bypass grafting
CA-MRSA	community-associated methicillin-resistant *Staphylococcus aureus*
CAPD	continuous ambulatory peritoneal dialysis
CBG	capillary blood glucose
CBT	cognitive–behavioral therapy
CCM	corneal confocal microscopy
CDA	Canadian Diabetes Association
CDC	cardiosphere-derived stem cell
CDC	Centers for Disease Control and Prevention
CDE	Certified Diabetes Educator
CEMACH	Confidential Enquiry into Maternal and Child Health
CETP	cholesteryl ester transfer protein
CGM	continuous glucose monitoring
CI	confidence interval
CKD	chronic kidney disease
CML	carboxymethyllysine
CNS	central nervous system
COC	combination oral contraceptive
COX	cyclooxygenase
CPC	cardiac progenitor cell
CRP	C-reactive protein
CSII	continuous subcutaneous insulin infusion
CT	computed tomography
CV	coefficient of variation
CVD	cardiovascular disease
DAWN	Diabetes Attitudes, Wishes, and Needs study
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis
DPP	dipeptidyl peptidase
DSN	diabetes specialist nurse
DVLA	Driver and Vehicle Licensing Agency
EASD	European Association for the Study of Diabetes
ECG	electrocardiography/electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ER	endoplasmic reticulum
ERCP	endoscopic retrograde cholangiopancreatography
ERK	extracellular signal-regulated kinase
ERM	ezrin–radixin–moesin
ESC	embryonic stem cell
ESRD	end-stage renal disease
ESRF	end-stage renal failure
FDA	Food and Drug Administration (USA)
FDC	fixed-dose combination
FDKP	fumaryldiketopiperazine
FFA	free fatty acid
FGF	fibroblast growth factor
FHWA	Federal Highways Administration
FMD	flow-mediated endothelium-dependent arterial dilation
FOXO	forkhead box O
FXR	farnesoid-X receptor
G6P	glucose-6-phosphatase
G-6-P	glucose-6-phosphate
G6PD	glucose-6-phosphate dehydrogenase
GAD	glutamine acid decarboxylase
GCGR	glucagon receptor
GCK	glucokinase
G-CSF	granulocyte colony-stimulating factor

GDF	growth differentiation factor
GDM	gestational diabetes mellitus
CF	cystic fibrosis
GI	gastrointestinal
GLO	glyoxalase
GLP-1RA	GLP-1 receptor agonist
GLUT	glucose transporter
GPR	G-protein-coupled receptor
GRPP	glicentin-related pancreatic polypeptide
GWA	genome-wide association
GWAS	genome-wide association studies
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA_{1c}	hemoglobin A_{1c}
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HGF	hepatocyte growth factor
hGH	human recombinant growth hormone
HHS	hyperosmolar non-ketotic hyperglycemic state
HR	hazard ratio
HRT	hormone replacement therapy
HRV	heart rate variability
HSC	hematopoietic stem cell
hsCRP	high-sensitivity C-reactive protein
IADPSG	International Association of Diabetes Pregnancy Study Groups
IAsp	insulin aspart
IAUC	incremental area under the blood glucose curve
ICA	islet cell antibody
ICU	intensive care unit
i.d.	intradermal
IDDM	insulin-dependent diabetes mellitus
IDeg	insulin degludec
IDF	International Diabetes Federation
IDL	intermediate-density lipoprotein
IDRS	Indian Diabetes Risk Score
IgG	immunoglobulin G
IGR	impaired glucose regulation
IGT	impaired glucose tolerance
IKKβ	inhibitor κB kinase-β
IL	interleukin
IMT	intima-media thickness
InsR	insulin receptor
IRMA	intraretinal microvascular abnormality
ISPAD	International Society for Pediatric and Adolescent Diabetes
IT	information technology
IVUS	intravascular ultrasound
IWGDF	International Working Group on the Diabetic Foot
JBDS	Joint British Diabetes Societies
KDIGO	Kidney Disease: Improving Global Outcomes
K_m	Michaelis constant
LADA	latent autoimmune diabetes in adults
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LGA	large-for-gestational age
LIRKO	liver-specific InsR knockout
LPS	lipopolysaccharide
Lst	limostatin
LV	left ventricular
LVEF	left ventricular ejection fraction
MAOI	monoamine oxidase inhibitor
MDI	multiple daily injection
MDRD	Modification of Diet in Renal Disease
MG53	mitsugumin 53
mGDP	mitochondrial glycerolphosphate dehydrogenase
MGO	methylglyoxal
MI	myocardial infarction
MIBG	*m*-iodobenzylguanidine
MIRKO	muscle-specific InsR knockout
MODY	maturity-onset diabetes of the young
MPGF	major proglucagon fragment
MPO	myeloperoxidase
MRI	magnetic resonance imaging
MSC	mesenchymal stem cell
MS	mass spectrometry
mTOR	mammalian or mechanistic target of rapamycin
mTORC1	mechanistic target of rapamycin complex 1
MTPI	microsomal transfer protein inhibitor
NAD	nicotinamide adenine dinucleotide
NaDIA	National Diabetes Inpatient Audit
NAFLD	non-alcoholic fatty liver disease
NANC	non-adrenergic, non-cholinergic
NCV	nerve conduction velocity
NEFA	non-esterified fatty acid
MFMU	Maternal–Fetal Medicine Units Network
NEP	neutral endopeptidase
NFκB	nuclear factor κB
Ngn3	neurogenin 3
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDM	non-insulin-dependent diabetes mellitus
NIH	National Institutes of Health
NMU	neuromedin U
Nox	NAD(P)H oxidase
NOD	non-obese diabetic
NPH	neutral protamine Hagedorn
NRTI	nucleoside reverse-transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NT-3	neurotrophin-3
NT-proBNP	N-terminal pro-brain-type natriuretic peptide
OCP	oral contraceptive pill
OGIS	oral glucose insulin sensitivity
OGTT	oral glucose tolerance test(ing)
OR	odds ratio
oxLDL	oxidation of low-density lipoprotein
PAS	periodic acid–Schiff
PBA	phenylboronic acid
PC	prohormone convertase
PCB	polychlorinated biphenyl
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PCSK-9	proprotein convertase subtilisin kexin type 9
PDH	pyruvate dehydrogenase
Pdx1	pancreatic duodenal homeobox 1
PGF	placental growth factor
PI	protease inhibitor

PI3K	phosphatidylinositol 3-kinase
PID	proportional integral derivative
P/KX	combined pancreas/kidney transplantation
PNDM	permanent neonatal diabetes mellitus
PPAR	peroxisome proliferator-activated receptor
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PTDM	post-transplantation diabetes mellitus
PTP1B	protein tyrosine phosphatase 1B
PYY	polypeptide YY
QoL	quality of life
RA	receptor agonist
RAMP	receptor activity-modifying protein
RCT	randomized controlled trial
RDN	renal denervation
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes
REMS	Risk Evaluation and Mitigation Strategy
rHuPH20	recombinant human hyaluronidase
RMR	resting metabolic rate
ROS	reactive oxygen species
RR	relative risk
RR	risk ratio
RT-PCR	reverse transcriptase polymerase chain reaction
SCFA	short-chain fatty acid
s.c.	subcutaneous
sdHDL	small, dense high-density lipoprotein
sdLDL	small, dense low-density lipoprotein
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SGA	second-generation antipsychotics
SHP	short heterodimer protein
SMBG	self-monitoring of blood glucose
SMI	severe mental illness
SNP	sub-basal nerve plexus
SSRI	selective serotonin reuptake inhibitor
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TAG	triacylglyceride
TB	tuberculosis
TCF7L2	transcription factor 7 like 2
TE	transient elastography
TIND	treatment-induced neuropathy in diabetes
TLR	toll-like receptor
TNDM	transient neonatal diabetes mellitus
TNFα	tumor necrosis factor alpha
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
TZD	thiazolidinedione
UKPDS	UK Prospective Diabetes Study
US	ultrasound
UT	University of Texas
VEGF	vascular endothelial growth factor
VLCD	very low calorie diet
VLDL	very low-density lipoprotein
VRIII	variable-rate intravenous insulin infusion
WGS	whole-genome sequencing
WHO	World Health Organization
XO	xanthine oxidase
YY1	Yin Yang 1

1 Diabetes in its Historical and Social Context

1 The History of Diabetes Mellitus

Robert B. Tattersall[1] and David R. Matthews[2]
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[2] University of Oxford, Oxford, UK

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

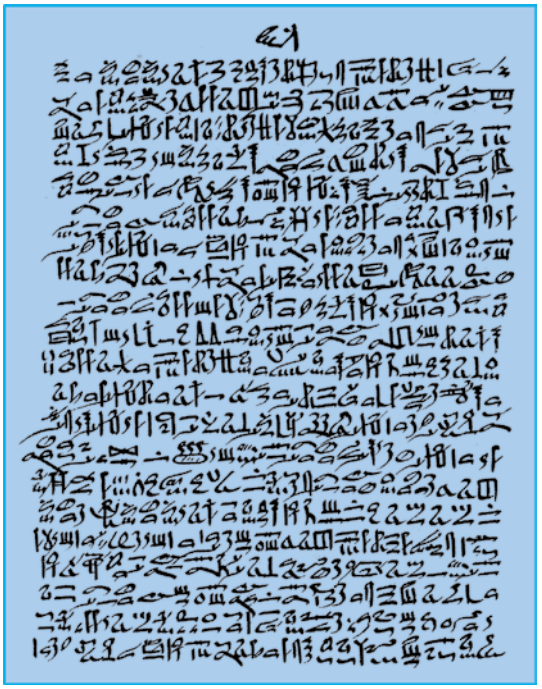


Figure 1.1 The Ebers papyrus. Source: Courtesy of the Wellcome Library, London.

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'.

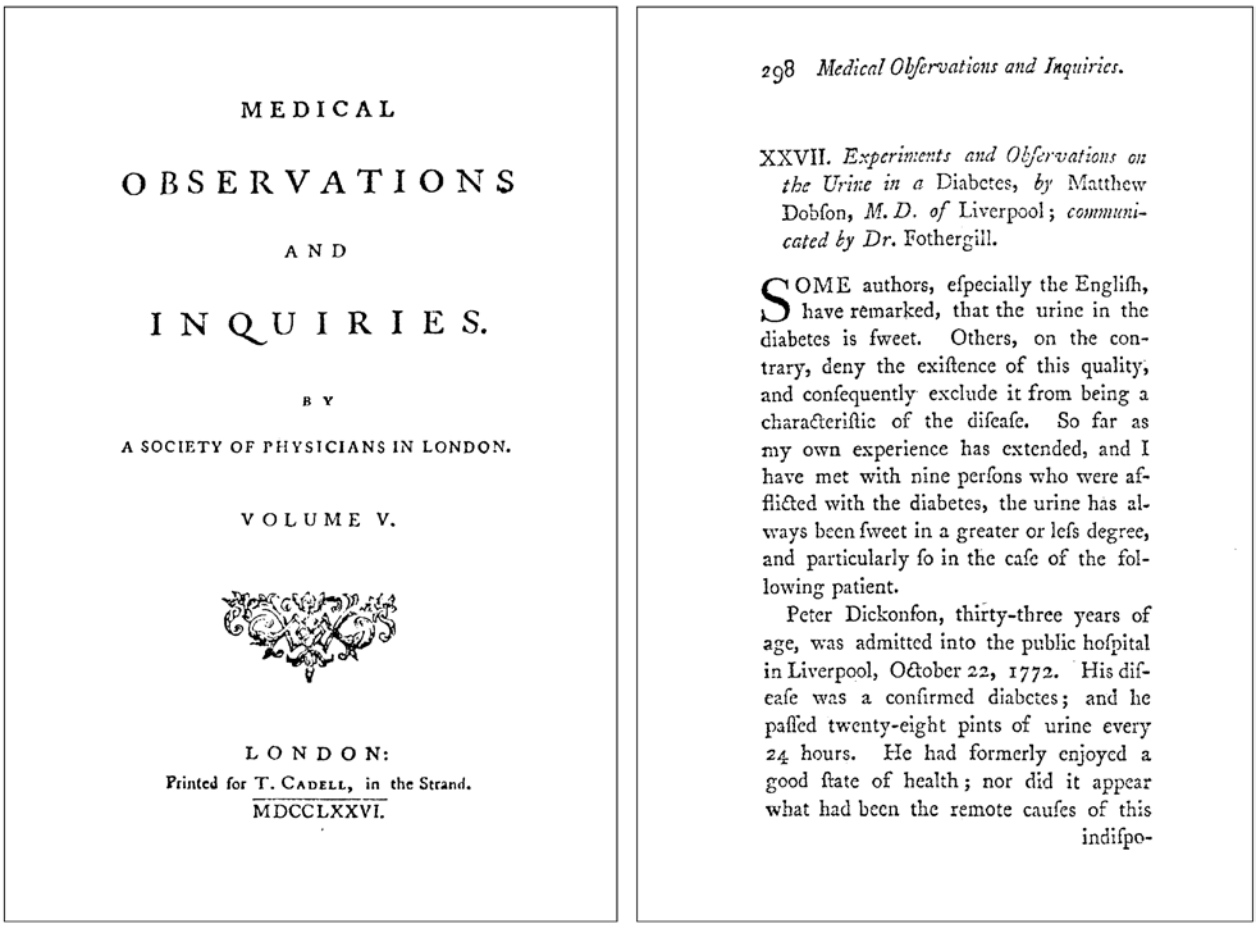
The Edinburgh-trained surgeon, John Rollo (*d.* 1809) was the first to apply the adjective *mellitus* (from the Latin word meaning *honey*). He also achieved fame with his *animal diet*, which became the standard treatment for most of the nineteenth century.

(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.

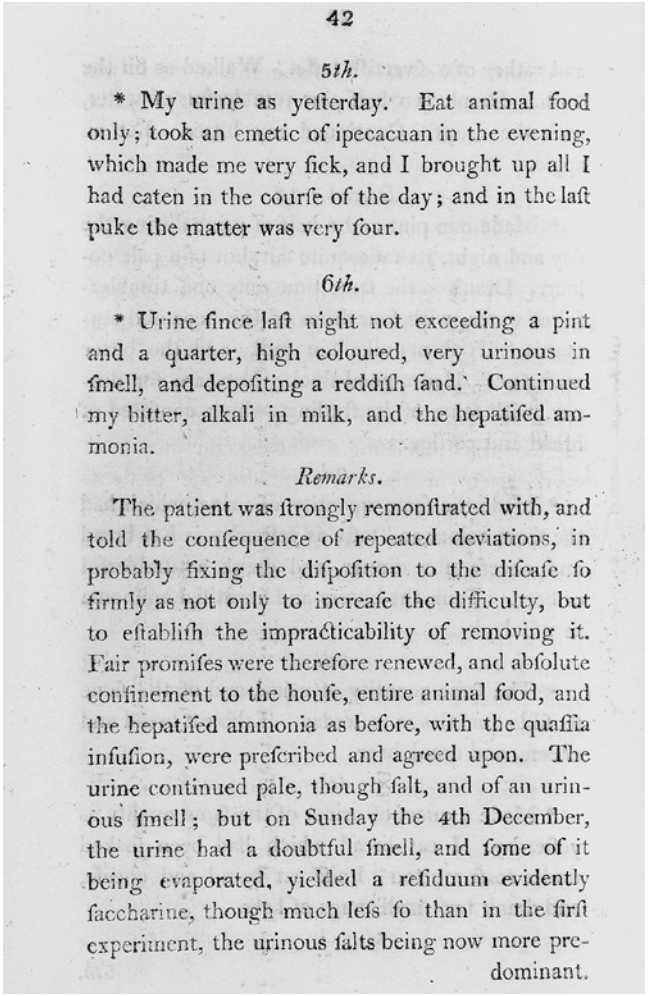
SOME authors, eſpecially the Engliſh, have remarked, that the urine in the diabetes is ſweet. Others, on the contrary, deny the exiſtence of this quality, and conſequently exclude it from being a characteriſtic of the diſeaſe. So far as my own experience has extended, and I have met with nine perſons 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 caten 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

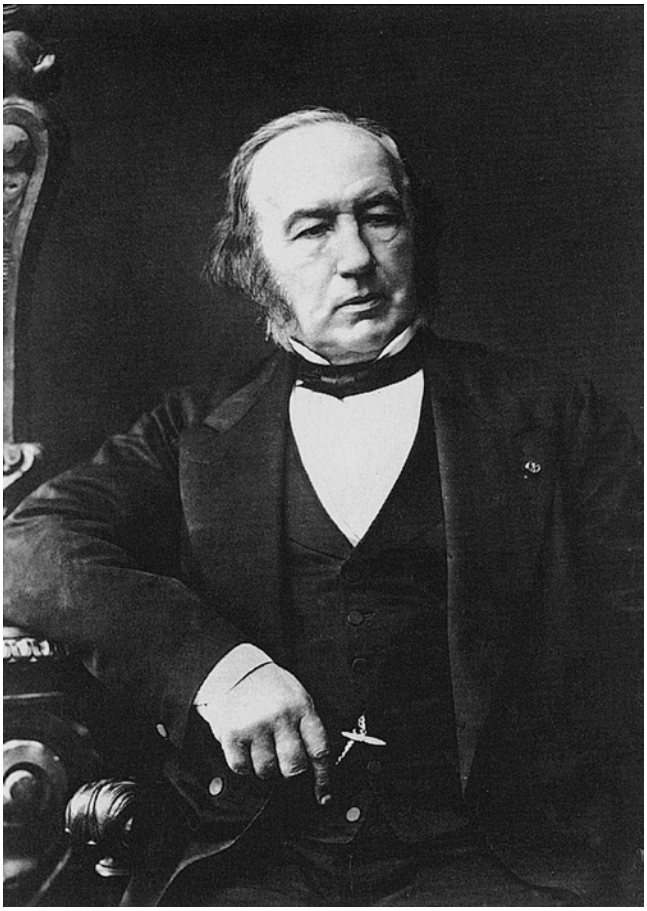


Figure 1.5 Claude Bernard (1813–1878). Source: Courtesy of the Wellcome Library, London.

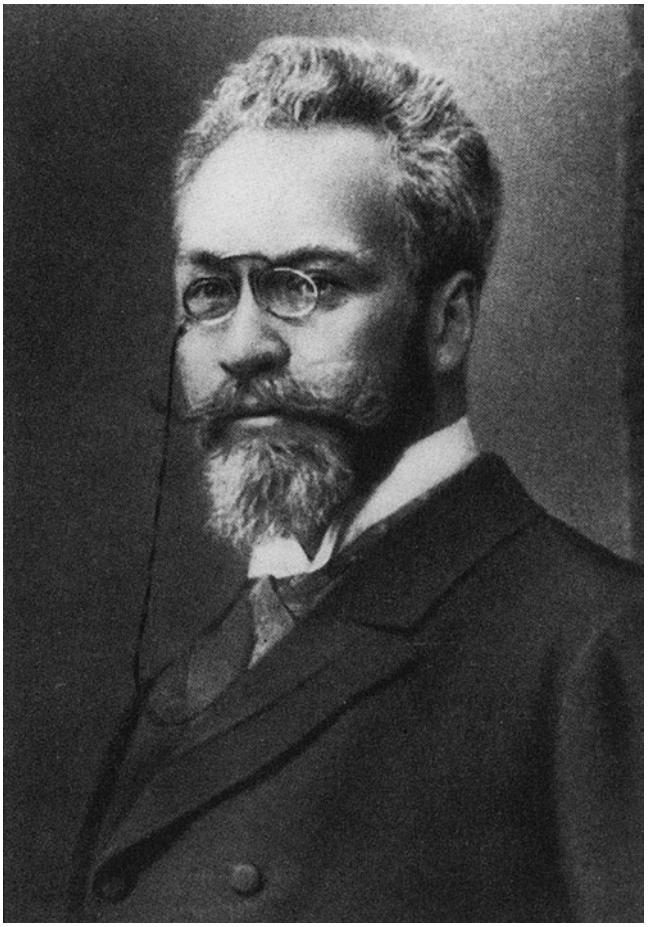


Figure 1.6 Oskar Minkowski (1858–1931).

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

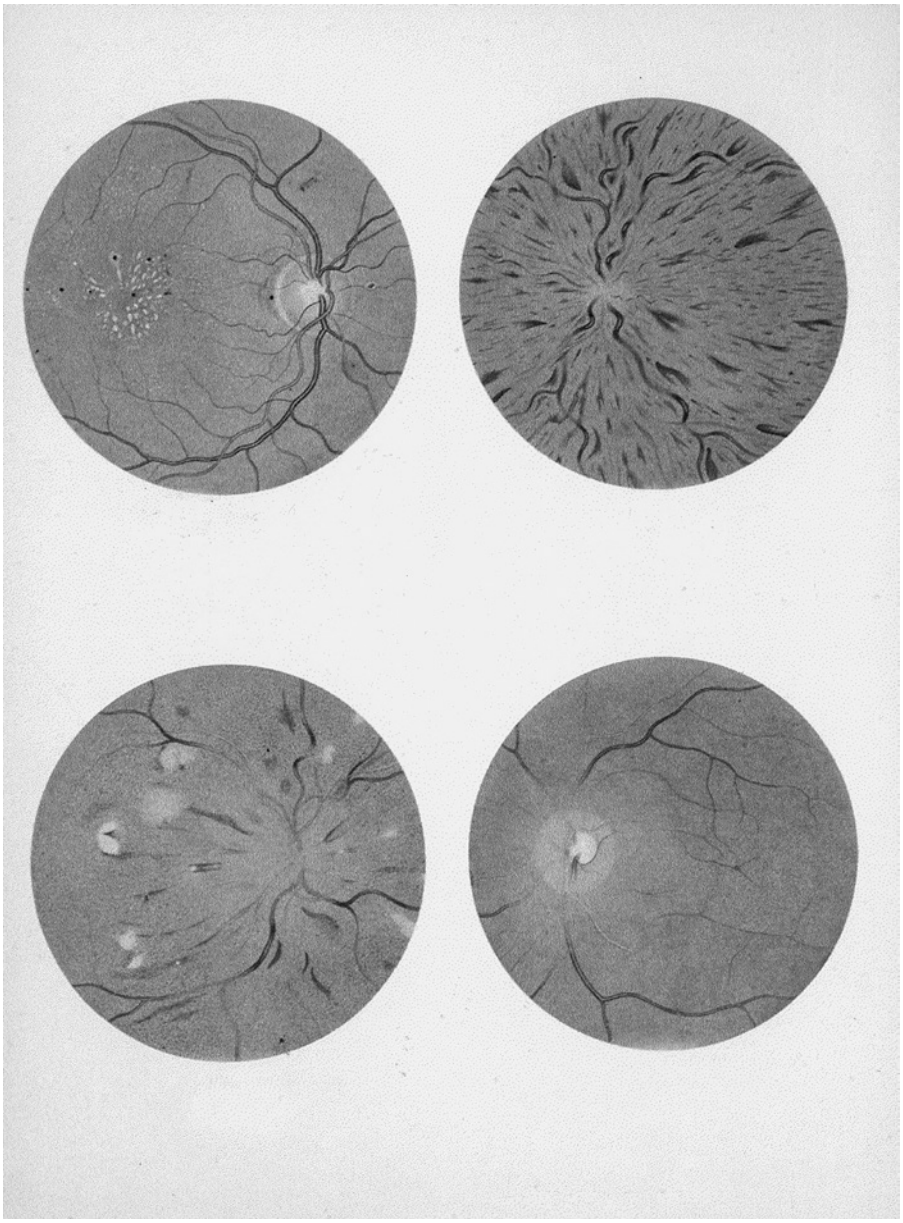


Figure 1.8 Pictures from *Jaeger's Atlas of the Optic Fundus*, 1869 [14]. Top left: Bright's disease. Top right: Jaeger's retinitis haemorrhagica is now recognized as central retinal vein occlusion. Bottom left: A 22-year-old man with suspected diabetes. Bottom right: Central retinal artery occlusion.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

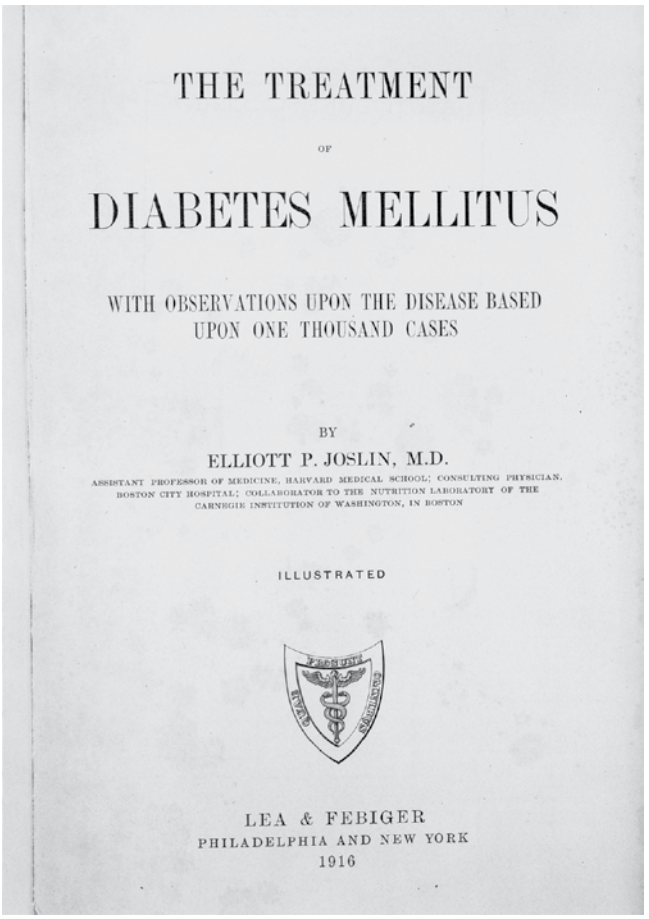
Discovery of insulin

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