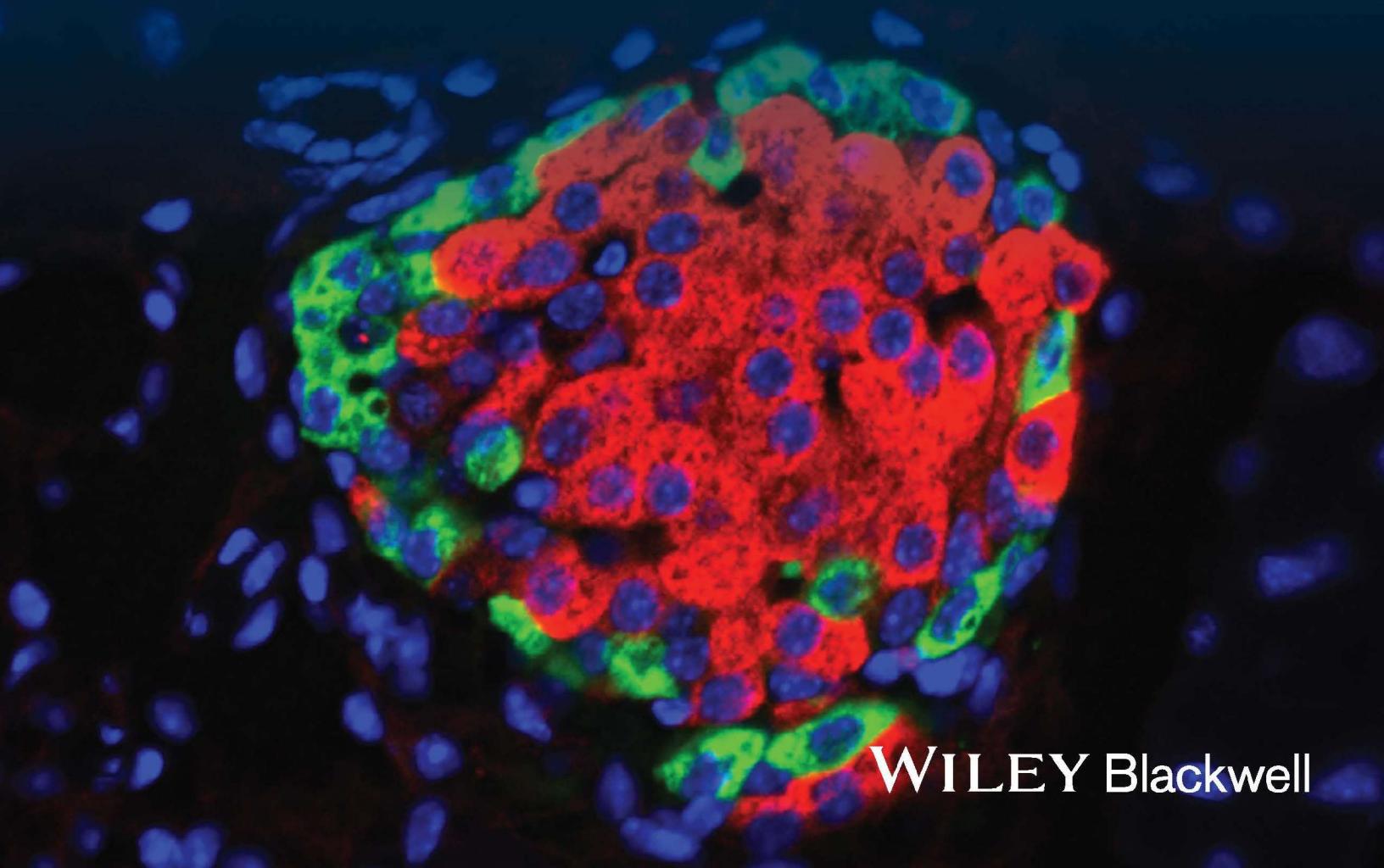


Sixth Edition

Textbook of **Diabetes**

Edited by **Richard I.G. Holt • Allan Flyvbjerg**



WILEY Blackwell

Textbook of Diabetes

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.

Textbook of Diabetes

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SIXTH EDITION

WILEY Blackwell

This sixth edition first published 2024

© 2024 John Wiley & Sons Ltd.

Edition History

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

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

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

List of Abbreviations

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

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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, Lagesse 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 Lundbaek 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.

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

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 <i>diabetes</i>
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 Pav (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

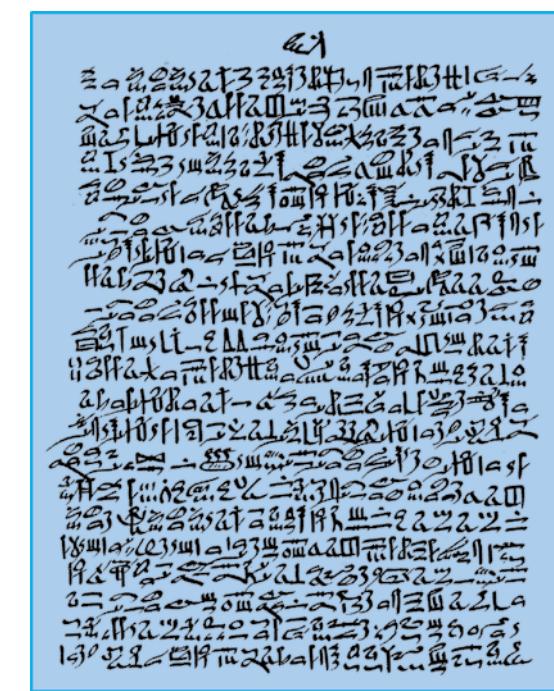


Figure 1.1 The Ebers papyrus. Source: Courtesy of the Wellcome Library, London.

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).

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)

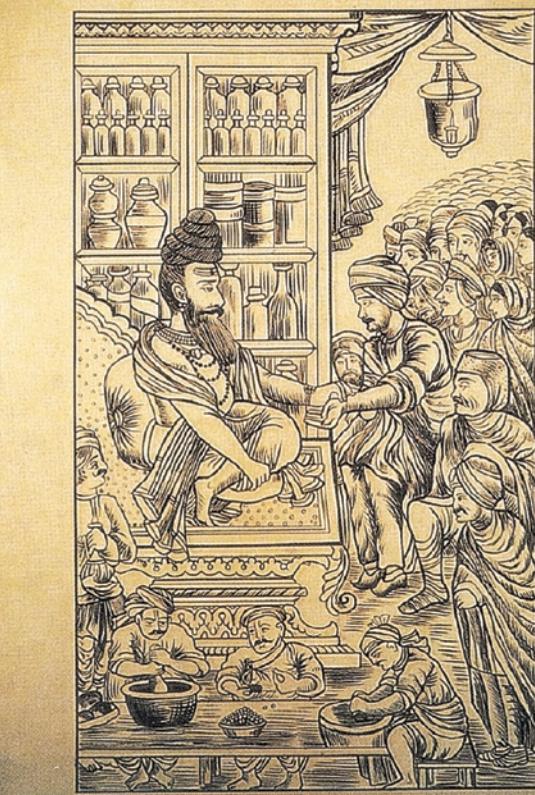
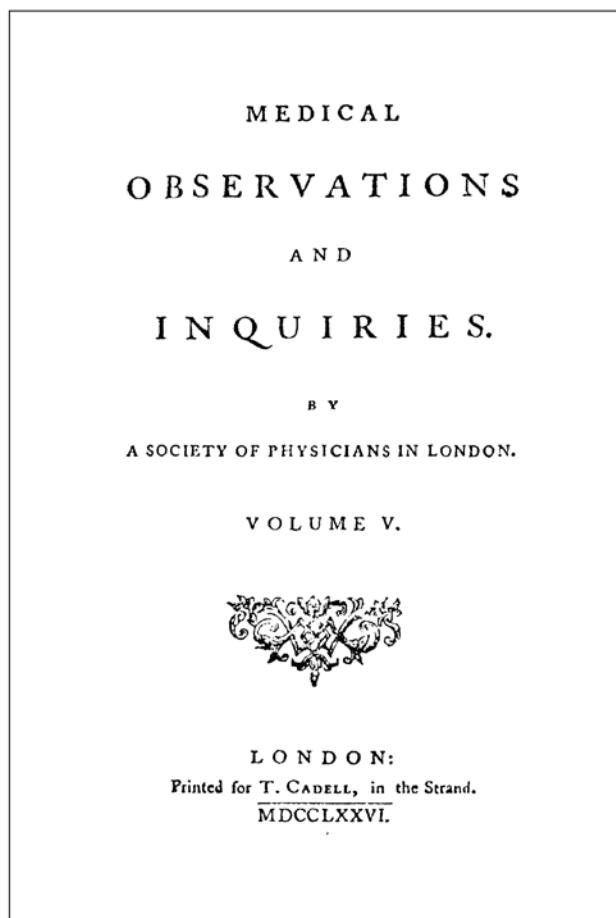


Figure 1.2 (a) Clinical description of diabetes by Aretaeus of Cappadocia (second century ce). Source: Adapted from Papaspyros, N.S. (1952) *The History of Diabetes Mellitus*. (b) Sushrut (Susrata), an Indian physician who wrote medical texts with Charak (Charaka) between 500 BCE and 400 BCE.



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 Dickonfon, 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 Laguerre (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 <i>insuline</i>
Frederick Banting, Charles Best, J.J.R. Macleod, James Collip (Canada, 1922)	Isolation of insulin
Richard Murlin (USA, 1923)	Discovered and named glucagon
Bernardo 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)

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

* 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.

* 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 quaffia 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.

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 (*pique 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 (<i>insulitis</i> ; 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 <i>insulitis</i> 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

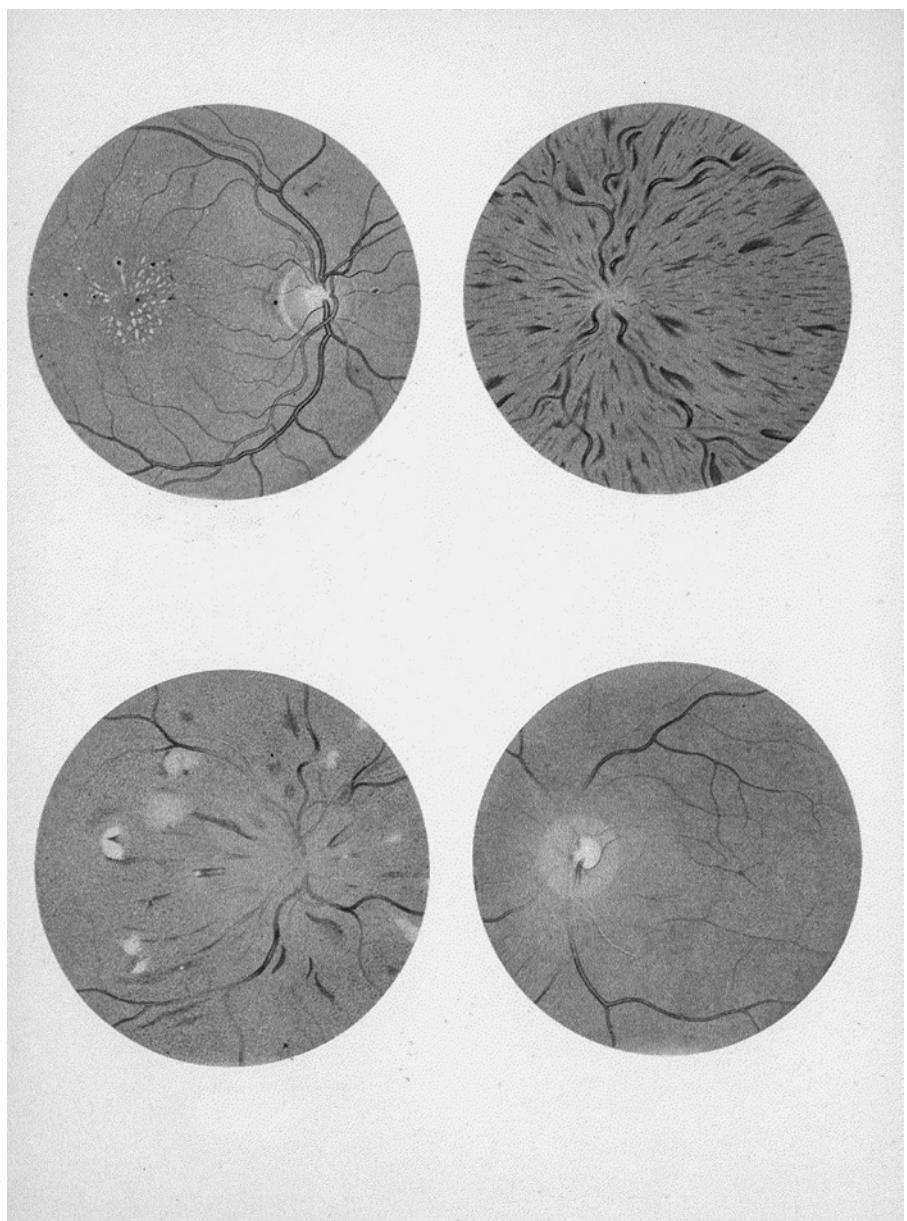


Figure 1.8 Pictures from *Jaeger's Atlas of the Optic Fundus*, 1869 [14]. Top left: Bright's disease. Top right: Jaeger's retinitis haemorrhagica is now recognized as central retinal vein occlusion. Bottom left: A 22-year-old man with suspected diabetes. Bottom right: Central retinal artery occlusion. 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/m²).

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)

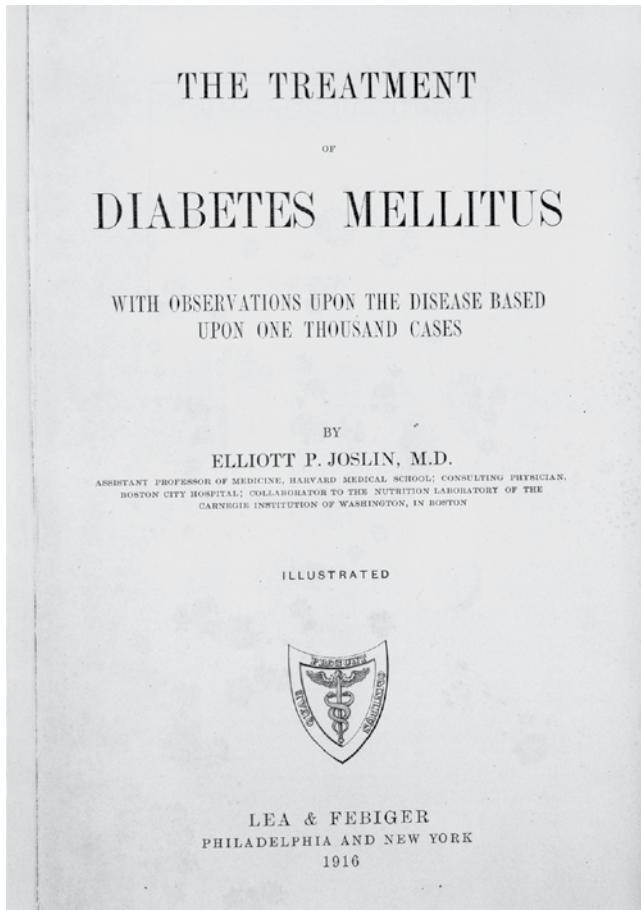


Figure 1.9 (a) Elliott P. Joslin (1869–1962), arguably the most famous diabetes specialist of the twentieth century, and (b) the frontispiece to his 1916 textbook [21].
Source: Courtesy of the Wellcome Library, London.

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 B²) 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

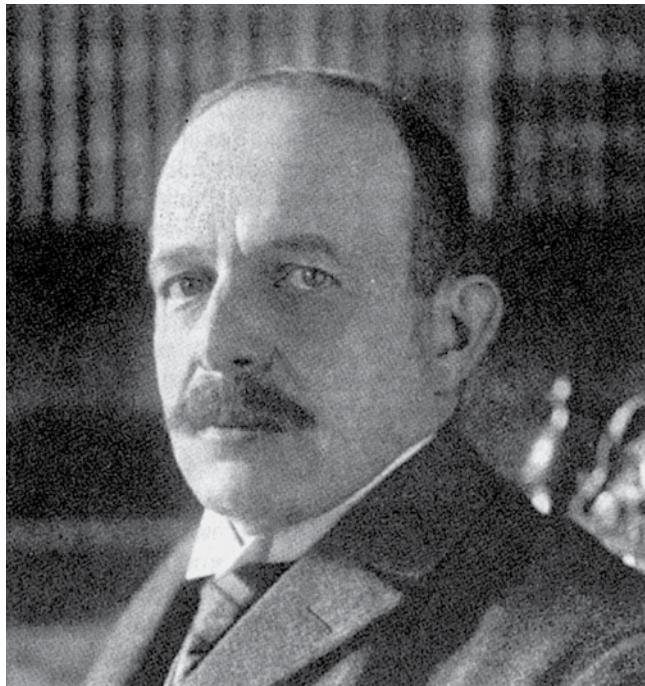
marked clinical improvement and complete elimination of glycosuria and ketonuria. Initial clinical results in seven cases were published in the March 1922 issue of the *Canadian Medical Association Journal* [27], which had the following dramatic conclusions:

- 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 zeige, 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 dauernd³⁾ 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 Nebennierensaftes⁴⁾, 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 angesichtigt, 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 Prof. 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)

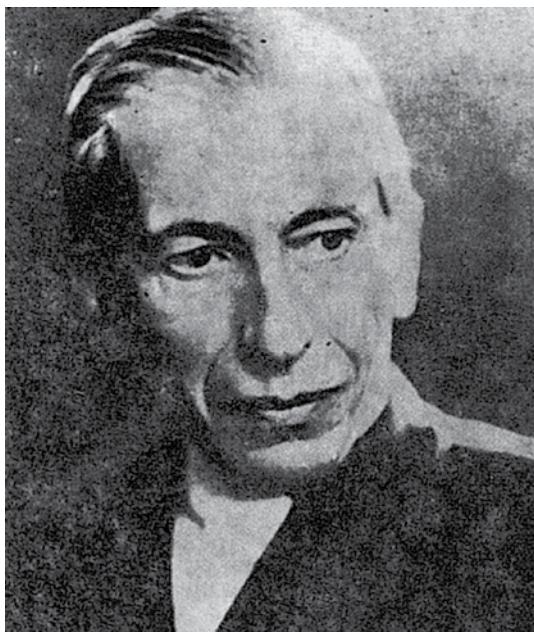


Figure 1.10 (a) Georg Zuelzer (1840–1949) and (b) the title page from his paper (1907) reporting that a pancreatic extract reduced glycosuria in pancreatectomized dogs [23]. (c) Nicolas Paulesco (1869–1931).

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

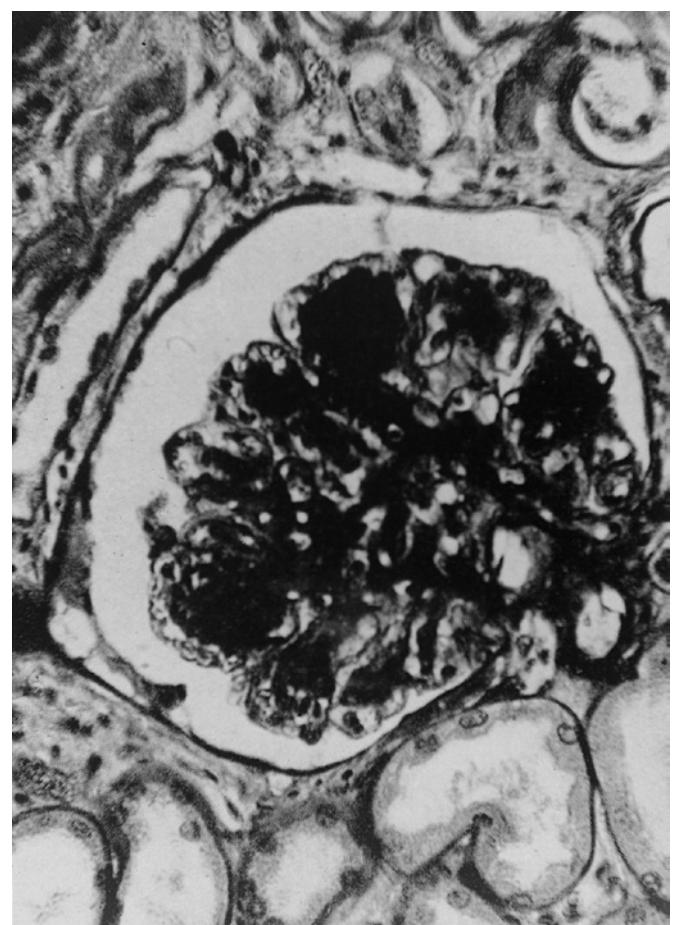


Figure 1.13 Nodular glomerulosclerosis. Figure from the paper by Kimmelstiel and Wilson, 1936 [41]. Source: Courtesy of the British Medical Association Library.

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’.

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

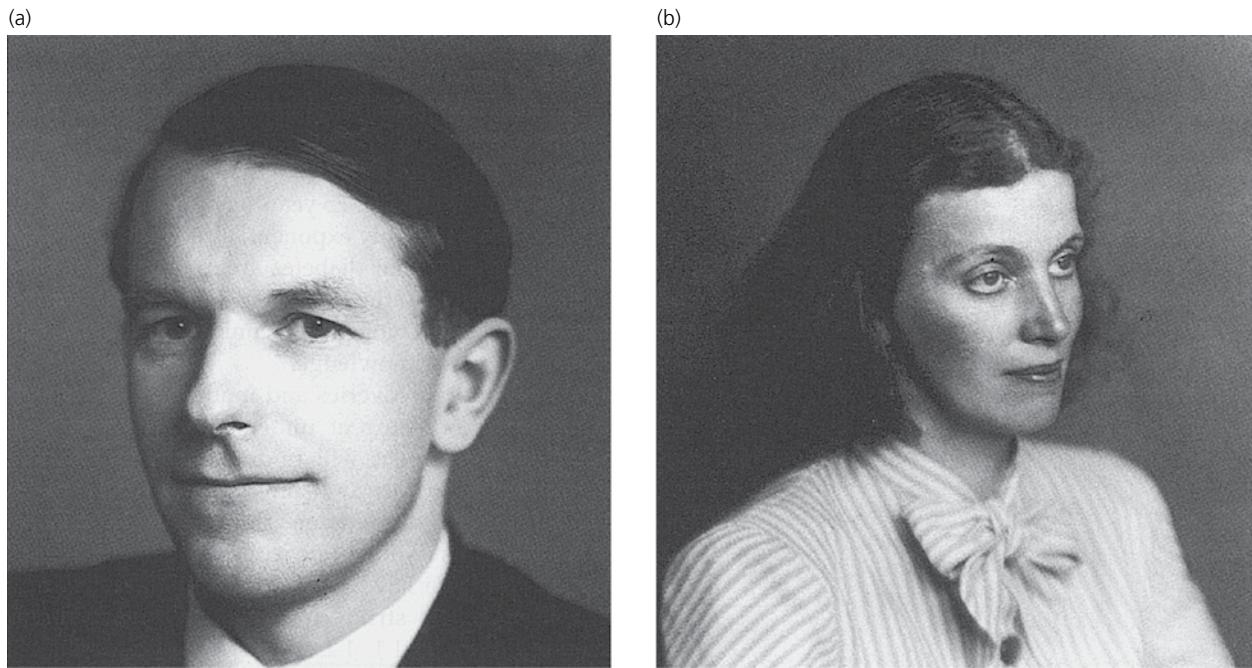


Figure 1.15 (a) Frederick Sanger (1918–2013) and (b) Dorothy Hodgkin, née Crowfoot (1910–1994). Source: Courtesy of Godfrey Argent Studio, London.



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 Petrin (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 sulfonylureas
Auguste Loubatières (France, 1942)	Discovered hypoglycaemic action of prototype sulfonylurea Carbutamide introduced
H. Franke and J. Fuchs (Germany, 1955)	Phenformin introduced
G. Ungar (USA, 1957)	Troglitazone, first thiazolidinedione introduced
Parke-Davis (1997)	Exenatide, first GLP-1 receptor agonist introduced
Eli Lilly (2005)	Sitagliptin, first DPP-4 inhibitor introduced
MSD (2007)	Canagliflozin, first SGLT2 inhibitors
Janssen (2013)	
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 <i>Retinitis proliferans</i>
Gerd Meyer-Schwickerath (Germany, 1964)	First use of Xenon photoocoagulation
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 insulin, 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, synthalitin, 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 Karlsruhe, 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

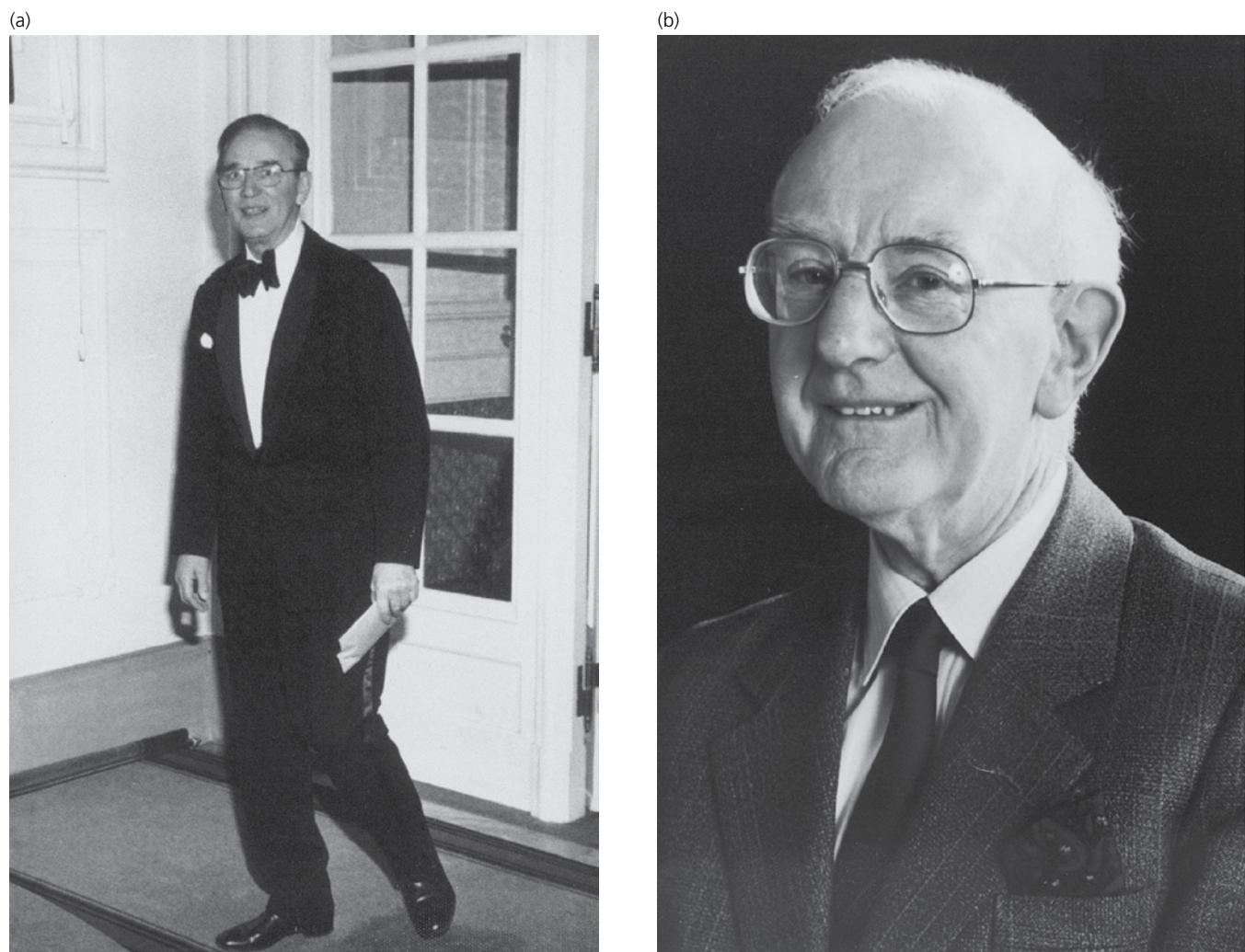


Figure 1.20 (a) Jørgen Pedersen (1914–1978) and (b) Ivo Drury (1905–1988), pioneers, with Priscilla White (1900–1989), in the management of pregnancy in women with type 1 diabetes. Source: Courtesy of Dr Carl Erik Mogensen and the Royal College of Physicians of Ireland.

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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Archives

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2

Classification and Diagnosis of Diabetes

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Key points

- Diabetes is a complex metabolic disease characterized by high levels of blood glucose and/or glycated haemoglobin (HbA_{1c}) resulting from defects in insulin secretion, insulin action, or both.
- There are three main types of diabetes and other less common specific types of diabetes with varied and overlapping aetiology.
- Although blood glucose remains the mainstay for the diagnosis of diabetes, HbA_{1c} is approved as an alternative diagnostic test for hyperglycaemia and in many countries is being increasingly used in place of glucose.
- Recent suggestions to classify diabetes according to β -cell defects may facilitate personalized, optimal therapy, but the diagnostic tests are too costly or unavailable in most laboratories.
- Varied diagnostic criteria for gestational diabetes are still being used.
- Impaired glucose tolerance (IGT) is a predictor of future type 2 diabetes and is also a cardiovascular risk factor.

Diabetes is one of the most common metabolic diseases with a complex, multifactorial aetiology and has varied clinical and biochemical manifestations. Multiple and varied therapeutic approaches are required for the glycaemic management of the different types of diabetes. The main pathological abnormalities of diabetes are an inadequate secretion and/or impaired action of insulin on target tissues. The severity of the resultant hyperglycaemia and the symptoms and signs vary widely. The development of diabetes-related microvascular complications depends largely on the degree and duration of hyperglycaemia.

Diabetes mellitus has been known since ancient times. The term *diabetes* was probably first used by Apollonius of Memphis around 250 BCE. The Latin word *mellitus* was added later, as the urine of people with diabetes was sweet and was used to distinguish diabetes mellitus from diabetes insipidus caused by defects in vasopressin [1].

Diabetes was described as early as 1500 BCE by Hindu scholars and Egyptian and Greek physicians as a mysterious disease causing emaciation and excess urination. If the urine tasted sweet, diabetes was diagnosed [2]. It was only in the 1800s that chemical tests were developed to detect the presence of sugar in the urine. The early descriptions were probably related to severe forms of the disease, either type 1 diabetes or overt type 2 diabetes.

In the late nineteenth century two categories were recognized: one category was described as occurring in young people with a short time course before ketoacidosis occurred, and the second one was described as common in older people and those with obesity. In 1936, Himsworth showed that diabetes could be divided into insulin-resistant and insulin-sensitive types, with the former being more common among older people [3].

Definition

Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Diabetes is distinguished by disturbances in carbohydrate, fat, and protein metabolism. The clinical symptoms include polyuria, polydipsia, polyphagia, weight loss, tiredness, and blurring of vision. With severe metabolic dysregulation, ketoacidosis or hyperosmolar non-ketotic coma may occur. However, symptoms may be mild or absent among people with type 2 diabetes for many years, especially when hyperglycaemia is minimal. Although the disease may remain undetected, tissue damage may develop and therefore diabetes-related complications may be present at the time of diagnosis [4,5]. Chronic hyperglycaemia may impair growth in children and increase the susceptibility to certain infections. In addition to the classic symptoms, people with diabetes may present with vague symptoms such as unexplained weight loss, fatigue, restlessness, and body pain.

Diabetes is associated with the development of long-term complications that can be divided into two main types. Microvascular complications include retinopathy (with potential loss of vision), nephropathy (leading to renal impairment), peripheral neuropathy (with risk of foot ulcers, amputations, or Charcot joints), and autonomic neuropathy (causing gastrointestinal, genitourinary, and cardiovascular symptoms, and sexual dysfunction) [4,5]. Macrovascular complications include cardiovascular diseases with increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular diseases as well as heart failure. Hypertension and dyslipidaemia often coexist in people with diabetes.

Diagnosis and classification of diabetes

Although variations in the presentation and course of diabetes have been known for many centuries, a clear distinction between two types of diabetes emerged only in the twentieth century. The first real attempt to classify diabetes was by the World Health Organization (WHO) Expert Committee on Diabetes Mellitus, which classified diabetes based on the age of onset of the disease into juvenile-onset diabetes and maturity-onset diabetes [6]. Although other phenotypes such as the brittle, gestational, pancreatic, endocrine, insulin-resistant, and iatrogenic varieties were described at that time, there was no clear understanding of the aetiology.

Blood glucose measurements became common, but no standard criteria for diagnosis were used. The diagnosis was usually made if there were clinical symptoms with high blood glucose levels and glycosuria. In juvenile-onset diabetes, ketonuria was noted to be common. Later on, with the availability of insulin measurement using radioimmunoassay, insulin deficiency or lack of insulin secretion in juvenile-onset diabetes and apparently normal or raised levels in maturity-onset diabetes could be demonstrated.

The WHO has published several guidelines for the diagnosis of diabetes since 1965 [5–7]. Its second report, published in 1980 [7], marked the beginning of the modern classification, which was a revision of the criteria published by the National Diabetes Data Group (NDDG) [8]. For the first time, four major groups were defined: insulin-dependent diabetes mellitus (IDDM, type 1); non-insulin-dependent diabetes mellitus (NIDDM, type 2); the ‘other types’; and gestational diabetes mellitus. Two risk classes, previous abnormality of glucose intolerance and potential abnormality of glucose tolerance, were also suggested in place of the terms *pre-diabetes* or *potential diabetes*.

Both diagnosis and classification were reviewed in 1985 [9] and 1999 [5]. At the same time the American Diabetes Association (ADA) published a report of an expert committee on the diagnosis and classification of diabetes [10]. Both WHO and ADA classifications attempted to encompass both aetiology and clinical stages of the disease based on the suggestions of Kuzuya and Matsuda [11].

It was known that diabetes could progress through several clinical stages from normoglycaemia to ketoacidosis. With the discovery of human leucocyte antigen (HLA) and islet cell antibodies, it became clear that juvenile-onset diabetes or insulin-independent diabetes had an autoimmune aetiology. Although maturity-onset diabetes was thought to be a *milder* form of the disease, it was recognized that people with type 2 diabetes could progress through varying levels of hyperglycaemia to a stage where insulin was required. By contrast, it was also possible to revert from a stage of requiring insulin to a point where normoglycaemia could be maintained through non-pharmacological intervention with modification of health behaviours, which is now termed *remission of diabetes*.

Methods and criteria for diagnosing diabetes

The criteria for the diagnosis of diabetes recommended by the ADA in 2021 [12] and approved by the WHO [13] and the International Diabetes Federation (IDF) are shown in Table 2.1.

Table 2.1 Criteria for the diagnosis of diabetes.

FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

OR

2 h PG ≥ 200 mg/dl (11.1 mmol/l) during OGTT. The test should be performed, as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OR

HbA_{1C} $\geq 6.5\%$ (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP-certified and standardized to the DCCT assay.

OR

In a person with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).

In the absence of unequivocal hyperglycaemia, the diagnosis requires two abnormal test results from the same sample or in two separate test samples.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; NGSP, National Glycohemoglobin Standardization Program; OGTT, oral glucose tolerance test; PG, plasma glucose; WHO, World Health Organization.

Source: Reproduced from the American Diabetes Association Standards of Care 2021 [12].

Diagnostic thresholds

The thresholds for the diagnosis of diabetes are currently based on the glycaemic levels above which diabetes-related microvascular complications mostly occur. However, these thresholds have changed over time. The oral glucose tolerance test (OGTT) was first introduced by Hofmeister in 1889, but this was not standardized and various amounts of glucose with different two-hour thresholds were used throughout the 1960s and 1970s. The second WHO report published in 1980 [7] marked a breakthrough in harmonizing the diagnosis of diabetes. The report established that diabetes could be diagnosed with a casual plasma glucose of >11.0 mmol/l (200 mg/dl) or with a 75 g OGTT using fasting and two-hour thresholds of ≥ 8.0 mmol/l (145 mg/dl) and >11.0 mmol/l (200 mg/dl), respectively. The two-hour threshold was based on the observed risk of developing retinopathy in several populations, but there were less robust data for the fasting glucose threshold, which was later revised to the current value of 7.0 mmol/l (126 mg/dl).

In the development of diabetes, there is a stage when the blood glucose values are above normal, but below the thresholds used for defining diabetes, which is termed *pre-diabetes* or *intermediate hyperglycaemia*. Pre-diabetes encompasses abnormalities in fasting glucose (impaired fasting glycaemia) and two-hour post-glucose challenge glucose (impaired glucose tolerance, IGT). Both impaired fasting glycaemia and IGT increase the risk of developing diabetes, with approximately one-third of people with IGT developing type 2 diabetes; the annual incidence rate ranges between 2% and 10% depending on the population and the presence of risk factors [13]. Use of the term ‘pre-diabetes’ has been criticized on the basis that not all people with this condition progress to type 2 diabetes, and the term ‘intermediate hyperglycaemia’ is preferred by many. The diagnostic thresholds for pre-diabetes have also changed over time. The category of IGT was introduced by the WHO in 1965 and after a few iterations it was defined as a fasting glucose value of <7 mmol/l (126 mg/dl) and post-glucose value between ≥ 7.8 mmol/l (140 mg/dl) and

<11.1 mmol/l (200 mg/dl) [14]. The 1997 ADA and 1999 WHO criteria defined impaired fasting glucose (IFG) as a fasting glucose value between ≥ 6.1 mmol/l (110 mg/dl) and <7.0 mmol/l (126 mg/dl). In 2003, the ADA revised the lower cut-off value to ≥ 100 mg/dl (5.7 mmol/l). The reduction of normal fasting value to ≤ 100 mg/dl was partly to ensure that the prevalence of IFG was similar to that of IGT. Furthermore, many studies have shown that 5.6 mmol/mol (100 mg/dl) provides the best cut-point for predicting future diabetes and the level at which insulin secretion becomes abnormal. However, lowering this threshold significantly increases the prevalence of pre-diabetes, which has important personal and public health implications [15, 16]. As such, the WHO and other organizations did not adopt this change [15].

In 2011, glycated haemoglobin (HbA_{1c}) was also introduced as a further diagnostic criterion for diabetes, with a threshold of 6.5% (48 mmol/mol) [4, 17]. The HbA_{1c} test should be performed using the method certified by the National Glycohemoglobin Standardization Program or International Federation of Clinical Chemistry. A value of $<6.5\%$ (<48 mmol/mol) does not exclude diabetes diagnosed using glucose tests. The ADA report recognizes that individuals with an HbA_{1c} between 5.7% and 6.5% are at risk of diabetes and includes HbA_{1c} as a means of diagnosing pre-diabetes [17]. It should be noted that the risk of diabetes is continuous, can extend below the lower limit of the range, and is disproportionately greater at the higher end of the range [4].

Number of abnormal tests required

In an individual with classic symptoms of hyperglycaemia, only one measurement of glucose or HbA_{1c} above the diagnostic threshold is required to make the diagnosis. In the absence of a clear history of diabetes symptoms, however, the diagnosis of diabetes requires two abnormal test results from the same sample or in two separate test samples. Where there is uncertainty, the WHO and ADA recommend that a standard 75 g OGTT is used if possible in conjunction with HbA_{1c} measurement. However, clinical practice is changing and in many high-income countries, where procedures for the accurate measurement of HbA_{1c} are readily available, the OGTT is being used less and less frequently. In these settings, a single blood sample with measure of either fasting or random glucose and HbA_{1c} is more commonly used for the diagnosis.

Further considerations of method of diagnosis

When used on a population basis, fasting glucose, two-hour glucose, and HbA_{1c} identify slightly different groups of people as having diabetes. Thus, an individual may test positive for diabetes with one test but not another. As the OGTT combines both fasting and two-hour glucose, using fasting glucose alone will identify fewer people with diabetes than an OGTT. Studies in Asian populations [18] and the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) study [19] showed that if only fasting blood glucose was used, nearly one-third of cases with diabetes might be missed at diagnosis. There are similar concerns about HbA_{1c} , but with time the groups coalesce to the point where all three tests become positive.

Analytical considerations

Blood glucose measurement has been the mainstay of diagnosis and monitoring glycaemic levels in diabetes for many decades. The OGTT is a comparatively inexpensive, sensitive index of hyperglycaemia including impaired glucose homeostasis. Standard enzymatic methods of glucose estimation are in widespread use.

Table 2.2 Advantages and limitations of using HbA_{1c} .

Advantages	Limitations
<ul style="list-style-type: none"> • Random sampling • Fasting not required • High sample stability • Negligible biological variability • Highly reproducible • Indicator of long-term glycaemic status • Single whole blood sample • Minimal assay variability and accuracy are assured when standard methods are used • Standardized across instruments • Guides physicians on the appropriate treatment • Predictive of development of vascular complications • Point-of-care tests are available in high-income countries 	<ul style="list-style-type: none"> • Depends on changes in lifespan of erythrocytes • Genetic and ethnic variations • Affected by haemoglobinopathies • Affected by severe anaemia, hence may not be valid in people with chronic renal and liver diseases • May be unreliable in individuals with human immunodeficiency virus (HIV) • May not be valid in children, in older people, and in pregnancy • Assays are not standardized in many middle- and low-income countries • High cost • Lack of awareness among citizens and physicians in developing countries

However, high biological variability, poor reproducibility, and influence by acute factors such as stress, food, exercise, and some medications are the main disadvantages of using blood glucose. Moreover, precautions must be taken to reduce the lowering of sample glucose by glycolysis by adding anti-glycolytic agents, such as sodium fluoride. Despite this, the rate of decline in glucose concentration continues for up to four hours in small quantities. In addition, there are differences in glucose concentrations in whole blood, plasma and serum and between capillary and venous blood. The availability of point-of-care testing with glucometers has helped to reduce the disadvantages of blood glucose measurement to some extent. Moreover, rapid bedside measurements have also become possible with these meters.

HbA_{1c} , initially identified as an index of chronic hyperglycaemia, has now evolved into a valuable tool to monitor glycaemic management, for screening and diagnosis of diabetes and pre-diabetes, and as a predictor of micro- and macrovascular complications [20, 21]. Presently the results are traceable to the Diabetes Control and Complications Trial (DCCT) assay values (measured as %) [22] and can also be compared to the highly accurate International Federation of Clinical Chemistry (IFCC) standardized values (mmol/mol) [20]. Measuring HbA_{1c} has multiple advantages over blood glucose, but also has a few limitations, particularly in middle- and low-income developing countries (Table 2.2). Healthcare professionals using the test should be aware of these limitations and employ their discretion in interpreting the results [20, 23].

Classification of diabetes types

The aetiological classification of diabetes was described by the WHO [5] and also approved by the ADA [12]. The classification of type 2 diabetes is largely characterized by exclusion. The most recent WHO classification published in 2019 is shown in Table 2.3 [13].

As new causes are discovered they are included as 'other specific types', such as maturity-onset diabetes of the young (MODY).

Table 2.3 Classification of diabetes.

Type of diabetes	Brief description
Type 1 diabetes	β -cell destruction (mostly immune mediated) and absolute insulin deficiency; onset most common in childhood and early adulthood
Type 2 diabetes	Most common type, various degrees of β -cell dysfunction and insulin resistance; commonly associated with overweight and obesity
Hybrid forms of diabetes	
Slowly evolving, immune-mediated diabetes of adults	Similar to slowly evolving type 1 diabetes in adults, but more often has features of the metabolic syndrome, has a single glutamic acid decarboxylase (GAD) autoantibody, and retains greater β -cell function
Ketosis-prone type 2 diabetes	Presents with ketosis and insulin deficiency but later does not require insulin; common episodes of ketosis, not immune mediated
Other specific types	
Monogenic diabetes	Caused by specific gene mutations; has several clinical manifestations requiring different treatment, some occurring in the neonatal period, others by early adulthood
Monogenic defects of β -cell function	Caused by specific gene mutations; has features of severe insulin resistance without obesity; diabetes develops when β cells do not compensate for insulin resistance
Monogenic defects in insulin action	Various conditions that affect the pancreas can result in hyperglycaemia (trauma, tumour, inflammation, etc.)
Diseases of the exocrine pancreas	Occur in diseases with excess secretion of hormones that are insulin antagonists
Endocrine disorders	Some medicines and chemicals impair insulin secretion or action, some can destroy β cells
Drug or chemical induced	Some viruses have been associated with direct β -cell destruction
Infection-related diabetes	Associated with rare immune-mediated diseases
Uncommon specific forms of immune-mediated diabetes	Many genetic disorders and chromosomal abnormalities increase the risk of diabetes
Other genetic syndromes sometimes associated with diabetes	
Unclassified diabetes	Used to describe diabetes that does not clearly fit into other categories. This category should be used temporarily when there is not a clear diagnostic category, especially close to the time of diagnosis
Hyperglycaemia first detected during pregnancy	
Diabetes in pregnancy	Type 1 diabetes or type 2 diabetes first diagnosed during pregnancy
Gestational diabetes	Hyperglycaemia below diagnostic thresholds for diabetes in pregnancy

Source: Adapted from the World Health Organization Report, 2019 [13].

The WHO has revisited the classification several times with no major modifications. IGT was removed from the formal classification of type 2 diabetes, but was retained as a risk state. A new category of risk status, IFG, was introduced.

Type 1 diabetes

In most cases, type 1 diabetes occurs as a result of cellular-mediated autoimmune destruction of pancreatic β cells, causing an absolute deficiency of endogenous insulin. People with type 1 diabetes are dependent on exogenous insulin for survival and are ketosis prone. Markers of the immune destruction of the β cell include islet cell autoantibodies, autoantibodies to insulin, glutamic acid decarboxylase (GAD), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2 β . One or more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycaemia is initially detected. The disease also has strong HLA associations, with linkage to the DQA and DQB genes, and is influenced by the DRB genes.

The rate of destruction of β cells is usually rapid in infants, young children, and adolescents and they often have ketoacidosis at the time of first presentation. Some people with type 1 diabetes, mostly adults, have a slower deterioration of β -cell function and show detectable levels of plasma C-peptide for many years. Type 1 diabetes is associated with other autoimmune disorders such as Graves' disease,

Hashimoto's thyroiditis, Addison's disease, vitiligo, coeliac-sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anaemia.

About 2–12% of people diagnosed with type 1 diabetes show phenotypic characteristics of type 2 diabetes at diagnosis and initially have glucose levels within target on oral anti-diabetes agents, before rapidly progressing to requiring insulin. They also show the presence of autoimmune markers of β -cell destruction, such as GAD autoantibodies. This subgroup was termed *latent autoimmune diabetes of adults* (LADA), but in the recent WHO classification the term LADA was removed because there was considerable controversy as to whether this was a separate condition to type 1 diabetes. It now comes under hybrid forms of diabetes with slowly evolving immune-mediated diabetes of adults [13].

A few people with type 1 diabetes may have no evidence of autoimmunity, but are prone to episodic ketoacidosis and may exhibit varying degrees of insulin deficiency and insulin dependency during those periods. This form, termed *idiopathic diabetes*, is commonly seen in people of African and Asian ethnicity and is strongly familial [4].

Type 2 diabetes

Type 2 diabetes constitutes more than 95% of the total population with diabetes. Its prevalence is increasing globally, but the most striking changes are now seen in low- and middle-income

countries. Type 2 diabetes may remain asymptomatic for many years and is undetected in nearly 50% of people affected by the disease [4, 5]. It is commonly diagnosed incidentally when a medical check-up is done for other reasons. Type 2 diabetes is characterized by a relative insulin deficiency; although there is insulin secretion, this is insufficient to overcome insulin resistance. Though many people with type 2 diabetes manage their diabetes with lifestyle changes alone, with time oral anti-diabetes agents are needed to maintain normoglycaemia, with many people eventually requiring insulin. Chronic exhaustion of β -cell function is a major cause of this.

Although research studies have focused on the molecular mechanisms underlying type 2 diabetes, only modest success has been achieved in unravelling the genetic abnormalities. In the past two decades, type 2 diabetes in children and adolescents has become common in Asian populations and could be partly attributed to the rising rates of obesity and changing lifestyle patterns [24]. A minority of people with type 2 diabetes are prone to episodes of ketosis. They have insulin deficiency but no immune markers. This hybrid form is termed ketosis-prone type 2 diabetes [13].

There has been a proposal to modify the classification of type 2 diabetes to identify people at increased risk of complications and support precision treatment by tailoring the type of therapy with greatest benefit for the individual with diabetes. Recently, a sub-stratification in 8980 individuals with newly diagnosed diabetes was undertaken in Sweden using clusters based on six variables: GAD antibodies, age at diagnosis, body mass index (BMI), HbA_{1c}, and estimates of β -cell function and insulin resistance. The analysis was based on prospective data from medical prescriptions and development of complications from electronic records of the examined individuals [25]. Five clusters of phenotypes with distinct characteristics were identified. Individuals in cluster 1 (severe autoimmune diabetes) had early-onset disease, low BMI, relatively higher HbA_{1c}, insulin deficiency, and presence of GAD antibodies. Cluster 2 (severe insulin-deficient diabetes) was GAD antibody negative, with low age at onset, low BMI, low insulin secretion, and relatively higher HbA_{1c}. Cluster 3 (severe insulin-resistant diabetes) had high insulin resistance and high BMI, while cluster 4 (mild obesity-related diabetes) had obesity but not insulin resistance. Cluster 5 (mild age-related diabetes) was older but was similar to cluster 4 with modest metabolic derangements. Among these the highest percentage (39.1%) was cluster 5 and the lowest cluster 1 (6.4%).

The clusters had varied dispositions to specific complications of diabetes such as kidney disease, coronary events, and stroke. Clusters 1 and 2 had a higher HbA_{1c} at diagnosis than the other clusters and a higher frequency of ketoacidosis. Cluster 2 had the highest risk of retinopathy, and cluster 3 had the highest prevalence of non-alcoholic fatty liver disease and chronic kidney disease. Cluster 4 had an increased risk of diabetes kidney disease and cluster 5 appeared to have a lower risk of renal disease.

The authors suggested that further improvement in the stratification may be possible through the inclusion of additional variables such as biomarkers, genotypes, or genetic risk scores. Therefore, the study suggested the superiority of identifying the new clusters during classification, which will possibly provide better guidance for appropriate treatment regimens. However, the tests required for identifying the clusters are costly and are available only in a limited number of advanced research institutions and hospitals. More detailed clinical trials are required to confirm the utility of this classification.

Other specific types

These forms of diabetes are relatively less common. The underlying defects of the disease processes can be identified in these forms, such as those listed in Table 2.3. Some of these defects are remediable and the diabetes can be cured [4, 5].

Gestational diabetes

For many years, gestational diabetes was defined a state of carbohydrate intolerance resulting in hyperglycaemia of variable severity, with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has previously gone unrecognized. The definition applies irrespective of whether or not insulin is used for treatment or whether the condition persists after pregnancy [12, 13]. According to this definition, gestational diabetes may develop at any stage of pregnancy, but many now consider diabetes detected during the first trimester of pregnancy to be previously undiagnosed pre-existing diabetes. The term gestational diabetes is then reserved for diagnoses made in the second or third trimester of pregnancy. Women who have diabetes and subsequently become pregnant are termed as having *diabetes mellitus and pregnancy* and should be treated accordingly during and after the pregnancy. This is discussed in greater detail in Chapter 71. The International Association of Diabetes and Pregnancy Study Groups' (IADPSG) criteria for diagnosis of gestational diabetes are shown in Table 2.4 [27]. These criteria have been adopted by main national guidelines, including

Table 2.4 Screening for and diagnosis of gestational diabetes.

One-step strategy

Perform a 75 g OGTT, with plasma glucose measurement when the individual is fasting and at 1 h and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes. The OGTT should be performed in the morning after an overnight fast of at least 8 h. The diagnosis of gestational diabetes is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dl (5.1 mmol/l)
- 1 h: 180 mg/dl (10.0 mmol/l)
- 2 h: 153 mg/dl (8.5 mmol/l)

Two-step strategy

Step 1: Perform a 50 g GLT (non-fasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes. If the plasma glucose level measured 1 h after the load is ≥ 130 , 135, or 140 mg/dl (7.2, 7.5, or 7.8 mmol/l, respectively), proceed to a 100 g OGTT.

Step 2: The 100 g OGTT should be performed when the individual is fasting. The diagnosis of gestational diabetes is made when at least two^a of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded:

- Fasting: 95 mg/dl (5.3 mmol/l)
- 1 h: 180 mg/dl (10.0 mmol/l)
- 2 h: 155 mg/dl (8.6 mmol/l)
- 3 h: 140 mg/dl (7.8 mmol/l)

GLT, glucose load test; OGTT, oral glucose tolerance test.

^aAmerican College of Obstetricians and Gynaecologists notes that one elevated value can be used for diagnosis [26].

Source: Adapted from American Diabetes Association, 2021 [12].

those of the ADA, but not by all countries [12]. Establishing a uniform approach to diagnosis will have extensive benefits for women, caregivers, and policy makers.

Women with any of the following risk factors should be screened with an appropriate blood test as shown in Table 2.4, during the first prenatal visit; if the result is found to be normal, they should be tested again between 24 and 28 weeks of pregnancy [12, 13]. The risk factors for gestational diabetes include older age, obesity ($BMI > 30 \text{ kg/m}^2$), history of elevated blood glucose levels or gestational diabetes during previous pregnancy, women who have large-for-gestational age babies, a strong family history of diabetes, and women from high-risk ethnic groups such as Asians [28].

Hyperglycaemia may resolve after the delivery, but 5–10% of women may continue to have diabetes, most often type 2 diabetes. These women require treatment with lifestyle changes and appropriate anti-diabetes agents. Women with gestational diabetes should be screened for diabetes immediately postpartum and again at 6–12 weeks postpartum using non-pregnant OGTT criteria [29]. HbA_{1c} cannot be used in the immediate postpartum period, but is an effective alternative way of screening for persistent glucose abnormalities from 12 weeks postpartum where the facilities for accurate measurement are available. Women with gestational diabetes are at risk of future diabetes outside pregnancy and should be offered screening on an annual basis. Women who show impaired glucose regulation at this

stage should be treated with lifestyle interventions and in some circumstances metformin.

Conclusion

The advances made in the past two decades in diagnostic and research methodologies for identifying pathophysiological components of various types of diabetes have provided significant clarity in the classification and diagnosis of diabetes [26]. This has helped to establish some uniformity in data collection and has also allowed comparison of the international profile of the disease. Consensus in establishing diagnostic criteria for gestational diabetes is lacking. Emphasis should be given to identifying the pre-diabetes states that are the strongest predictors of incident type 2 diabetes.

The classification of diabetes should facilitate optimal personalized diabetes care. There are many diabetes subtypes, especially among type 2 diabetes, type 1 diabetes, and the autoimmune type of diabetes. The current state of knowledge suggests that the classification should be based on β -cell pathology contributing to β -cell dysfunction [30]. At present, the facilities for specialized analysis required for such a classification, such as genotyping and advanced immune pathology, are available only in a few advanced specialized research laboratories and are too costly [31, 32]. Nevertheless, the classification of diabetes continues to evolve as underlying genetic and other factors become identified with increasing precision.

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3

The Global Burden of Diabetes

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Key points

- Diabetes results in a range of distressing symptoms, altered daily functioning (requiring attentive self-care, health monitoring, and treatments), changed family roles, higher healthcare costs, lost productivity, disability, and premature mortality, which are felt by individuals, households, communities, and national economies.
- The prevalence of diabetes has grown worldwide, with no country or region spared. Concerningly, estimates of prevalence and absolute numbers of people living with diabetes have consistently outpaced each previous projection. Projections for 2045 suggest that the greatest increases will be seen in low- and middle-income countries.
- In contrast, evidence from predominantly high-income countries suggests that diabetes incidence may have started to decline in more recent years.
- Diabetes is a leading cause of death in the world with 4.2 million deaths annually, equivalent to one death every eight seconds. Diabetes-related mortality disproportionately affects low- and middle-income countries, the young, and economically active populations.
- Declining mortality among people with diabetes will increase the total years of life spent living with diabetes and may drive the emergence of new diabetes-related complications such as cancer, mental health disorders, cognitive impairment, and disability. A longer life lived with diabetes may also exacerbate the risk of established diabetes macrovascular and microvascular complications, as well as infections, including the newly emerged Covid-19.
- In 2019, the global direct health expenditure of diabetes was estimated to be US \$760 billion and is expected to grow substantially in the coming decades. The majority of this spending (~90%) is in high-income countries, despite a greater absolute diabetes burden in low- and middle-income countries, exacerbating existing disparities between high-income countries and low- and middle-income countries.
- Diabetes impairs one's ability to perform domestic and occupational activities. Decreased workplace productivity, impaired interpersonal relationships, and perceived discrimination can impede diabetes self-management and affect an individual's ability to integrate fully into society.
- Preparation for the increasing diabetes burden requires progress in the wider collection of reliable data in a standardized manner across various countries. In particular, there is a current scarcity of data from low- and middle-income countries regarding diabetes-related mortality, complications, disability, and costs.
- Confronting the increasing burden of diabetes, particularly in vulnerable subpopulations, will require addressing the underlying political, social, cultural, behavioural, and economic factors that impede the translation of known effective strategies to reduce diabetes risk in the population.

Diabetes is one of the fastest-growing health challenges of the twenty-first century. The number of adults living with diabetes has more than tripled over the past 20 years, with serious health-related and socioeconomic impacts on individuals and populations alike. Pandemic growth of diabetes is spurred on by transitioning demographic (e.g. population ageing), nutritional, and lifestyle patterns, and an affiliated proliferation of overweight and obesity in adults and children [1–3]. The International Diabetes Federation (IDF) estimated that there were 463 million people with diabetes worldwide in 2019 and projects that the absolute number will reach 700 million by 2045 if current trends persist [1]. The overwhelming

majority of this escalation will be attributable to an increase in type 2 diabetes, with the greatest impact expected in low- and middle-income countries (LMIC) due to rapid socioeconomic and lifestyle transformations [4–6].

Current estimates suggest that three-quarters of those affected by diabetes live in LMIC [1, 7]. This challenges previously held paradigms that distinguished chronic non-communicable diseases as problems of affluent countries alone. Although the greater absolute burden of diabetes may be partially explained by the larger population size of LMIC, the growth rates for non-communicable diseases in rapidly transitioning LMIC are much higher than those in more

affluent high-income countries (HIC) [8]. For example, it was previously estimated that by 2025, the number of people with diabetes will increase by 170% in LMIC, compared with a 41% increase in HIC [9].

Thus far, the attention on health burdens in LMIC has justifiably focused on the persistence of infectious diseases, reproductive health problems, and nutritional deficiencies. However, these same countries must also contend with 80% of the global mortality associated with chronic diseases [10, 11]. Projections suggest that this already overwhelming ‘double burden’ will be exacerbated by the further growth of non-communicable diseases such as diabetes. Altogether, projected increases in diabetes in all corners of the world will result in a corresponding escalation of burdens in the form of serious morbidity, disability, diminished life expectancy, reduction in quality of life, loss of human and social capital, and individual and national income losses. This chapter describes these burdens in a global context, and systematically introduces data regarding regional patterns and associated themes.

Prevalence

In recent decades, large increases in diabetes prevalence have been demonstrated in virtually all regions of the world, largely attributed to a rise in type 2 diabetes and its risk factors. In 2019, 1 in 11 adults aged 20–79 was living with diabetes (463 million people), of whom 79% were living in LMIC [1]. Quantification of the prevalence of diabetes is important for healthcare planning and resource allocation and facilitates the formulation of appropriate disease prevention and control strategies. However, there are still insufficient representative and rigorous epidemiological data from many LMIC to reliably capture the true global diabetes burden. Moreover, the utility of currently available estimates is hampered by methodological deficiencies (e.g. inconsistent diagnostic criteria, poor standardization of methods) and limited coverage (e.g. regional sampling with a predominance of urban studies even though many of the populations in question have large numbers of rural inhabitants) [12, 13]. To address these barriers, the IDF and World Health Organization (WHO) use sophisticated modelling approaches to provide global estimates, by country, for diabetes prevalence. In the

following, we highlight notable patterns in the three most common types of diabetes, type 1 diabetes, type 2 diabetes and gestational diabetes mellitus (GDM), and compare estimates by different income-group regions.

Type 1 diabetes

The prevalence of type 1 diabetes is increasing worldwide due to a combination of improved survival and an increase in incidence, thought to be driven by environmental and lifestyle-related changes [14], such as rapid weight gain and/or inappropriate feeding in infancy [15, 16]. In 2019, the number of children and adolescents aged 0–14 years and 0–19 years with type 1 diabetes was 600 900 and 1.1 million worldwide, respectively, with a large proportion residing in Europe and North America where incidence continues to increase [17–19] (Table 3.1). India, the USA, and Brazil have the largest numbers of children and adolescents living with type 1 diabetes, with 95 600, 94 200, and 51 500, respectively, as of 2019.

The prevalence of type 1 diabetes in adults is less well known and estimates typically rely on self-reporting of diabetes type and treatment status, thus are limited in their ability to accurately distinguish between type 1 and type 2 diabetes in adults [20, 21]. Consequently, a global perspective on the prevalence of type 1 diabetes in adults remains elusive.

Type 2 diabetes

In 2019, it was estimated that 9.3% of all adults aged 20–79 years (463 million) were living with diabetes, with the majority assumed to be type 2 diabetes. This is projected to increase to 10.9% (700.2 million) in 2045, with the greatest increases expected to be seen in LMIC. Age-adjusted comparative prevalence estimates are shown in Table 3.1 and vary by region, whereby the highest prevalence is seen in the Middle East and North Africa regions. The countries with the largest absolute number of adults aged 20–79 years with diabetes are China (116 million), India (77.0 million), and the USA (31 million), though countries with the highest age-adjusted prevalence of diabetes include some Pacific islands, Pakistan, Sudan,

Table 3.1 Estimated numbers of children and adolescents with type 1 diabetes and prevalence of type 2 diabetes in adults and gestational diabetes mellitus (GDM; hyperglycaemia in pregnancy) in pregnant women by region.

	Type 1 diabetes	Type 2 diabetes	GDM
Region	Number of children and adolescents (0–14 yr) with type 1 diabetes (in thousands)	Age-adjusted prevalence (%) and 95% confidence interval (CI) among adults aged 20–79	Age-adjusted prevalence (%) of GDM, and numbers of births (millions) among pregnant women
Africa	10.0	4.7 (3.2–8.1)	9.6 (3.5)
Europe	162.6	6.3 (4.9–9.2)	16.3 (2.0)
Middle East and North Africa	82.0	12.2 (8.3–16.1)	7.5 (1.9)
North American and Caribbean	121.4	11.1 (9.0–14.5)	20.8 (1.6)
South and Central America	69.0	8.5 (6.7–11.3)	13.5 (1.0)
South-East Asia	100.0	11.3 (8.0–15.9)	27.0 (6.6)
Western Pacific	56.0	11.4 (8.3–15.6)	12.3 (3.8)
World	600.9	8.3 (6.2–11.8)	14.4 (20.4)

Source: Data sourced from the 2019 IDF Diabetes Atlas [1].

Part 1 Diabetes in its Historical and Social Context

and other countries in the Middle East and North Africa. National prevalence estimates of 15–30% are reported in these countries.

The prevalence of type 2 diabetes also varies considerably between subpopulations within countries or regions. For example, in established market economies, those in lower socioeconomic groups (e.g. lower education, lower income) have a higher burden of diabetes relative to higher socioeconomic groups. In LMIC regions, the prevalence of diabetes typically remains lower in lower and middle socioeconomic classes; however, these groups tend to make up a larger proportion of the overall population and thus the absolute number of people affected by diabetes in these social groups is much higher than in their wealthier counterparts [22, 23]. Further, there are major differences in prevalence between ethnic groups. For example, both Hispanic and Asian populations have a higher prevalence of diabetes compared with European and sub-Saharan African populations [24, 25]. This is likely due to multiple factors, including genetic, epigenetic, lifestyle, and environment. More epidemiological data, especially from longitudinal studies, are needed to inform our understanding of pathophysiology, and studies are required to determine best practices and describe effective interventions to screen, prevent, and manage diabetes in country-specific settings. The following are some notable examples of within-country and within-region variations based on available data. The regions are based on groupings used by the IDF.

Sub-Saharan Africa

- Diabetes prevalence varies considerably between countries in this region, with age-adjusted prevalence estimates ranging from a low of 1.0% in Benin to a high of 12.7% in South Africa [1]. There is also great variability in rural versus urban prevalence, with urban areas facing the brunt of the burden [26–28]. The wide variation in diabetes prevalence may be explained partly by regional differences in lifestyle and body mass index (BMI).
- A higher prevalence of diabetes has been noted among people of Egyptian and Asian Indian origin as compared with Indigenous African people [13, 29].
- Data on diabetes prevalence in sub-Saharan Africa originate from just a few localized centres in certain parts of the continent, and estimates vary widely, between 0% and 3% in rural areas and 6% and 12% in urban environments [13, 30]. Further, data on population-level dietary and physical activity patterns, suspected to be key drivers leading to an increase in diabetes, are severely lacking in African countries.
- As human immunodeficiency virus (HIV) mortality declines through widespread uptake of anti-retroviral therapies, the direct (e.g. pancreatic dysfunction associated with therapy) and indirect (e.g. increased life expectancy) effects are likely to have an impact on diabetes prevalence [31].

Europe

- Across 56 countries that vary markedly in size, language, ethnic groups, and affluence, the age-adjusted prevalence ranges from 2.1% in Greenland to 11.1% in Turkey [1].
- Structural deprivation may explain part of the regional differences, along with individual socioeconomic status and ethnic mix [32, 33].

Middle East and North Africa

- The Middle East and North Africa region has some of the highest age-adjusted diabetes prevalence estimates in the world, ranging from 5.4% in Yemen to 22.1% in Sudan [1].

- The Gulf region has experienced an especially marked and sudden increase in rates of diabetes, where Kuwait (12.2%), Saudi Arabia (15.8%), and Bahrain (15.6%) now rank among the countries with the highest prevalence of type 2 diabetes worldwide [1].

North America and Caribbean

- Diabetes prevalence is, generally, higher in Caribbean than in North American countries, with age-adjusted estimates ranging from 6.6% in Haiti to 14.2% in the British Virgin Islands (vs 7.6% in Canada and 10.8% in the USA) [1].
- In the USA, the variations by race and ethnicity have been extensively described, with ethnic minorities more likely to have a higher burden of diabetes. For example, a 2019 study demonstrated that among adults, the prevalence was 12.1%, 20.4%, 22.1%, and 19.5% in adults of white European, non-Hispanic Black, Hispanic, and non-Hispanic Asian ancestry, respectively [34].
- In Canada and the USA, diabetes prevalence is considerably higher in Indigenous than in non-Indigenous groups. In Canada, First Nations people living on reserve have an age-adjusted prevalence of 17.2% compared to 10.3% among First Nations living off reserve, and 5.0% among non-Indigenous Canadians [35]. The US Pima Indians have the highest prevalence of type 2 diabetes in the world, with 34.2% for Pima men and 40.8% for Pima women (compared to 9.3% in the calendar year-matched general US population) [36].
- Life expectancy of people with diabetes in North America, although reduced compared with the general population [37], is markedly higher than in LMIC.

South and Central America

- The average age-adjusted prevalence of diabetes is 8.5%, but ranges from 5.5% in Ecuador to 13.7% in Puerto Rico [1], reflecting the diversity of ethnicities and stages of development between countries [7].
- Indigenous populations are estimated to have a high prevalence of metabolic dysfunction and diabetes, as has been noted in Brazil [38], but the patterns and proportions of Indigenous peoples in each country are not clearly documented [39].

South-East Asia

- The age-adjusted prevalence ranges from 7.2% in Nepal to 22.0% in Mauritius [1].
- South-East Asian adults are confronted with diabetes risk being manifest at younger ages and at lower BMIs compared with populations in other regions [40], possibly due to lower insulin secretion and a greater tendency for deposition of metabolically active visceral adiposity [41–43].
- Rural–urban differences in prevalence of diabetes among Asians suggests genetic, and environmental factors, and their interactions all have a role to play [44].

Western Pacific

- The age-adjusted prevalence ranges from 3.9% in Myanmar to 30.5% in the Marshall Islands [1].
- Indigenous populations in Australian and New Zealand, similar to those in Canada and the USA, are disproportionately burdened by diabetes. In Australia and New Zealand, Indigenous [45] and Māori and Pacific [46] peoples are three times more likely to have diabetes compared to their non-Indigenous counterparts.
- In China, rural areas have historically had a lower prevalence of diabetes compared with urban areas. However, a 2020 study reported that diabetes prevalence in rural regions has increased at a

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- IDF *see* International Diabetes Federation
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