英文影印版

第18版 EIGHTEENTH EDITION

DAVIDSON'S Principles and Practice of MEDICINE

戴维森内科学

EDITED BY
Christopher Haslett
Edwin R. Chilvers
John A.A. Hunter
Nicholas A. Boon

科学出版社
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The Editors

Christopher Haslett BSc (Hons) FRCPE FRCP
Professor of Respiratory Medieine, University of Edinburgh
Chairman of the Division of Clinical and Community Science, University of Edinburgh
Honorary Consultant Physician, Royal Infirmary of Edinburgh

Edwin R. Chilvers BMedSci BMBS PhD FRCPE
Professor of Respiratory Medicine, University of Cambridge School of Clinical Medicine
Honorary Consultant Physician, Addenbroode's and Papworth Hospitals, Cambridge

John A.A. Hunter OBE BA MD FRCPE
Professor of Dermatology. University of Edinburgh
Honorary Consultant Dermatologist, Royal Infirmary of Edinburgh

Nicholas A. Boon MA MD FRCPE
Consultant Cardiologist, Royal Infirmary of Edinburgh
Honorary Senior Lecturer, Department of Medicine, University of Edinburgh

Illustrated by
Robert Britton

SCIENCE PRESS
Harcourt Asia
Churchill Livingstone

Christopher Haslett, Edwin R. Chilvers, John A.A. Hunter, Nicholas A. Boon: Davidson's Principles and Practice of Mediceine, 18th Edition

Reprint ISBN 981-4066-75-3

北京市版权局版权登记号： 01-2000-3874

图书在版编目（CIP）数据

戴维森内科学：英文 / （美）哈斯利特（Haslett, C）著.
—影印版. —北京：科学出版社，2001.1
ISBN 7-03-008856-5

Ⅰ.戴… Ⅱ.哈… Ⅲ.内科学—教材—英文 Ⅳ.R5

中国版本图书馆 CIP 数据核字 （2000） 第 76249 号

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科学出版社 出版
北京东黄城根北街 16 号
邮政编码：100717
中国科学院印刷厂 印刷
科学出版社发行 各地新华书店经销
*
2001 年 1 月第 一 版 开本：850×1168 1/16
2001 年 1 月第一次印刷 印张：74 1/4
印数：1—3 000 字数：1 800 000
定价：186.00 元
（如有印装质量问题，我社负责调换〈环伟〉）

SCIENCE PRESS
A division of China science Publishing Group
16 Donghuangchenggen North Street,
Beijing 100717
China

HARCOURT ASIA PTE.LTD
A Harcourt Publishers International Company
583 Orchard Road #09-01 Forum
Singapore 238884

Distribute in the Mainland China by Science Press,
16 Donghuangchenggen North Street, Beijing 100717, China.

Printed in China by HARCOURT ASIA PTE, LTD and SCIENCE PRESS under special arrangement with Churchill Livingstone, A Harcourt Health Science Company. This edition is the only authorized complete and unabridged reproduction of the laest American Edition, published and priced for sale in China only, not including Hong Kong SAR and Taiwan.

This Edition First Printed in China in 2001
ISBN 7-03-008856-5/R · 630
Reprint ISBN 981-4066-75-3

Printed in China

Preface

Medicine is the most dynamic of biological disciplines; while the basic principles remain unaltered, current practice is undergoing exponential change. With this new edition of *Davidson's Principles and Practice of Medicine*, the central aim of the editors and contributors has been to reflect this transformation, whilst at the same time continuing our tradition of providing a concise yet up-to-date and comprehensive text on clinical medicine which meets the requirements of medical students preparing for their final examinations. Many doctors preparing for postgraduate qualifications such as the MRCP use 'Davidson' as a core text, together with *Macleod's Clinical Examination*, which focuses on clinical methods. Response from our readers reveals that a large number of general practitioners, nurses, pharmacists and other health-care professionals also value 'Davidson' as an easy-to-use reference source.

This truly international textbook has a large following of medical students and doctors all around the globe; their numerous comments have helped shape the development of this latest edition. Increased travel to the tropics only serves to reinforce our desire to continue to provide full and accurate coverage of infectious and tropical diseases.

The previous edition, which featured the introduction of colour, represented a new milestone in the long history of this textbook. This and other changes have been very well received and we thank the retiring editors, Professors Christopher Edwards and Ian Bouchier, for their work. Nevertheless, the content and presentation of this, the eighteenth, edition have been completely reworked and new chapters introduced without adding to the overall length (and weight!) of the book. This has been achieved by optimising the mix of text, information boxes, tables and illustrations. Popular innovations from the last edition have been reinforced. For example, the recognition that patients do not present with a 'disease' but with certain symptoms, or a constellation of symptoms, has led us to develop the 'major manifestations' sections in most chapters; indeed the neurology chapter is now almost entirely based on this approach.

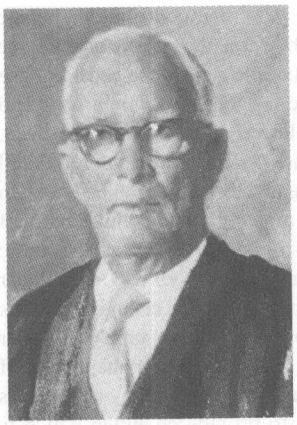
Most of the chapters have new or additional contributors, all of whom are leading figures in the teaching of medicine in their specialties. One of the purposes of this edition is to link recent scientific advances to disease pathogenesis and therapeutic innovations; many of our contributors pursue basic research in the diseases they describe and are able to give an exciting appreciation — 'from the gene to the bedside'. The boundaries between such topics as genetics, immunology and inflammation have become blurred, if not entirely removed, by the recent explosion of knowledge in molecular and cell biology. As a consequence, the eighteenth edition begins with a new chapter devoted to the molecular and cellular basis of disease which gives an up-to-date account of the basic machinery of life, taking the reader from DNA and intracellular processes through the biology of orchestrated cellular responses in inflammation and immunology to human genetics. Other major changes include a new chapter on the management of patients in the intensive care unit; the dermatology chapter has been extended and enhanced to provide coverage which is sufficient to meet the requirements of final examinations; the gastrointestinal chapter has been completely rewritten and contains more than 50 new illustrations; and the chapters on diabetes, nutrition and metabolic diseases, psychiatry, and oncology and palliative care have been focused to concentrate on important principles as they relate to medical practice.

'Davidson' has one of the longest pedigrees of any textbook designed for medical students, and this edition represents a further transformation. We hope that these changes considerably improve its value without losing its much-loved qualities of 'approachability and readability'. The editors believe that the eighteenth edition, in terms of content and presentation, is indeed a medical text which meets the needs of tomorrow's doctors.

Edinburgh and Cambridge 1999

C.H.
E.R.C.
J.A.A.H.
N.A.B.

Sir Stanley Davidson (1894–1981)



This famous textbook was inspired by one of the great Professors of Medicine of the present century. Stanley, as he was known by all, began his medical undergraduate training at Trinity College, Cambridge, but this was interrupted by World War I and later resumed in Edinburgh. He served in the Gordon Highlanders until he was seriously wounded in Belgium. That this period had a profound effect on his subsequent attitudes and values was clear from his emotional recollection, in later years, of the carnage and useless wastage of young life.

In the 1920s he favoured appointments in bacteriology, and this is reflected in his early interests. However, he soon decided to dedicate his life to clinical medicine and clinical research. Exciting contemporary discoveries led to an affection for haematology which he always retained and which was transmitted to many of his disciples.

In 1930 Stanley was appointed Professor of Medicine at the University of Aberdeen. This was one of the first full-time Chairs of Medicine anywhere, and the first in Scotland. The period in Aberdeen was marked by several developing qualities of academic leadership: toughness, fairness and integrity which quickly earned respect; finding and attracting young talent; recognition of the need for decent facilities and accommodation for teaching and research; and research emphasis on the needs of the community.

Appointment to the Chair of Medicine at his Alma Mater, Edinburgh, came in 1938 and he was to remain in this post until retirement in 1959. World War II was to inhibit and delay Stanley's aspirations for the Edinburgh Medical School, but those of us who were privileged to be undergraduate students at the time have much to remember. He was a splendid educator and a particularly gifted bedside teacher where everything had to be questioned and explained. He seemed to be totally at ease with everyone, and would stop and talk with students, nurses, domestic staff and frequently with a complete stranger. He had endless time to listen to and communicate with his patients, who quickly seemed at ease with him. His main thesis was that if you could take a good history and do a careful physical examination, the rest might not be too difficult or expensive. He gave most of the systematic lectures in Medicine himself, the substance of which was made available in typewritten notes; these were marked by an emphasis on essentials and far surpassed any textbook available at the time.

When the war ended Stanley's first priority was to develop the old municipal hospitals in the north of Edinburgh, to extend the teaching capacity of the Medical School and to recognise and establish units for the specialist branches of medicine that were beginning to emerge. These units were to be headed by the best physicians and teachers that could be found and were to retain commitment to general internal medicine. Within a few years Stanley's far-sightedness became reality.

But Stanley will be best remembered for this textbook, *The Principles and Practice of Medicine*. He conceived the idea in the late 1940s. It was to be of modest size and price and yet sufficiently comprehensive and up to date to provide the good student with the main elements of sound medical practice.

The origins of the book were Stanley's lecture notes. Each of the senior members of Stanley's now extended departmental family was given a chapter to write. In the early days there was occasional annoyance when a carefully drafted manuscript was massacred by Stanley's editorial pencil; but no offence was taken because none was intended. The book was to be readable without ambiguity, uncertainty or wordiness. The result, a masterpiece of clarity and uniformity of style, is the basis from which this eighteenth edition has evolved. Although the format and presentation have seen many changes, Stanley's original vision and objectives remain.

It is an honour to salute the memory of a great physician and teacher and, for a fortunate few, a great mentor and friend.

Edinburgh 1999 Professor John Richmond

Portrait reproduced by courtesy of the Royal College of Physicians of Edinburgh

Acknowledgements

Since the last edition of *Davidson's Principles and Practice of Medicine* Professor John Hunter and Dr Nick Boon have joined the Editorial Board and a total of 24 new authors have written or contributed new chapter material. While these changes have increased the breadth and depth of expertise necessary in any major revision, we are indebted for the invaluable past contributions from Dr Joyce D. Baird, Professor David J.H. Brock, Dr Anthony D.M. Bryceson, Dr Roger E. Cull, Professor Anne Ferguson, Professor Alasdair M. Geddes, Dr Alexander A.H. Lawson, Professor William J. MacLennan, Professor David J.C. Shearman, Dr Colin A. Soutar, Dr Roger N. Thin, Professor Robert G. Will and, in particular, Professor Ian A.D. Bouchier and Professor Christopher R.W. Edwards as previous senior editors.

We are also grateful for the critical reviews provided by a large number of consultant and specialist registrar colleagues and Drs A. Boyd, K. Brunt, K. Elliot, A. Marsland, A. Ryding and S. Forbes. Dr Jean-Michel Sallenave, Dr David A. Lomas, Dr David Gilligan and Dr Chris Summerton also provided advice at the page-proof stage. We would like to extend special thanks to Dr Simon Walker, Department of Clinical Biochemistry, University of Edinburgh, for his careful revision of the Appendices.

Once again we have had to beg, borrow and steal many of the new illustrations from our colleagues and we are grateful for their forbearance and support. These individuals are acknowledged on pages 1141–1142.

Finally, we are especially grateful to all those working for Churchill Livingstone, in particular Laurence Hunter, Wendy Lee and Robert Britton, for their expertise in the shaping, collation and illustration of this edition.

Edinburgh and Cambridge 1999

C.H.
E.R.C.
J.A.A.H.
N.A.B.

Contributors

C.M.C. Allen MA MD FRCP
Consultant Neurologist, Addenbrooke's Hospital, Cambridge; Clinical Dean, University of Cambridge School of Clinical Medicine

J.K. Aronson MA DPhil FRCP
Clinical Reader in Clinical Pharmacology and Honorary Consultant Physician, University of Oxford

Peter Bloomfield MD FRCP FACC
Consultant Cardiologist, Royal Infirmary of Edinburgh

Nicholas A. Boon MA MD FRCPE FESC
Consultant Cardiologist, Royal Infirmary of Edinburgh; Honorary Senior Lecturer, Department of Medicine, University of Edinburgh

Edwin R. Chilvers BMedSci BMBS PhD FRCPE
Professor of Respiratory Medicine, University of Cambridge School of Clinical Medicine; Honorary Consultant Physician, Addenbrooke's and Papworth Hospitals, Cambridge

Peter L. Chiodini BSc PhD FRCP FRCPath
Consultant Parasitologist, Hospital for Tropical Diseases, London; Honorary Senior Lecturer, London School of Hygiene and Tropical Medicine

Nicki R. Colledge BSc (Hons) MB ChB FRCPE
Consultant Geriatrician, Liberton Hospital, Edinburgh and Royal Infirmary of Edinburgh; Honorary Senior Lecturer, Department of Medicine, University of Edinburgh

Graham K. Crompton MB ChB FRCPE
Consultant Physician, Respiratory Unit, Western General Hospital; Part-time Senior Lecturer, Department of Medicine, University of Edinburgh

Allan D. Cumming MB ChB MD FRCPE
Senior Lecturer, Department of Medicine, University of Edinburgh; Honorary Consultant Physician, Department of Renal Medicine, Royal Infirmary of Edinburgh

Alex M. Davison MD FRCPE FRCP
Professor of Renal Medicine, University of Leeds; Consultant Renal Physician, St James's University Hospital, Leeds

Christopher R.W. Edwards MD FRCP FRCPE FRSE
Principal, Imperial College School of Medicine, London; Professor of Medicine, University of London

Niall D.C. Finlayson *OBE* PhD FRCP FRCPE
Consultant Physician, Royal Infirmary of Edinburgh; Honorary Senior Lecturer in Medicine, University of Edinburgh

Keith A.A. Fox BSc (Hons) MB ChB FRCP FESC
Duke of Edinburgh Professor of Cardiology and Honorary Consultant Cardiologist, University of Edinburgh and Royal Infirmary of Edinburgh

Brian M. Frier BSc (Hons) MD FRCPE FRCPG
Consultant Physician, Department of Diabetes, Royal Infirmary of Edinburgh; Part-time Reader in Medicine, University of Edinburgh

George E. Griffin BSc PhD FRCP FRCPE FRCPath
Professor of Infectious Diseases and Medicine, St George's Hospital Medical School (University of London), London; Honorary Consultant Physician, St George's Hospital, London

Christopher Haslett BSc (Hons) FRCPE FRCP
Professor of Respiratory Medicine, University of Edinburgh; Chairman of the Division of Clinical and Community Science, University of Edinburgh; Honorary Consultant Physician, Royal Infirmary of Edinburgh

Peter C. Hayes BMedSci MBChB MD PhD FRCPE
Professor of Hepatology, Department of Medicine, Royal Infirmary of Edinburgh

Andrew Haynes MA (Cantab) MRCP MRCPath DM
Leukaemia Research Fund Senior Lecturer in Haematological Oncology, City Hospital, Nottingham

John A.A. Hunter *OBE* BA MD FRCPE
Professor of Dermatology, University of Edinburgh; Honorary Consultant Dermatologist, Royal Infirmary of Edinburgh

Roland Jung MA MD FRCPE FRCP
Consultant Physician and Honorary Professor of Medicine;

Director of Research and Development, Ninewells Hospital and Medical School, Dundee

Jonathan R. Lamb BDS MA PhD FRCPath
Glaxo–Wellcome/British Lung Foundation Professor of Respiratory Science, Respiratory Medical Unit, University of Edinburgh

G.G. Lloyd MA MD MPhil FRCPE FRCP FRCPsych
Consultant Psychiatrist, Royal Free Hospital, London

Anne de Looy PhD PGDipDiet SRD
Professor of Dietetics and Head of Department, Department of Dietetics and Nutrition, Queen Margaret College, Edinburgh

Christopher A. Ludlam PhD FRCP FRCPath
Director, Haemophilia and Thrombosis Centre, Royal Infirmary of Edinburgh; Part-time Reader, Department of Medicine, University of Edinburgh

C.J. Lueck PhD FRCPE
Consultant Neurologist, Department of Clinical Neuroscience, Western General Hospital, Edinburgh

Raashid Luqmani DM FRCPE
Consultant Rheumatologist and Part-time Senior Lecturer in Rheumatology, Western General Hospital, Edinburgh

Michael J. Mackie BMedBiol MD FRCPath FRCPE
Consultant Haematologist, Western General Hospital, Edinburgh; Part-time Senior Lecturer, University of Edinburgh

David M. Mitchell MA MD MBA FRCP
Consultant Physician and Honorary Senior Lecturer in Medicine, St Mary's Hospital, Paddington and Imperial College School of Medicine, London

George Nuki FRCP FRCPE
Arthritis Research Campaign Professor of Rheumatology, University of Edinburgh; Honorary Consultant Rheumatologist, Western General Hospital and Royal Infirmary of Edinburgh

Kelvin R. Palmer MD FRCPE
Consultant Gastroenterologist, Western General Hospital, Edinburgh

I.D. Penman BSc MD MRCP
Consultant Gastroenterologist, Western General Hospital, Edinburgh; Part-time Senior Lecturer, Department of Medicine, University of Edinburgh

Alex T. Proudfoot BSc (Hons) FRCPE FRCP
Former Consultant Physician, Royal Infirmary of Edinburgh; Director, Scottish Poisons Information Bureau, Edinburgh

Stuart H. Ralston MB ChB MD FRCPG FRCPE
Professor of Medicine, Department of Medicine and Therapeutics, University of Aberdeen; Honorary Consultant Physician, Aberdeen Royal Hospitals, Aberdeen

Olivia M.V. Schofield MB MRCP
Consultant Dermatologist, Royal Infirmary of Edinburgh

James Shepherd MB PhD FRCPath FRCP FRSE
Clinical Director, Laboratory Medicine, GRI University NHS Trust, Glasgow

Claire L. Shovlin PhD MA MRCP
Wellcome Advanced Fellow, University of Edinburgh; Honorary Consultant Physician, Royal Infirmary of Edinburgh

Kenneth J. Simpson MD PhD MRCP
Consultant Physician, Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh; Part-time Senior Lecturer, University of Edinburgh

J.G.P. Sissons MD FRCP FRCPath
Professor of Medicine, Department of Medicine, School of Clinical Medicine, University of Cambridge

J.F. Smyth MA MD(Cantab) MSc FRCPE FRCP FRCSE FRCR FRSE
Imperial Cancer Research Fund Professor of Medical Oncology, University of Edinburgh; Honorary Consultant Physician, Western General Hospital, Edinburgh

Charles P. Swainson MB FRCPE
Consultant Renal Physician, Royal Infirmary of Edinburgh; Senior Lecturer, University of Edinburgh

A.D. Toft *CBE* BSc MD FRCP FRCPE FRCPG FRCPI FRCSE
Consultant Physician, Royal Infirmary of Edinburgh; Honorary Senior Lecturer, Department of Medicine, University of Edinburgh

D.F. Treacher MA FRCP
Consultant Physician and Director of Intensive Care, St Thomas's Hospital, London

A. Stewart Truswell MD DSc FRCP FRACP FFPHM
Professor of Human Nutrition, University of Sydney

A. Neil Turner PhD FRCP
Professor of Nephrology, Renal Medicine, University of Edinburgh, Royal Infirmary of Edinburgh

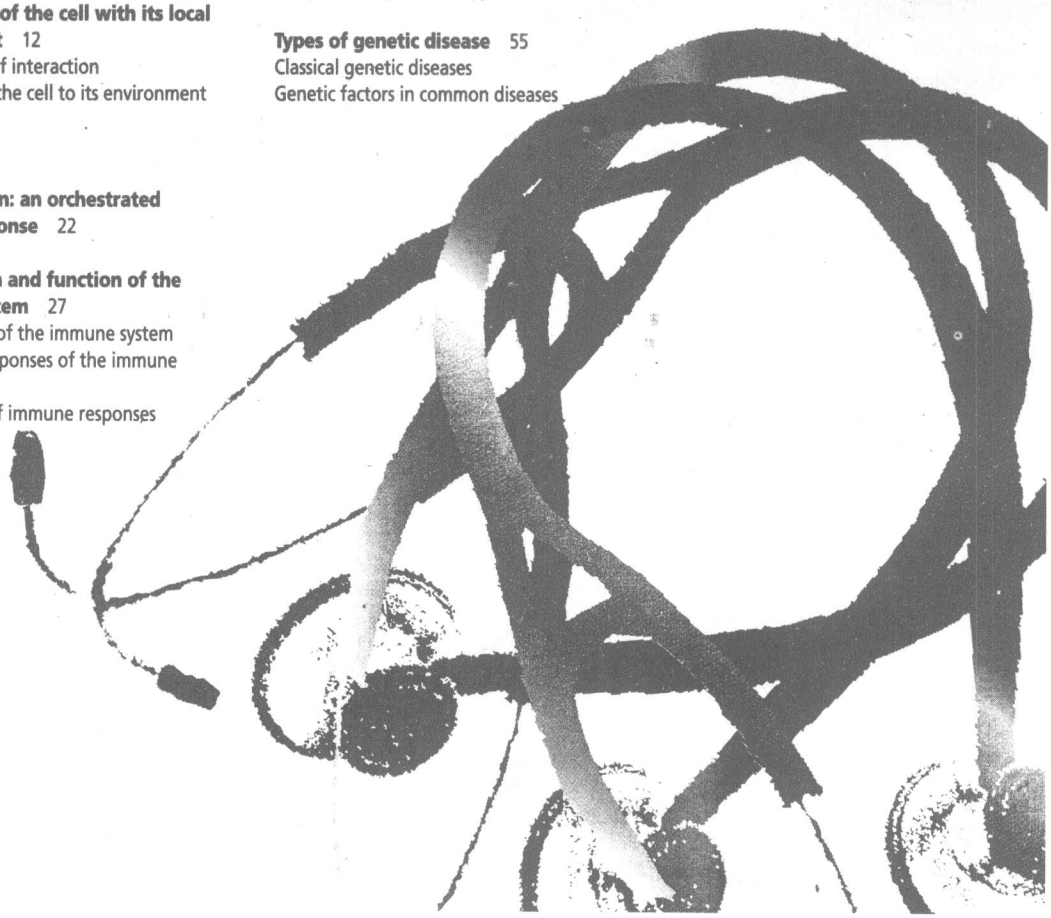
Brian R. Walker BSc MB ChB MD MRCP
British Heart Foundation Senior Research Fellow, University of Edinburgh; Honorary Consultant Physician, Western General Hospital, Edinburgh

Contents

The molecular and cellular basis of disease

1

C.L. SHOVLIN • J.R. LAMB • C. HASLETT



This chapter progresses through the essentials of molecular and cellular biology, from the sequence whereby DNA synthetic information is used to synthesise RNA then protein, to the means by which this generates the cell and extracellular structures, coordinates cellular interactions with each other, and regulates the more complex responses in a multicellular environment. In a sense, the chapter follows an evolutionary theme, as increasing levels of complexity are reached. Unfortunately, this necessitates starting with some of the most difficult material in the chapter. The reader may need to revisit the first section and should not be deterred from following the chapter through. We aim to review pre-clinical material with a particular emphasis on processes relevant to clinical medicine, providing selective examples of disease states. We also use the opportunity to introduce tools of investigative analysis in a manner which we hope will render them less daunting, and provide the basis for interpretation of scientific medical journals. Supplementary information useful for reference is given in Chapter 20. Figure 1.1 gives an overview of the sorts of processes which will be described in detail later in the chapter.

THE FUNDAMENTAL MOLECULAR MACHINERY OF THE CELL

DNA → RNA → PROTEIN

DNA

Cellular DNA (deoxyribose nucleic acid) contains all of the information required to synthesise cellular and extracellular structures, and to regulate the cell's development in the environment of the whole organism. This is possible because strict and orderly pairing of bases between two nucleic acid

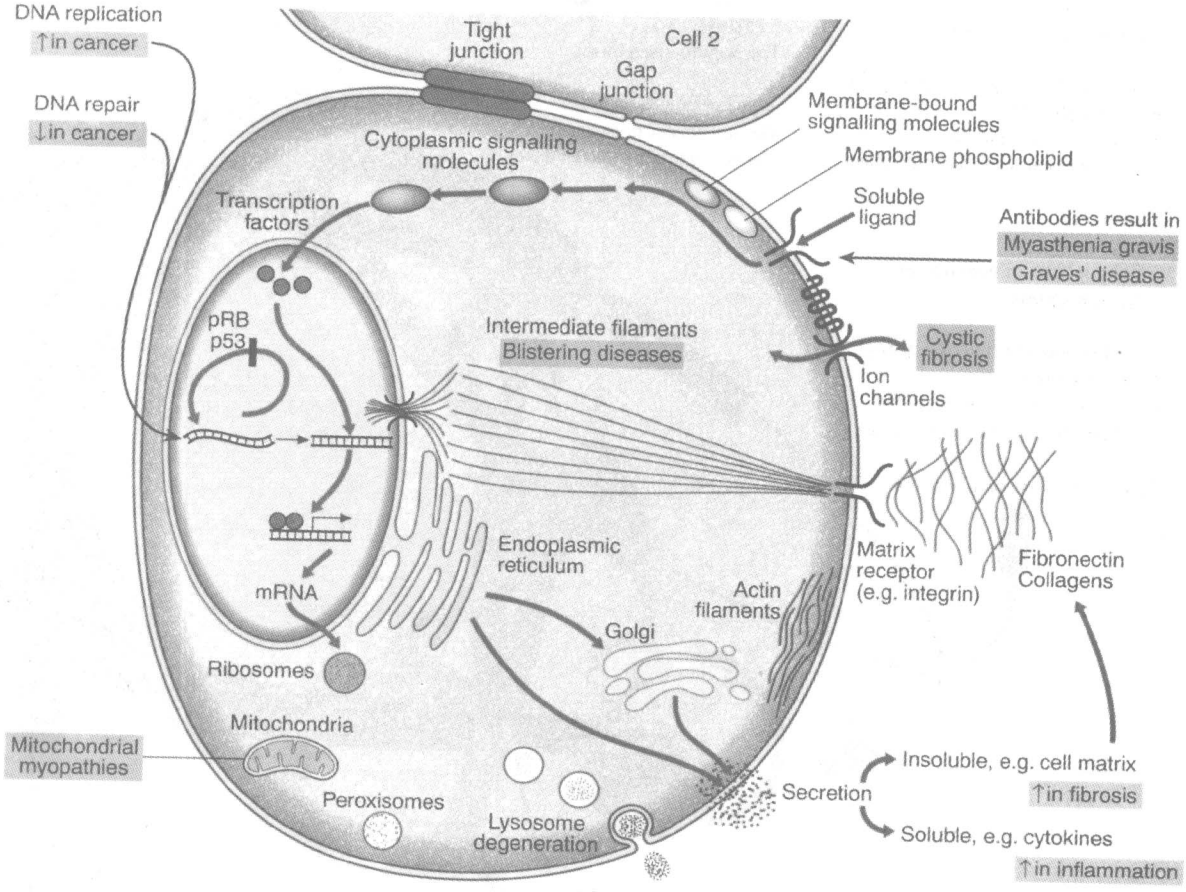


Fig. 1.1 The cell and important cellular processes. Note that diseases in green boxes result from excessive production or activity, whereas diseases in orange boxes result from loss of a particular activity or structure.

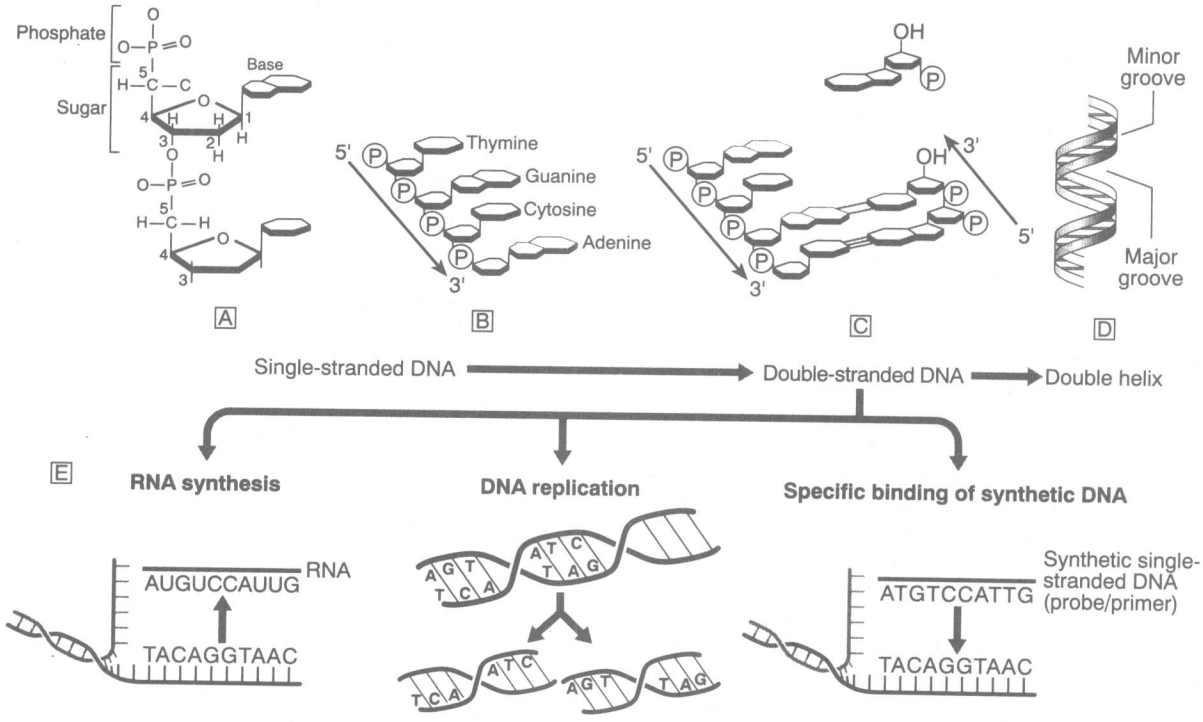


Fig. 1.2 DNA structure. A Biochemical structure of DNA indicating relationship of base, sugar and phosphate in two adjacent nucleotide units. B Cartoon illustrating single-stranded DNA with bases colour-coded. Note the base ring structures. C The formation of double-stranded DNA. Base ring structures and hydrogen bonding generate strict pairings between T–A and C–G. D Spiralling of the double-stranded DNA molecule creates the double helix. E Three consequences of base-pairing: RNA synthesis (see p. 4), DNA replication (see p. 6) and use of synthetic DNA in laboratory applications (see p. 46 and following section).

strands provides both coding potential and the capacity to be replicated faithfully from generation to generation.

As illustrated in Figure 1.2, a single strand of DNA is a linear polymer of *nucleotide* units, each consisting of a pentose sugar (deoxyribose) linked via its 5 prime (5') carbon to a phosphate group, and via its 1' carbon to one of four bases. Nucleotide units polymerise in a single strand by the formation of a sugar-phosphate-sugar-phosphate backbone, in which the orientation of the sugar carbons designates the direction of the strand 5' to 3'. The accompanying four bases can occur in any order, and comprise purines (guanine *(G)* and adenine *(A)*, which consist of two rings) and pyrimidines (cytosine *(C)* and thymine *(T)*, which consist of only one ring).

The critical feature of DNA is its ability to direct the sequential association of incoming nucleotide units which polymerise running in the opposite direction to the parent strand (see Fig. 1.2C). If these are deoxyribonucleotides, the second polymer will also be DNA and the two polymers will form a double-stranded structure through hydrogen bonding. Only two base-pairings are possible: G–C and A–T (see Table 1.1). This is because a stable structure requires three rings between the sugar-phosphate backbones, and optimal hydrogen bonding between bases on opposite strands. The double-stranded DNA unit of two nucleotides is referred to as a *base pair* (bp).

In turn, the most stable three-dimensional structure for the double-stranded DNA polymer to adopt is a helix, in which the sugar-phosphate backbones spiral around, with 10 base pairs per turn, the bases protected in the centre (see Fig. 1.2D). Since this is a spiralling duplex, two different grooves are generated in the structure—a narrow *minor groove* spanning the base-paired strands, and a wider *major groove* between consecutive spirals. Base pairs create specific

Table 1.1 Principles of Watson–Crick base-pairing

Base	Base type	Number of rings	Hydrogen bonds	Base pair
Guanine	Purine	2	3	G–C
Cytosine	Pyrimidine	1	3	
Adenine	Purine	2	2	A–T
Thymine	Pyrimidine	1	2	

patterns within the major groove, allowing their recognition by DNA binding proteins without breaking the helix. The helix is disrupted when DNA is required to act as a template, as in the natural and experimental situations illustrated in Figure 1.2E. DNA helicases catalyse the unwinding of DNA and separation of the hydrogen bonds between bases using energy derived from adenosine triphosphate (ATP) hydrolysis. Inherited defects in genes encoding helicases are responsible for a number of diseases characterised by premature age-related defects and malignancy, such as Werner's syndrome.

The genome

In humans, one copy of the entire double-stranded DNA content is referred to as the *haploid* genome and consists of approximately 3×10^9 base pairs in 23 separate molecules, each part of a different chromosome. However, virtually all cells are *diploid*, with two copies of this genome in 46 chromosomes: 22 pairs of autosomes (numbered 1 to 22, generally in order of size), and two sex chromosomes (X and X for women; X and Y for men). In addition to DNA, the chromosomes contain a chromatin scaffold which packages DNA with histones and other small chromosomal proteins. This is subjected to different orders of higher packing according to need. For example, DNA which is not required by the cell as a template at a given time is kept in a particularly inert state, tightly packaged within the chromatin scaffold of the chromosomes, as exemplified by the structure of inactive chromosomes segregating to daughter cells during cell division.

The genetic code, genes and loci

The genetic code by which DNA directs the synthesis of the protein constituents of the cell is a series of words running 5' to 3' along the linear coding strand of DNA. Each word is a three-nucleotide unit (triplet) which specifies a particular amino acid to be incorporated into the mature protein. There are 4^3 (64) different triplets: 61 specify one of the 20 amino acids. Three, TAA, TAG and TGA, are nonsense codons which do not specify an amino acid and instead terminate the growing polypeptide chain.

Only about 1% of human DNA is decoded into protein sequences; these discrete areas within the genome are referred to as *genes*. By contrast, a *locus* can be any area of the genome. Not all of the DNA within a gene codes for the eventual protein: sequences within the gene include coding regions (exons), non-coding regions (introns) and regulatory sequences (see Fig. 1.3). DNA is not decoded directly into protein, since during transcription, chromosomal DNA remains in the nucleus whereas protein synthesis requires metabolic apparatus associated with ribosomes in the cytoplasm. Instead, a mobile molecule (messenger RNA, *mRNA*) carries the DNA sequence from nucleus to cytoplasm.

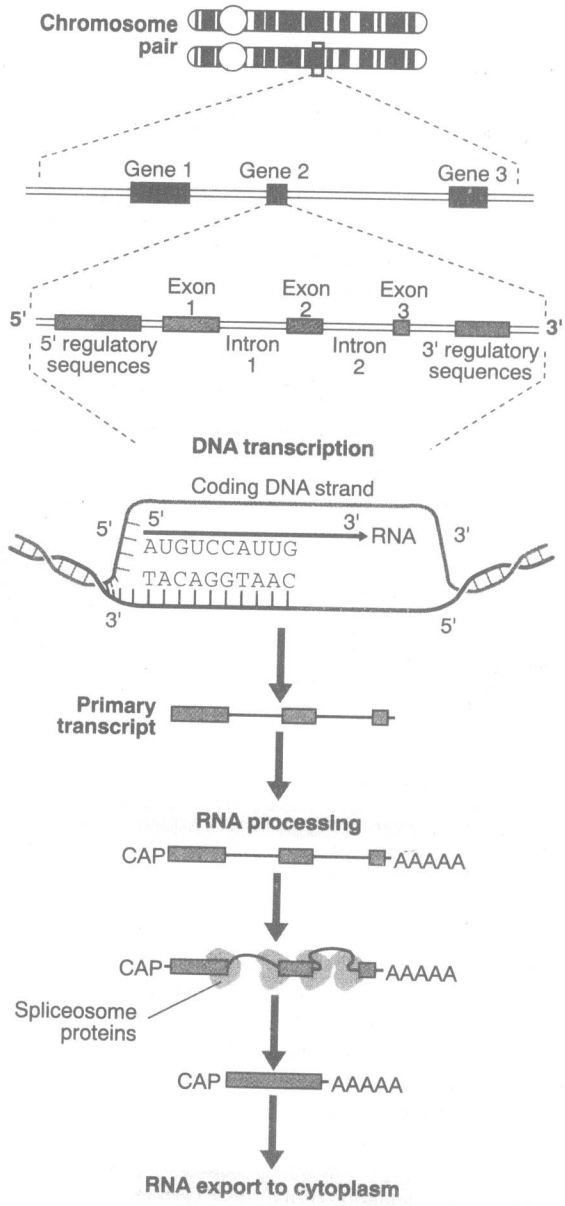


Fig. 1.3 RNA synthesis.

DNA → RNA

RNA synthesis and processing

To synthesise RNA in the process of DNA transcription, the enzyme RNA polymerase II and associated enzymes distort the chromatin structure to expose the underlying DNA, unwind a section of the double-stranded DNA helix, and disrupt the hydrogen bonds between the bases. As a result, a section of DNA can serve as a template for a new

polymer, based on incoming ribonucleotide triphosphate units (in which the pentose sugars are ribose with a 2' -OH group), as shown in Figures 1.2E and 1.3. Note that in RNA the base uracil (U) replaces thymine (T) to base-pair with adenine (A), and since the transcribed RNA has the same sequence as the coding parental DNA strand, the template strand for RNA synthesis is actually the non-coding or complementary strand.

Immediately after synthesis of the primary mRNA transcript, nuclear proteins associate with the newly transcribed polymer which, as it is complementary to the parent DNA, includes introns. As illustrated in Figure 1.3, the primary RNA transcript is modified first by addition of a 5' CAP structure, and a 3' polyadenine (polyA) tail, which stabilise the ends of the short single-stranded molecule to protect it against intracellular breakdown. Secondly, highly accurate splicing machinery removes introns, joins adjacent exons, and creates an exon-only complement. The reagents involved include *s*mall *n*uclear *RNA*s complexed to *p*roteins such as snRNPs U1 and U2. These assemble in a spliceosome complex which coordinates the recognition of splice site consensus sequences demarcating the exon-intron boundaries, and catalyses the requisite biochemical reactions. Splicing usually occurs exclusively between adjacent donor and receptor sites to excise a single intron accurately, although many genes have alternative splicing patterns, which may be exhibited in different tissues, at specific developmental stages or in response to exogenous stimuli.

The processed mRNA is then exported to the cytoplasm for translation into protein. Additional modifications may occur in specific tissues, and include mRNA editing, by which the actual coding sequence of the mRNA changes. For example, in apolipoprotein B, a C to U editing change produces a new termination codon resulting in a truncated apoB48 rather than apoB100 protein (see p. 535). In other settings, prior to the translation process, precise signals can induce the premature decay of mRNA, including progressive shortening of the polyA tail, decapping and enzymatic cleavage.

Regulation and initiation of DNA transcription

Transcription of individual genes is regulated and finely tuned to the requirements of the cell and its environment. Before initiating the RNA synthetic process outlined above, RNA polymerase II identifies a gene to be transcribed by the recognition of upstream DNA regulatory sequences to which it binds (see Fig. 1.4). Additional transcription factors also bind to the promoter and enhancers to increase or decrease the rate of transcription of the gene at specific times. The means by which transcription factors interact with DNA is illustrated in Figure 1.4. Structural features distinguish different families of transcription factors such as helix-turn-helix, zinc finger, leucine zipper and helix-loop-helix motifs. Examples of transcription factors which will be discussed in later sections are the family which

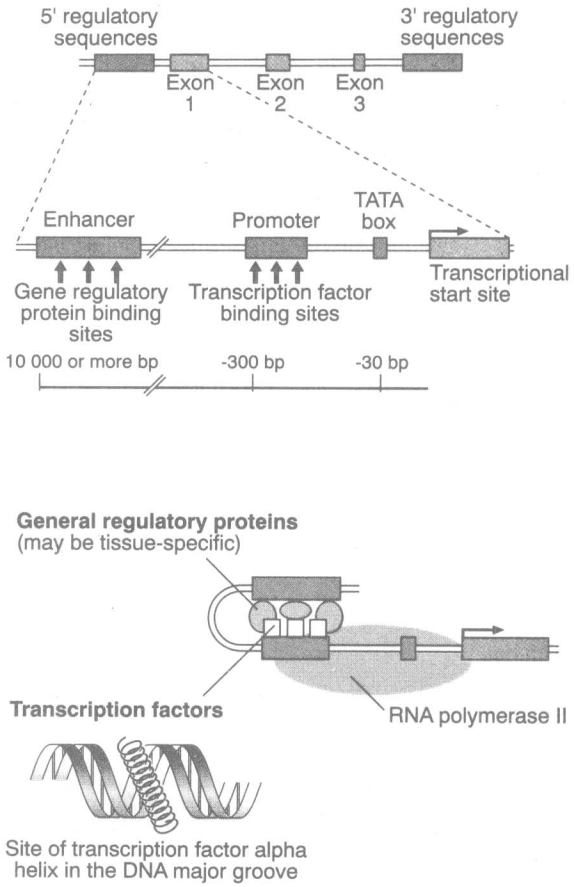


Fig. 1.4 Initiation and regulation of DNA transcription.

consists of homo- or heterodimers of c-Jun, c-Fos, bZIP and other proteins interacting at the common activating protein-1 (AP-1) DNA binding site.

PROTEIN SYNTHESIS (RNA TRANSCRIPTION)

Proteins are synthesised from mRNA in cytoplasmic RNA-protein complexes known as ribosomes. These contain synthetic enzymes, and bind small single-stranded transfer RNAs. Each *tRNA* carries one of the 20 amino acids and the complementary sequence to the corresponding triplet codon, known as the anticodon. To commence protein synthesis (see Fig. 1.5), an mRNA molecule binds via its 5' CAP structure to the small 40S ribosomal subunit, which scans along the mRNA for the start codon AUG. The ribosome-bound initiator $tRNA^{Met}$ molecule carrying the AUG anticodon (UAC) base-pairs to the mRNA, when it activates the methionine which it carries. The activated methionine can then form a peptide bond with the amino

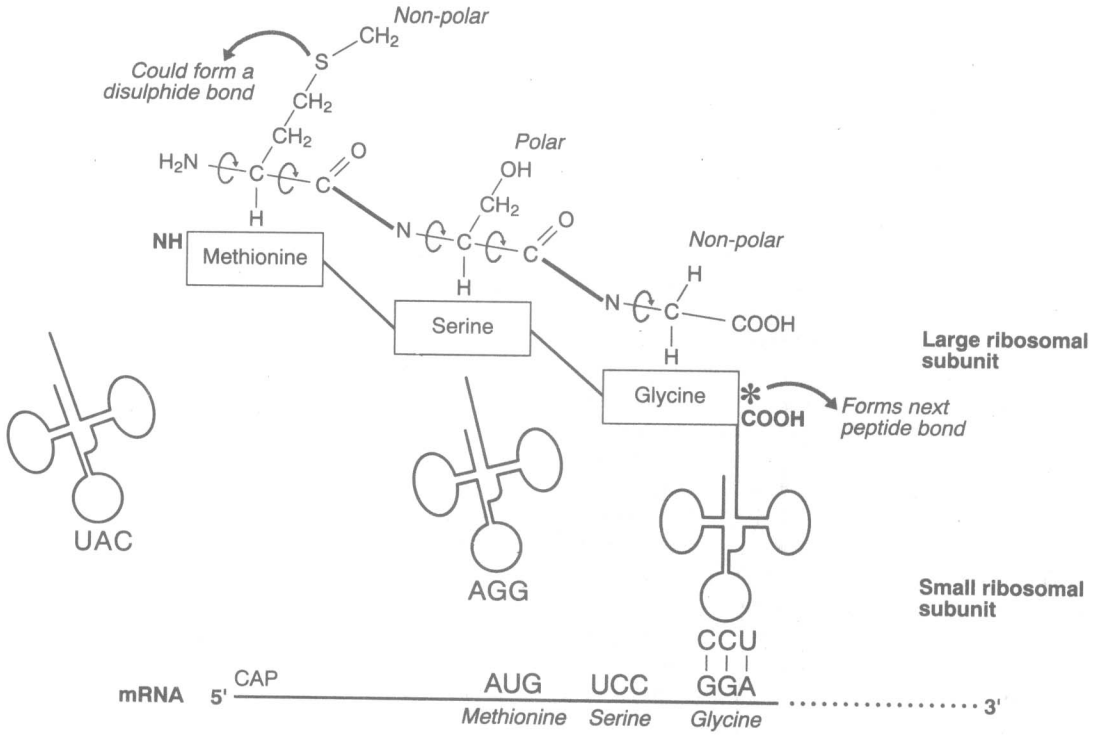


Fig. 1.5 Protein synthesis. Note that the 5' to 3' designation of mRNA corresponds to the amino-carboxyl orientation of the mature peptide. The secondary structure of the mature protein is determined by the degree of rotational freedom in the polymerising non-peptide bonds (indicated in green) and the nature of any side-chains such as their bulk, polarity or other features which may permit additional bonding—for example, between neighbouring sulphur atoms.

acid brought in by the next aminoacyl tRNA, before the ribosome releases the now-empty initiator tRNA. The polymerisation of the amino acids to form a peptide chain is catalysed by peptidyl transferase in the large 60S ribosomal subunit, and proceeds rapidly with about 1000 amino acids polymerised per minute. The stop codons UAA, UAG and UGA are not recognised by tRNAs, but by other proteins termed release factors, which lead to peptidyltransferase adding a water molecule rather than an amino acid to the activated peptide bond.

The mRNA, peptide chain and ribosomes then disassemble, leaving the ribosomes free to associate with another mRNA molecule. However, one of the signals which promotes mRNA decay is impaired translation—for example, failure to initiate translation, incorrect site of initiation, or arrest at a premature stop codon (a common pattern of human mutation—see Fig. 1.31, p. 39). If the mRNA does not decay, at any one time, it may be associated with multiple ribosomes transcribing different sections of the code. The limiting event in this setting is the rate of initiation of synthesis, which depends upon the supply of ribosome-bound initiator $tRNA^{Met}$ and adequate ribosomal initiation factors.

Nomenclature

Genes and the proteins which they encode are often designated by the same name. Common means of distinguishing the two include referring to the gene in italics (*c-abl*: c-abl) or adding a small 'p' to designate the protein (RB: pRB). In addition, many proteins are designated by their molecular weight in kDaltons (e.g. p53). Sometimes the name of the same protein described in a different organism is given as a superscript (e.g. $p34^{CDC2}$).

REPLICATION AND PRESERVATION OF THE DNA TEMPLATE

DNA REPLICATION AND RECOMBINATION

The principle of heredity is the ability of the sequence of DNA bases to be copied faithfully to new daughter DNA polymers to preserve the genetic code in the next generation. In a manner somewhat analogous to RNA transcription, the enzyme DNA polymerase separates the double strands, and initiates two daughter strands, each copied from one of the