TWELFTH EDITION

DAVIDSON'S PRINCIPLES AND PRACTICE OF MEDICINE

EDITED BY

JOHN MACLEOD

CHURCHILL LIVINGSTONE

Davidson's Principles and Practice of Medicine

A TEXTBOOK FOR STUDENTS AND DOCTORS

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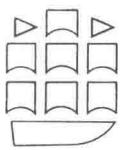

CHURCHILL LIVINGSTONE
EDINBURGH LONDON AND NEW YORK 1977

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by Longman Inc., 19 West 44th Street, New York, N.Y. 10036 and by associated companies, branches and representatives throughout the world.

First Edition	1952
Reprinted	1953
Second Edition	1954
Reprinted	1955
Third Edition	1956
Reprinted	1957
Fourth Edition	1958
Reprinted	1959
Fifth Edition	1960
Reprinted	1961
Sixth Edition	1962
Reprinted	1963
Seventh Edition	1964
Reprinted	1965
First ELBS Edition published	1965
Eighth Edition	1966
Reprinted	1968
ELBS Edition of Eighth Edition	1967
ELBS Edition reprinted	1968
Ninth Edition	1968
Reprinted	1969
Reprinted	1970
ELBS Edition of Ninth Edition	1968
ELBS Edition reprinted	1970
Tenth Edition	1971
Reprinted	1972
ELBS Edition of Tenth Edition	1971
ELBS Edition reprinted	1971
ELBS Edition reprinted	1972
ELBS Edition reprinted	1973
Eleventh Edition	1974
Reprinted	1976
ELBS Edition of Eleventh Edition	1974
ELBS Edition reprinted	1975
ELBS Edition reprinted	1976
Twelfth Edition (including Tropical Diseases)	1977
ELBS Edition of Twelfth Edition	1977

ISBN 0 443 01622 4 (cased)
ISBN 0 443 01566 X (limp)

British Library Cataloguing in Publication Data
Davidson, *Sir* Stanley
Davidson's principles and practice of medicine.
12th ed.
1. Pathology 2. Medicine
I. Macleod, John, b. 1915 II. Principles and practice of medicine
616 RB111 77–30073

Printed in Great Britain by Pitman Press, Bath

Davidson's Principles and Practice of Medicine

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Preface to the Twelfth Edition

With this new production, *Davidson's Principles and Practice of Medicine* will have appeared in 12 editions and over 20 reprints since it was first published a quarter of a century ago. The book has established an international reputation, and not only is it used extensively throughout the English speaking world but it has also been translated into Spanish, Italian, Greek and Croato-serbian. This continuing success is a remarkable tribute to the genius and vision of Sir Stanley Davidson and the editorial policy he instituted, but we are acutely aware that if the book is to retain its unique place in the field of medical education, it must be kept completely up to date in terms of both content and approach. This objective has, we hope, been achieved by consensus support for a progressive editorial policy and by the regular recruitment of younger authors.

There are major changes in the 12th edition. The chapters on genetics, diseases of the cardiovascular system, diseases of the liver and biliary tract, psychiatry and tropical diseases have been entirely or largely rewritten. Extensive changes have also been made throughout the remainder of the text to keep pace with new developments in rapidly advancing disciplines.

Tropical diseases have always figured prominently in 'Davidson'. At first, only those conditions were included which might be encountered in temperate climates or were of particular educational value. The demand for the textbook in Africa and Asia led to the publication in 1964 of a *Tropical Diseases Supplement* which is now in its 5th edition. In 1965 the parent textbook and the supplement were published together in Africa and Asia in a large paperback, at a greatly reduced price, under the auspices of the English Language Book Society. This joint publication has appeared in seven editions. Now the *Tropical Diseases Supplement* has been incorporated with the parent book, thus ensuring that all readers will have at least some knowledge of human needs and medical problems in countries other than their own. A more prosaic reason for this change in policy is that economies effected by publishing one textbook instead of three will enable the price to be kept at a modest level despite increasing costs at every stage of production.

Although much new material has been included, it has nevertheless proved possible to shorten the book by some 60 pages mainly by discarding what has been superseded. A close interrelationship has also been established with the 4th edition of *Clinical Examination*, in which several of the contributors and the editor participate.

The opening chapters of the 12th edition deal with fundamental general factors in disease such as genetics, immunology, infection, nutrition and electrolyte balance. These are followed by accounts of diseases of the various systems and by outlines of psychiatry and acute poisoning. The final chapter, on tropical disease and helminthic infections, ends with a short section on the promotion of health and prevention of disease, re-emphasising the prominence given to prophylaxis in every chapter. In recognition of the fact that education must be a continuing process, many of the chapters conclude with brief comments on prospects for the immediate future.

The task of preparing the 12th edition has been made easier for the editor and contributors by the pleasure and satisfaction derived from working as a team, by the stimulus provided by new authors and by the challenge of constructive criticism from

students and doctors all over the world. Our primary objective, as before, has been to ensure that the book provides a rational and easily comprehensible basis for the practice of medicine, and we hope that it will continue to make as substantial a contribution to the education of medical students, both undergraduate and postgraduate, in the future as it has done in the past.

Edinburgh, 1977 *John Macleod*

Acknowledgments

We have had generous help from many colleagues and we would like to express our thanks especially to Professor B. E. C. Nordin, Dr Roger Whitehead and Miss Erica Wheeler (nutrition), Mr C. V. Ruckley (thromboembolism), Dr D. H. Cummack (radiographs of alimentary tract), Dr A. J. Keay (cystic fibrosis of the pancreas), Dr J. F. Cullen (diabetic retinopathy), Dr H. A. Reid (snake bite), Dr D. A. Warrell (climate and altitude), Mr. J. E. Pizer (line drawings), Drs Donald Bain and Alison McCallum (proof reading) and Greta Proven and Pat Hollis (preparation of manuscript). Other acknowledgments are made in the text.

To Ellen Green we are particularly indebted for maintaining efficient and harmonious relationships between publishers, printers and editor.

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Contents

1. Genetic Factors in Disease

In recent years there has been an increasing awareness of the importance of genetic factors in the aetiology and pathogenesis of many disorders affecting man. Perhaps of more importance is that this knowledge has also led to possible means of prevention of such disorders through genetic counselling and antenatal diagnosis.

At the turn of the century morbidity and mortality in infancy and childhood could largely be attributed to environmental factors such as infections and nutritional deficiencies. With advances in medicine these problems are decreasing, at least in the developed countries, while others, in which genetic factors are largely or even entirely responsible, are becoming more obvious. In a survey carried out in Newcastle in 1970, no less than 42 per cent of childhood deaths could be attributed to diseases which are genetic in causation. The contribution of genetic factors to mortality and morbidity in adults is more difficult to assess but is also increasing.

It is useful to consider human disease as forming a spectrum at one end of which we have those diseases which are entirely genetic in origin and in which environmental factors play little if any part. This group of disorders includes *chromosomal abnormalities* and so-called *unifactorial disorders*. The latter are due to single gene defects (Mendelian factors); though individually rare there are over a thousand of them. They are usually serious disorders; they often present at birth or in childhood, though notable exceptions are Huntington's chorea, myotonic dystrophy and polyposis coli. The mode of inheritance is straightforward and follows Mendelian principles, and the risks of occurrence in relatives are high. For the vast majority of these unifactorial disorders there is as yet no effective treatment and prevention is the main approach to the problem.

At the other end of the spectrum are those diseases such as infections and nutritional deficiencies which are entirely environmental in aetiology. In the middle of the spectrum are many common conditions which are partly genetic and partly environmental in causation, so-called *multifactorial disorders*. These include many congenital malformations (such as congenital dislocation of the hip, club foot, congenital pyloric stenosis, congenital heart disease, anencephaly and spina bifida), 'diseases of modern society' (diabetes mellitus, essential hypertension, coronary artery disease) and possibly certain psychiatric disorders (such as schizophrenia and manic-depressive psychosis). In multifactorial disorders the genetic component is complex, probably involving in each case many genes. The risks to relatives are usually low.

Chemical Basis of Inheritance

Within the nucleus of every cell are the chromosomes which bear the genes which carry genetic information. Deoxyribonucleic acid (DNA) is the essential component of hereditary material and it is within the DNA of the gene that genetic information is stored.

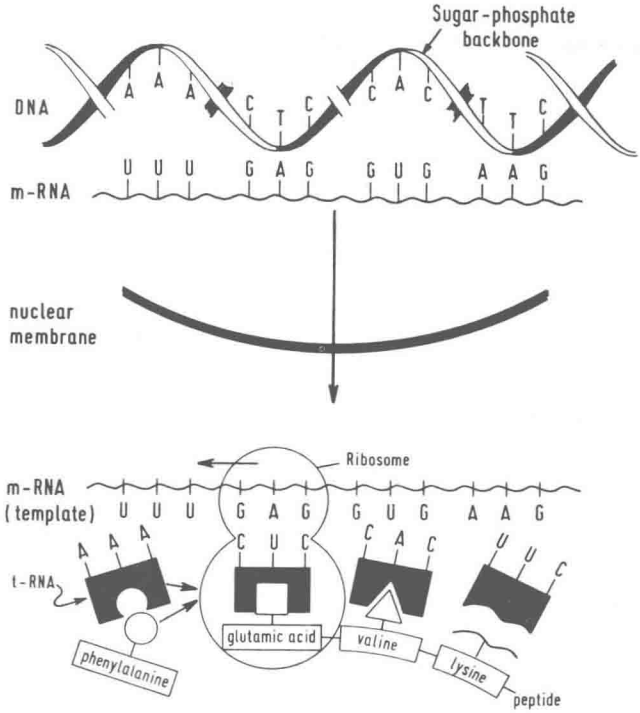

Fig. 1.1 Translation of genetic information into protein synthesis. Guanine (G) pairs with cytosine (C) and adenine (A) with thymine (T) or uracil (U).

DNA is composed of two polynucleotide chains, twisted together to form a double helix (Fig. 1.1). Each nucleotide is composed of a nitrogenous base, a sugar molecule (deoxyribose) and a phosphate molecule. The nitrogenous bases in DNA are adenine and guanine (purines) and cytosine and thymine (pyrimidines). The arrangement of the bases is not random: a purine in one chain always pairs with a pyrimidine on the other chain. There is also specific base pairing: guanine in one chain always pairs with cytosine in the other chain and adenine always pairs with thymine. This is the Watson-Crick model of DNA. It is postulated that at nuclear division the two strands of the DNA molecule separate and as a result of specific base pairing each chain then builds its complement. In this way, when a cell divides, genetic information is conserved and transmitted to each daughter cell.

The primary action of the gene is to synthesise protein by various combinations of 20 different amino acids. Genetic information is stored within the DNA molecule in the form of a triplet code such that a sequence of three bases determines the structure of one amino acid.

Whereas DNA is found mainly in the chromosomes, ribonucleic acid (RNA) is found mainly in the nucleolus and the cytoplasm. RNA has a structure similar to DNA (Fig. 1.1): both nucleic acids contain adenine, guanine and cytosine but thymine is replaced by uracil in RNA and the latter contains the sugar ribose. The information stored in the DNA code of the gene is transmitted to a particular type of RNA, so-called messenger-RNA (m-RNA). Each m-RNA is formed by a par-

ticular gene, such that every base in the m-RNA molecule is complementary to a corresponding base in the DNA of the gene: cytosine with guanine, thymine with adenine but adenine with uracil since the latter replaces thymine in RNA. The m-RNA then migrates out of the nucleus into the cytoplasm where it becomes associated with the ribosomes which are the site of protein synthesis. In the ribosomes the m-RNA forms the template or mould for arranging particular amino acids in sequence. In the cytoplasm there is yet another form of RNA referred to as transfer -RNA (t-RNA). Each amino acid in the cytoplasm becomes attached to a particular t-RNA. The other end of the t-RNA molecule consists of three bases which combine with complementary bases on the m-RNA. Thus a particular triplet in the m-RNA is related through t-RNA to specific amino acid. The ribosome moves along the m-RNA in a zipper-like fashion, the assembled amino acids linking up to form a polypeptide chain.

Structural and Control Genes. There are essentially two types of gene: structural genes which are responsible for the synthesis of specific proteins such as haemoglobin, collagen and enzymes, and control genes which are thought to modify the action of structural genes.

A change (mutation) of a base pair of the DNA molecule may result in any one of a number of possible effects. If the altered triplet codes for the same amino acid then of course the change will go undetected. Possibly 20 to 25 per cent of all possible single base changes are of this type. Alternatively a single base mutation may result in a triplet which codes for a different amino acid resulting in an altered protein. The latter may retain its biological activity (e.g. enzyme activity) but have altered physico-chemical properties such as electrophoretic mobility or stability so that it is more rapidly broken down. This is the case in many of the abnormal haemoglobinopathies in which the aberrant haemoglobin can be detected by its altered electrophoretic mobility. However the substitution of a different amino acid may result in reduced or even absent biological activity. In inborn errors of metabolism therefore the level of a particular enzyme may be reduced because it is not synthesised, or it is synthesised but has reduced activity or because of its instability it is more rapidly broken down.

Chromosomes and Chromosomal Disorders

Chromosome Structure and Number. Among higher animals each species bears within the nucleus of its cells a set of chromosomes which is characteristic both in number and in morphology for that species. Each nucleus in the somatic cells of man contains a set of 46 chromosomes. Two of these chromosomes determine the sex of the individual and are therefore known as *sex chromosomes*; the remaining 44 chromosomes are known as *autosomes*.

The DNA of higher organisms is coated with histone and non-histone proteins. This produces a deoxyribonucleoprotein fibre (chromatin) which forms the basic unit of chromosome structure. Although much information on the structure of chromosomes has been acquired by the use of a variety of techniques which include chemical analysis, X-ray diffraction, electronmicroscopy and autoradiography, the detailed nature of their structure still remains a subject of dispute. Several models have been put forward to explain the way in which the DNA and other chromosomal constituents are arranged but none are entirely satisfactory.

Chromosomes are in a suitable state for detailed study only during specific in-