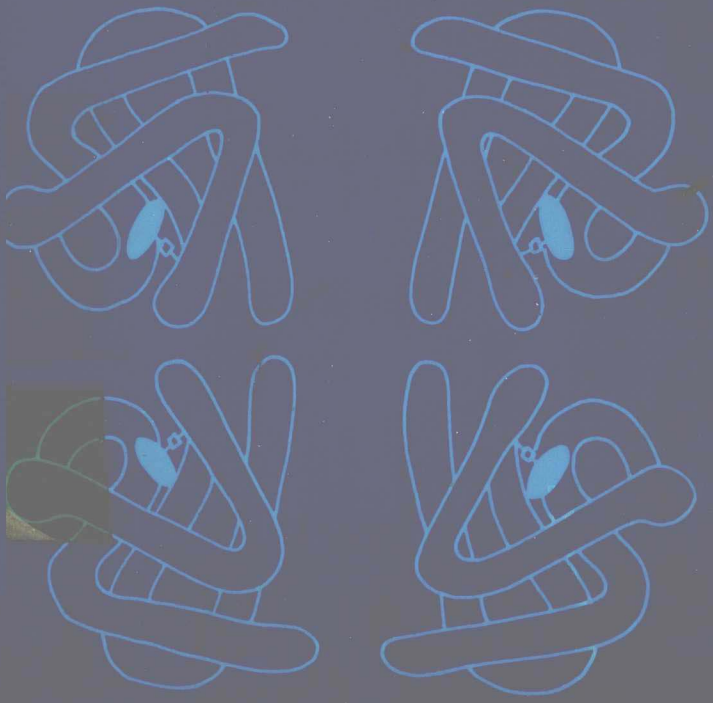
Medicine in the Tropics

SICKLE-CELL DISEASE

A Handbook for the General Clinician

EDITED BY
A. F. Fleming

Foreword by
H. LEHMANN



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Edited by

A.F. Fleming

on behalf of the Sickle-cell Club
of Nigeria

Foreword by

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Sickle-cell Disease

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To Our Patients

The royalties from the sale of this Handbook will be paid to the Sickle-cell Club of Nigeria and will be devoted to the welfare of Nigerian children with sickle-cell disease.

Foreword

The interest in the sickling phenomenon arose outside Africa some 70 years ago. The people to whom it was a vital concern were, however, of African descent. It is true to say that there can hardly be an African south of the Sahara and north of the River Zambezi to whom 'sickling' and all that it involves is not of vital interest. Yet although there has been an intensive literature on sickle-cell anaemia and on sickle-cell trait in the continents of Europe and America, this present volume is the first of its kind written in Africa for Africans. Although primarily aimed at tropical Africa, it will be welcomed around the shores of the Mediterranean Sea, the Middle East and India, and indeed the Americas North and South, i.e. wherever sickle-cell disease confronts the medical profession, the public health administrator and the general public. The population movements since the Second World War have seen to it that few London Hospitals and doctors in the Midlands of England can remain aloof. Though numbers may not be large, immigrants from Greece and Italy have carried the gene to the antipodes.

Of the merits of this book are foremost the encompassing range it offers to the medical practitioner of the aspects of the disease itself, its genetics (so important for family advice), its history and its interplay with malaria, particularly in Africa, where it protects the young sickle-cell trait carrier against the deadly malignant tertian or falciparum malaria.

It is a short time in years but a long one in human endeavour that I was asking why sickle-cell anaemia, so well described in the United States, was not seen in Uganda. We now know that the affected infants died before they could develop the classical picture. With increasing treatment of infections and malnutrition the children are now growing up and surmounting the handicaps which used to weed out the hereditary anaemia before it developed. It is worth recalling that even in the United States there was a considerable interval of time between the description of sickle cells by Herrick in 1910 and the gradual realisation that sickle-cell anaemia is a

frequent disorder of public health interest. I have described elsewhere my visit to Herrick in 1954 when he told me that he did not want to be remembered for the discovery of the 'bizarre' phenomenon of sickle cells but for his description of myocardial infarction. Similarly, the problem of sickle-cell disorders is now well recognised in India, yet I recall that it was more than 40 years after Herrick's discovery when Mary Cutbush (now Crookston) and I went to India with the specific purpose to search for sickling there, and it was only when the search was successful that the criticism of this 'hair-brained' expedition came to an end.

This book is the first authoritative volume on sickle-cell disorders coming from Africa. It is profoundly gratifying that Dr Fleming, the editor of this book, and his collaborators, all like him members of medical faculties in Africa, have dedicated their royalties to the Sickle-Cell Club of Nigeria, a club of which they can already be proud, just as I predict they will be proud of this present volume in years to come.

H. Lehmann

Preface

The authors agreed to write this book because so many patients are today receiving treatment and being given advice which they, the authors, think is inappropriate. The aim of this book is simply to provide the knowledge which is necessary to any doctor who has the care of patients with sickle-cell disease. As it has been estimated that in Nigeria alone, 30 000 children are born each year with sickle-cell disease, the need for a comprehensive text on the condition is apparent.

It is hoped that this book will be read by medical students preparing for their qualifying examinations and by doctors working in Africa or anywhere else in the world where the disease is encountered. Each chapter has been kept as short as possible and is followed by a list of suggested further reading; only for the historical introduction (Ch. 1) and the account of recent advances (Ch. 9) are there comprehensive lists of references.

The history of our knowledge of sickle-cell disease is discussed in the first chapter, both in oral traditions of Africa and in modern medicine since the original description by Herrick in 1910. The chapter continues with an account of the chemistry, function and inheritance of normal and abnormal haemoglobins in man, with emphasis on the peculiar nature of sickle haemoglobin (Hb-S). A true understanding of the clinical course of sickle-cell disease cannot be achieved unless the chemistry of this molecular disease is mastered.

The expression of these chemical abnormalities when Hb-S is inherited in the heterozygous state (sickle-cell trait) is the subject of Chapter 2. The high frequency of the sickle gene is due to the advantage enjoyed by sickle-cell trait carriers in areas where *Plasmodium falciparum* malaria is endemic. The nature and extent of this advantage are described, as are the extremely minor disadvantages which result from sickle-cell trait. The chapter closes with comments on the controversial subject of genetic counselling. The changes in the blood in sickle-cell disease and its laboratory di-

agnosis are the subjects of the third chapter; attention is focused on a handful only of laboratory tests, which are all that are required for the accurate diagnosis of sickle-cell disease.

The pathological effects of sickling on the blood and on the solid tissues of the body are discussed in Chapter 4 as an introduction to the three chapters covering the clinical manifestations and management of sickle-cell disease in childhood (Ch. 5), during and after puberty (Ch. 6), and during pregnancy (Ch. 7). These clinical chapters are complemented by an account of the radiological changes (Ch. 8).

Recent advances and some current research are described in the final chapter. Many claims are being made for treatment of sickle-cell disease, but at the time of writing, no specific treatment has been proved to be both safe and effective. A cautionary note is sounded which we hope will be heeded by any doctor who has some inspiration as to a cure for sickle-cell disease, or who is approached by others wishing to sell such a supposed cure. A beneficial and specific treatment will come sometime for certain, but it will not be ethically correct to administer it to all patients until its safety has been demonstrated and its effectiveness proved by carefully conducted trials. Until that day dawns, the authors hope that this text will be a guide to all who seek to ameliorate the course of sickle-cell disease in their patients.

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A.F.F.

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Definitions and abbreviations

Sickle-cell trait (Hb-AS): the inheritance of one normal gene controlling the formation of the β chains of haemoglobin and one sickle gene; in the absence of other coincidental disease, the haemoglobin concentration and other red cell indices are normal, the proportion of the total haemoglobin which is Hb-A is greater than that which is Hb-S, and there is a normal proportion of Hb-F.

Sickle-cell disease: the condition resulting from the inheritance of two abnormal allelemorphic genes controlling the formation of the β chains of haemoglobin, at least one of which is the sickle gene; sickle-cell disease includes, therefore, Hb-SS, Hb-SC, Hb-S/β thal and other doubly heterozygous conditions.

Sickle-cell anaemia (Hb-SS): the condition resulting from the inheritance of two sickle genes.

Sickle-cell-haemoglobin C (Hb-SC) disease: the condition resulting from the inheritance of the sickle gene and the Hb-C gene.

Sickle-cell-β-thalassaemia (Hb-S/β thal): the conditions resulting from the inheritance of the sickle gene and one of the various β-thalassaemia genes. For the purposes of this text, these genes are referred to as

(i) β°thal, leading to *complete* suppression of synthesis of β-chains of adult haemoglobin, and

(ii) β^{+}thal, leading to *incomplete* suppression of synthesis of β-chains of adult haemoglobin.

The doubly heterozygous inheritance leads to either Hb-S/β°thal or Hb-S/β^{+}thal.

Sickle-cell-hereditary persistence of fetal haemoglobin (Hb-S/HPFH): the condition resulting from the inheritance of the sickle gene and the gene for HPFH (see below).

Hereditary persistence of fetal haemoglobin (HPFH): a condition characterised by the persistent production of fetal haemoglobin

(Hb-F) into adult life in the absence of any haematological abnormality. There is a uniform distribution of Hb-F in all red cells. There are two main forms, the 'Negro' and the 'Greek'. In Negro heterozygotes, Hb-F is about 25 per cent of the total haemoglobin and the Hb-A_2 is slightly reduced. In the homozygous state, the haemoglobin consists entirely of Hb-F.

Contents

Historical introduction. Molecular biology and inheritance

HISTORICAL INTRODUCTION

There is some evidence that sickle-cell disease had been recognised in Africa by black Africans long before the earliest descriptions in the medical literature at the beginning of the twentieth century. Most of this evidence comes from Ghana (Konotey-Ahulu, 1974). It would appear that various ethnic groups in Ghana, including the Twi, Ewe and Ga peoples, identified sickle-cell disease as an entity to the extent of pinpointing some cardinal features, such as the recurrent attacks of pain in the bones and joints, the variable severity of the disease and its familial tendency, but with the parents of affected children appearing normal. Their descriptions were so accurate that in one particular family belonging to the Krobo tribe, Dr Konotey-Ahulu was able to trace the existence of sickle-cell disease in nine generations, dating back to 1670. There is, however, no convincing evidence that these ethnic groups in Ghana related the various symptoms of sickle-cell disease to a disorder of the blood.

Other communities in black Africa, including West Africa, cannot claim this degree of accuracy in the recognition of sickle-cell disease prior to descriptions in modern medical literature. In Nigeria, the largest black African nation, sickle-cell disease apparently remained unrecognised as a distinct disorder by the various ethnic groups until recent times. The Nigerian languages abound with words and phrases which describe various symptoms commonly found in patients with sickle-cell disease. These expressions are however not necessarily specific for this disorder. In the Hausa language for example, expressions such as *rashin jini* (lack of blood), *ciwon ga' bo'bi sai sai* or *amosanin kashi* (recurrent pain in bones and joints) and *rashin kuzari* (lack of energy) are frequently used in relation to sickle-cell disease by patients, their relatives and by traditional healers. However, this current usage of words does not appear to be associated with any long-standing knowledge of

sickle-cell disease in the Hausa community. Age-old concepts of *ogbanje* (Ibo) and *abiku* (Yoruba) provide a traditional explanation for recurrent deaths of children in some families. It is just possible that sickle-cell disease may have caused some of these deaths. Interestingly, a disorder in childhood termed *vende wanye* had been recognised for some centuries by the Tivs (one of the largest Nigerian ethnic minorities). Though the descriptions of this disorder may apply to some children suffering from sickle-cell disease, on further investigation *vende wanye* is apparently non-specific and may refer also to other illnesses of childhood, including kwashiokor. Thus, unequivocal and incontrovertible evidence that sickle-cell disease was identified as a distinct abnormality in the traditional societies of Nigeria before its recognition in 'Western' medicine is lacking. However, the earliest descriptions in the Western medical press were inevitably based on features of the disorder as observed in the descendants of Africans (predominantly West Africans) living in the New World.

In 1904, Dr James B. Herrick, a physician practising in Chicago, USA, first noted the presence of red cells which were shaped like a sickle in the blood of an anaemic West Indian medical student. This historic observation linked the 'peculiar and elongated sickle-shaped red blood corpuscles' with severe anaemia (Herrick, 1910). Surprisingly, Herrick preferred to be remembered for his work on coronary thrombosis rather than on the sickling of red cells, a phenomenon he regarded as a 'minor peculiarity'!

As information on the clinical features of sickle-cell disease gradually accumulated over the ensuing years, workers became increasingly preoccupied with the nature and pathogenesis of the disorder. Significant contributions included the work of Emmel (1917), who made pertinent obervations about the familial nature of the disease and suggested that sickling of the red cells might be related to diminished oxygen supply. Huck (1923) noted that sickling was a reversible process. One year later, Sydenstricker (1924) reported additional findings, including the variability in the course of the illness. Hahn and Gillespie (1927) confirmed the intimate relationship between the sickling of red cells and a reduced supply of oxygen, and also demonstrated that sickled red cells could revert to their normal shape when exposed to adequate amounts of oxygen. Significantly, these two workers, as early as 1927, also rightly attributed the defect in the sickling phenomenon to the haemoglobin contained within the red cell and not to the red cell itself. Scriver and Waugh (1930) confirmed *in vivo* Hahn and Gillespie's earlier findings, and demonstrated the formation of sickled cells in

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