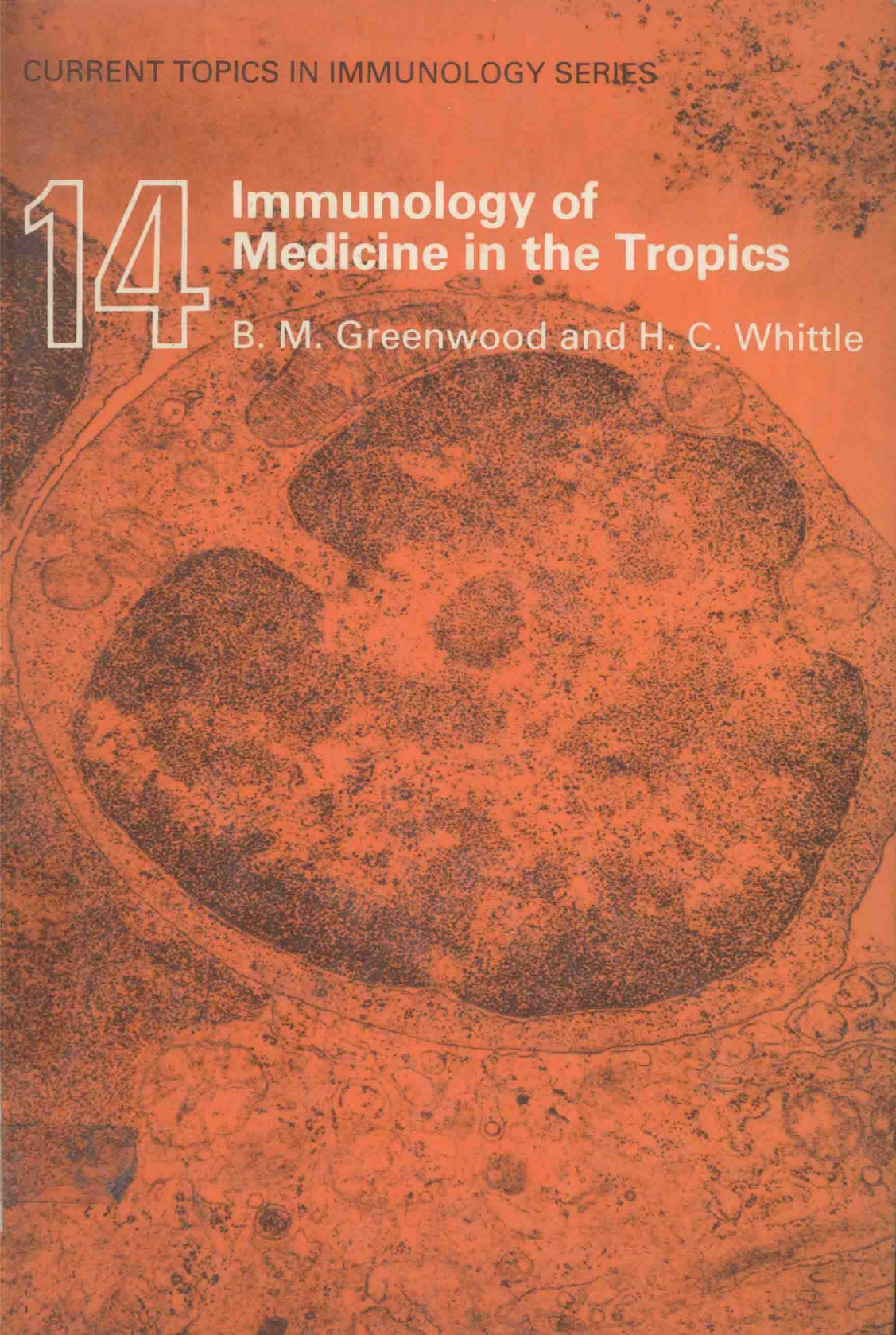
CURRENT TOPICS IN IMMUNOLOGY SERIES

14 Immunology of Medicine in the Tropics

B. M. Greenwood and H. C. Whittle



Immunology of Medicine in the Tropics

B. M. Greenwood MD, FRCP

MRC External Staff, MRC Laboratories, Fajara, The Gambia;
Formerly Senior Lecturer in Medicine, Ahmadu Bello University,
Zaria, Nigeria

H. C. Whittle FRCP

MRC External Staff, MRC Laboratories, Fajara, The Gambia;
Formerly Senior Lecturer in Medicine, Ahmadu Bello University,
Zaria, Nigeria

Edward Arnold

First published 1981
by Edward Arnold (Publishers) Ltd.
41 Bedford Square, London WC1B 3DQ

British Library Cataloguing in Publication Data

Greenwood, B M
Immunology of medicine in the tropics – (current topics in immunology series; 14 ISSN 0141 – 3368).
1. Tropical medicine 2. Immunology
I. Title II. Whittle, H C
619.9'88' 3 RC 961.5

ISBN 0–7131–4368–1
ISSN 0305–8204

Typeset by Macmillan India Ltd.,
Bangalore 1.

Printed in Great Britain by Spottiswoode Ballantyne Ltd.,
Colchester and London

CURRENT TOPICS IN IMMUNOLOGY

General editor: Professor John Turk

Titles now published

1 The Practice of Clinical Immunology, *2nd Edition*
2 Cancer and the Immune Response, *2nd Edition*
3 Blood Group Topics
4 Organ Grafts
5 Allergic Drug Reactions
6 Immunodeficiency
7 Immunology of the Rheumatic Diseases: Aspects of Autoimmunity
8 Immunology of Gastrointestinal and Liver Disease
9 HLA and H-2—Basic Immunogenetics, Biology and Clinical Relevance
10 Immunology of the Lung
11 The Immunopathology of the Kidney
12 Immunology of Nutritional Disorders
13 Immunology of Contraception
14 Immunology of Medicine in the Tropics

In preparation

15 Immunology and Skin Diseases

To our colleagues in the Faculty of Medicine,
Ahmadu Bello University, Zaria, Nigeria

General Preface to Series

The impact of immunological thought on medical practice has been increasing at a steady rate now for nearly twenty years. There appear to be very few fields to which the immunologist cannot contribute. Initially the immunological approach was limited to assistance in diagnosis and in sera and vaccine production. New approaches in the field of therapy are not only in the use of vaccines, sera and immunosuppressive agents, but also in the more rational use of conventional therapeutic agents. Immunological knowledge is especially necessary in the field of tumour therapy, particularly in the balanced use of surgery and radiotherapy. Moreover, immunological knowledge in other fields has allowed us to understand more readily the mechanisms whereby a single aetiological agent can produce a wide range of different clinical manifestations. Different disease patterns occur depending on the nature of the immunological reaction causing tissue damage. A completely different symptom complex from reactions involving soluble immune complexes reacting with the complement cascade will be found in those involving the reaction of specifically sensitized lymphocytes with antigen as part of a cell-mediated or delayed hypersensitivity reaction.

As a massive amount of new scientific material accumulates in this field, the clinician is frequently left behind and perplexed. Each year a new scientific journal is published specializing in fields as diverse as immunogenetics, immunochemistry or immunological techniques. We have journals emanating from continents as well as countries. The wealth of material is often bewildering. Simple textbooks of immunology are often too simple, whereas review articles may be too complicated for the specialist physician or surgeon who wants a treatise on those aspects of the subject particularly relevant to his own field of interest. It is hoped that this series will fulfil some of these needs by giving comparatively short reviews that will lay emphasis on immunological subjects which should appeal to both clinicians and those working in clinical laboratories. The aim is to provide the busy clinician in a particular field of medicine with a short volume relevant to his practice written by a specialist. It should introduce the reader to the immunological approach to his subject and indicate how modern immunological thought might influence his day to day work in the wards or clinical laboratory.

John Turk
The Royal College of Surgeons of England
London.

Preface

Throughout much of the tropics, infectious diseases and malnutrition are still the dominant health problems, regardless of variations in climate and race. Therefore we have concentrated on these topics in this book and we have not considered the many other immunologically-mediated diseases encountered in developing as well as in developed countries.

In writing this book we have had two audiences in mind. For our clinical colleagues we have tried to show how immunology can help in the diagnosis, management and prevention of infectious diseases and how the immunological consequences of malnutrition play a critical role in the complex interactions between nutrition and infection. The immunological features of four common tropical tumours which are associated with specific virus infections are also discussed. We have assumed that the reader has some knowledge of immunology, but a glossary of basic immunological terms has been included which we hope will be of help to those who have difficulty with the jargon of modern immunology.

During the past few years a considerable number of immunologists in Europe and America have turned their attention to the problems of parasite immunology, a trend that has been encouraged by the World Health Organization, acting through its Special Programme for Research and Training in Tropical Diseases and other major grant-giving bodies. We hope that this book gives an indication of the many areas in which immunologists can help to improve the health of those living in the developing world. Some of these scientists may not have had the privilege of working in the tropics and for them we have included brief clinical descriptions of the major tropical diseases discussed in the book.

A comprehensive review of the immunology of infectious diseases and malnutrition is beyond the scope of a book such as this and we have had to be very selective in the topics that we have discussed. We have concentrated on areas where there have been recent advances which we think are of practical importance for those practising medicine in the tropics. Our personal interests have inevitably intruded and many of the examples that we have chosen to illustrate general principles are biased towards the problems of tropical Africa, where we both have had our experience of tropical medicine. We apologize to those working in other parts of the tropics who may feel that the problems of their areas have not received the attention that they deserve. Selection of references proved at least as difficult as selection of topics for discussion. In general we have given few references to general immunological topics, as these are readily available elsewhere, and we have concentrated on specifically tropical problems. Whenever possible we have quoted reviews and recent articles in the hope that these will lead those seeking further

information in the field to the many important studies that have not been specifically mentioned.

Many people have contributed to the making of this book. We thank our colleagues Dr Peter Ball and Dr Anthony Bryceson for reviewing the whole text and Dr Muri Abdurrahman, Dr Maureen Duggan, Dr Fola Fakunle, Professor Alan Fleming and Dr Andrew Tomkins who have made helpful comments on individual chapters. We thank Mrs Nicola Wilson-Smith, Mr Cletus Chukwunyere, Mrs Margaret Jaiyeboa and Miss Grace Dabo for the typing and Mrs Susan Renner and Mr Linus Nwanko for the preparation of the figures and diagrams. Not least, we thank our families for putting up with the usual tribulations of the households of medical authors. None of our work at Zaria would have been possible without continued support from the Faculty of Medicine or without the generous financial assistance provided by the Medical Research Council.

1980 BMG
HCW

Abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
ADP	Adenosine diphosphate
AFP	Alphafetoprotein
AMP	Adenosine monophosphate
ASO	Antistreptolysin O antibody
ATP	Adenosine triphosphate
ATS	Antitetanus serum
BCG	Bacillus Calmette-Guérin
BL	Burkitt's lymphoma
CAH	Chronic active hepatitis
CFT	Complement fixation test
CIE	Countercurrent immunoelectrophoresis
C3NeF	C3 nephritic factor
CSF	Cerebrospinal fluid
DEC	Diethylcarbamazine
DHF	Dengue haemorrhagic fever
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
DNCB	Di-nitro chlorobenzene
DSS	Dengue shock syndrome
EA	Early antigen (Epstein-Barr virus)
EBNA	Epstein-Barr virus nuclear antigen
EBV	Epstein-Barr virus
ECF	Eosinophil chemotactic factor
ELISA	Enzyme linked immunosorbent assay
EMA	Early membrane antigen (Epstein-Barr virus)
EMF	Endomyocardial fibrosis
ENL	Erythema nodosum leprosum
ESR	Erythrocyte sedimentation rate
Fab	Antigen-binding fragment (immunoglobulin molecule)
Fc	Crystalline fragment (immunoglobulin molecule)
GMP	Guanosine monophosphate
G-6-P-D	Glucose-6-phosphate dehydrogenase
HA	Haemagglutination
H and E	Haematoxylin and eosin (stain)
HAI	Haemagglutination inhibition
HB_cAg	Hepatitis B core antigen
HB_sAg	Hepatitis B surface antigen
HLA	Human leucocyte antigen
ID	Immunodiffusion

IFAT (or IFT)	Immunofluorescent antibody test
KAF	Conglutinogen activating factor
LYDMA	Lymphocyte membrane determined antigen (Epstein-Barr virus)
MW	Molecular weight
NADP	Nicotinamide adenine dinucleotide phosphate
NPC	Nasopharyngeal carcinoma
PHA	Phytohaemagglutinin
P-K	Praustnitz-Küstner
PMN	Polymorphonuclear neutrophil leucocyte
PPD	Purified protein derivative (tuberculin)
PWM	Pokeweed mitogen
RES	Reticuloendothelial system
RIA	Radioimmunoassay
RNA	Ribonucleic acid
SLE	Systemic lupus erythematosus
SSPE	Subacute sclerosing panencephalitis
SRS	Slow reacting substance
SS	Sickle cell (disease)
TAB	Typhoid, paratyphoid A and paratyphoid B combined vaccine
$TCID_{50}$	Tissue culture infectious dose
TSS	Tropical splenomegaly syndrome
VCA	Viral capsid antigen (Epstein-Barr virus)

Contents

1

Immunological Changes in Healthy Individuals Living in the Tropics

Introduction

Definition of the normal can be difficult in any community but often proves to be especially so in the tropics. A peasant farmer able to carry out a full day's work in the fields and to live a normal social life is considered a 'healthy normal' in many developing communities. However, by the medical standards of industrialized countries he would be considered far from healthy. He is likely to have had repeated attacks of acute malaria since early childhood and still to have episodes of asymptomatic malaria parasitaemia. He may well have schistosomiasis, although now this produces little in the way of symptoms, and he probably has two or three types of intestinal worm. He may have asymptomatic filariasis. In addition, he is likely to have passed through a period of malnutrition at the time of weaning which may have had permanent effects on the immune system. Such a 'healthy normal' shows immunological changes that are not found among protected individuals living in industrialized societies. Some of these changes are listed in Table 1.1 and are considered further in this chapter.

Table 1.1 Immunological 'abnormalities' which may be found in healthy individuals in tropical communities

Humoral
↑ Serum IgG, IgM and IgE
↑ Prevalence of rheumatoid factor and other autoantibodies
↑ Prevalence of heterophile and Wasserman antibodies
↑ Levels of immune complexes
Cellular
Alterations in lymphocyte sub-populations

Changes in plasma proteins

It was realized many years ago that a high proportion of healthy individuals living in tropical areas had a higher erythrocyte sedimentation rate (ESR) than those living in industrialized countries (Trowell, 1960). The ESR values obtained in a group of healthy Nigerians are shown in Fig. 1.1. Although the factors controlling the ESR are still not completely understood, it is known that two of the most important are the plasma fibrinogen level and the serum γ-globulin level. These observations on the ESR were, therefore, one of the first indications that the plasma protein profile of those living in the tropics might differ from that found in healthy subjects living in Europe and America.

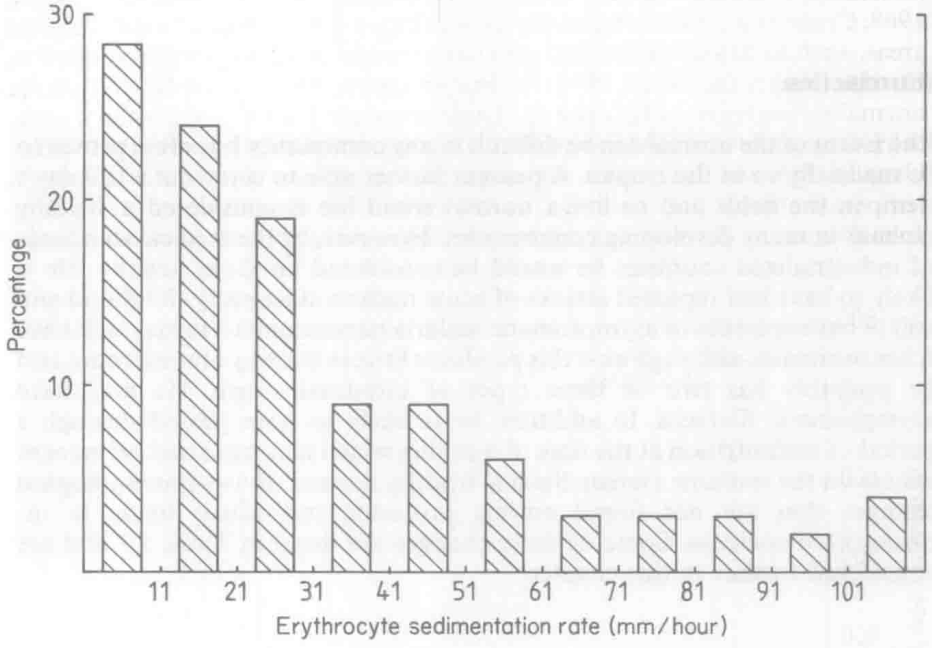


Fig. 1.1 Erythrocyte sedimentation rate (ESR) in 513 apparently healthy rural Nigerians. The upper limit of normal for Europeans is 15 mm/hour.

Introduction of the technique of plasma protein electrophoresis showed that this supposition was correct. It was shown that those living in the tropics tended to have a higher γ-globulin level and a lower serum albumin level than healthy Europeans or Americans. This pattern of an altered albumin: globulin ratio was found in many parts of the tropics with different patterns of infection and nutrition (Trowell, 1960). More detailed studies showed that the γ-globulin level of normal subjects could vary considerably within the same area, dependent upon the population group studied. Thus, at Ibadan in Western Nigeria it was found that the mean γ-globulin level (expressed as a

percentage of the total plasma protein) was about one and a half times higher in those living in a rural area than the mean level found in Nigerian University staff (Edozien, 1961). Similar results were obtained in Uganda (Holmes *et al.*, 1955). Studies carried out in the Gambia (Cohen *et al.*, 1961) showed that the rate of γ-globulin synthesis in healthy Africans was about seven times that found in healthy Europeans, although their serum levels of γ-globulin were only about twice the European value.

Development of simple techniques for the measurement of individual immunoglobulins has allowed the nature of the hypergammaglobulinaemia found in the tropics to be studied in more detail. Study of the immunoglobulin pattern of normal individuals has been undertaken in many tropical areas and a common pattern has been found in tropical Africa and in Papua New Guinea (Michaux, 1966; Turner and Voller, 1966; Johansson *et al.*, 1968; Rowe *et al.*, 1968; Crane *et al.*, 1971); this is depicted in Fig. 1.2. However, in other tropical areas, such as Malaysia, immunoglobulin levels are similar to those found in Europe (Yadav and Shah, 1973). Several studies in Africa have shown that the normal serum levels of IgG and IgM are increased to about two or three times the European level whilst the normal IgE level is even more markedly elevated. Usually, IgA and IgD levels are similar to those found in countries with a temperate climate but raised IgD levels were found in children in Ethiopia by Johansson *et al.* (1968). Generally, higher IgG and IgM levels have been found

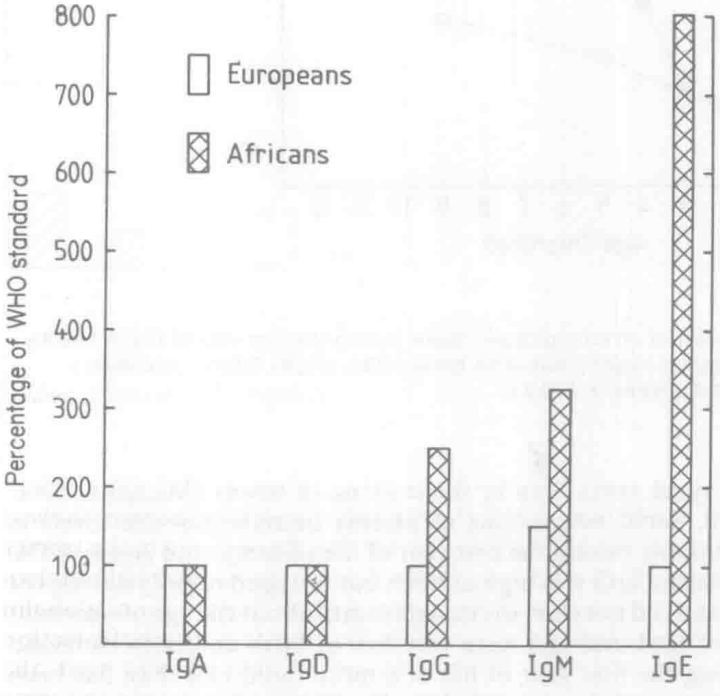


Fig. 1.2 The characteristic immunoglobulin pattern of healthy Africans in comparison with that of healthy Europeans.

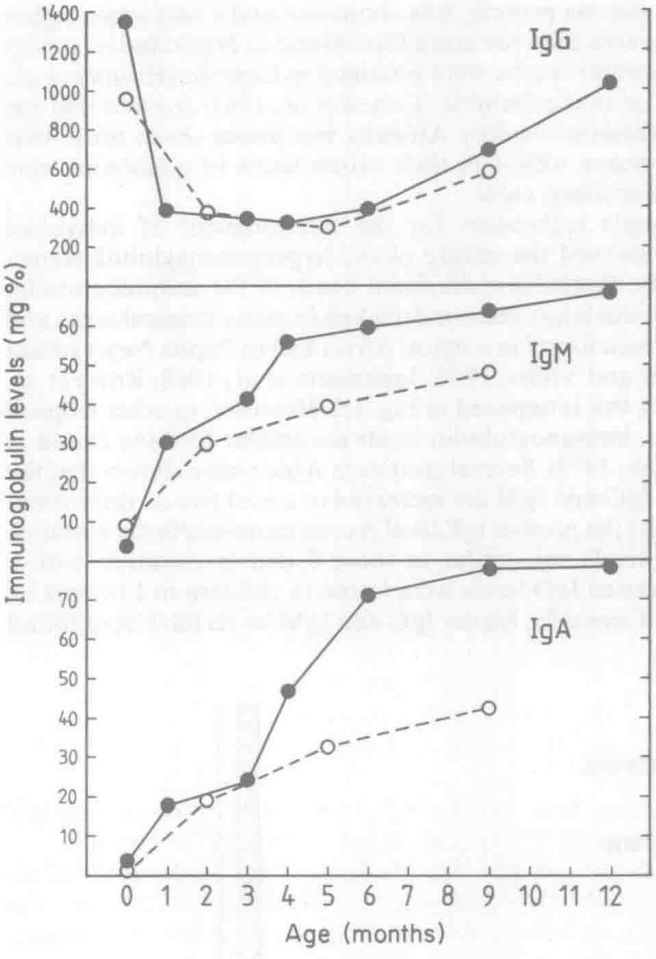


Fig. 1.3 A comparison of immunoglobulin levels during the first year of life in healthy African infants (●) and in healthy American babies (○). (From Adeniyi and Ayeni, 1976 and Stiehm and Fudenberg, 1966.)

in those living in rural areas than in those living in towns (Michaux, 1966; Logie *et al.*, 1973). Serial estimations of plasma immunoglobulin levels in healthy Nigerian infants during the first year of life (Adeniyi and Ayeni, 1976) showed that the plasma IgG was high at birth but dropped rapidly during the first month of life and did not start to rise again until about the age of 6 months (Fig. 1.3). Levels of IgM and IgA were very low at birth and both increased progressively during the first year of life at a more rapid rate than has been observed in European and American babies. Similar results were obtained in the Gambia (Rowe *et al.*, 1968) where it was shown that the serum IgA and IgG levels reached a plateau at about the age of 10 years old, whilst the serum IgM