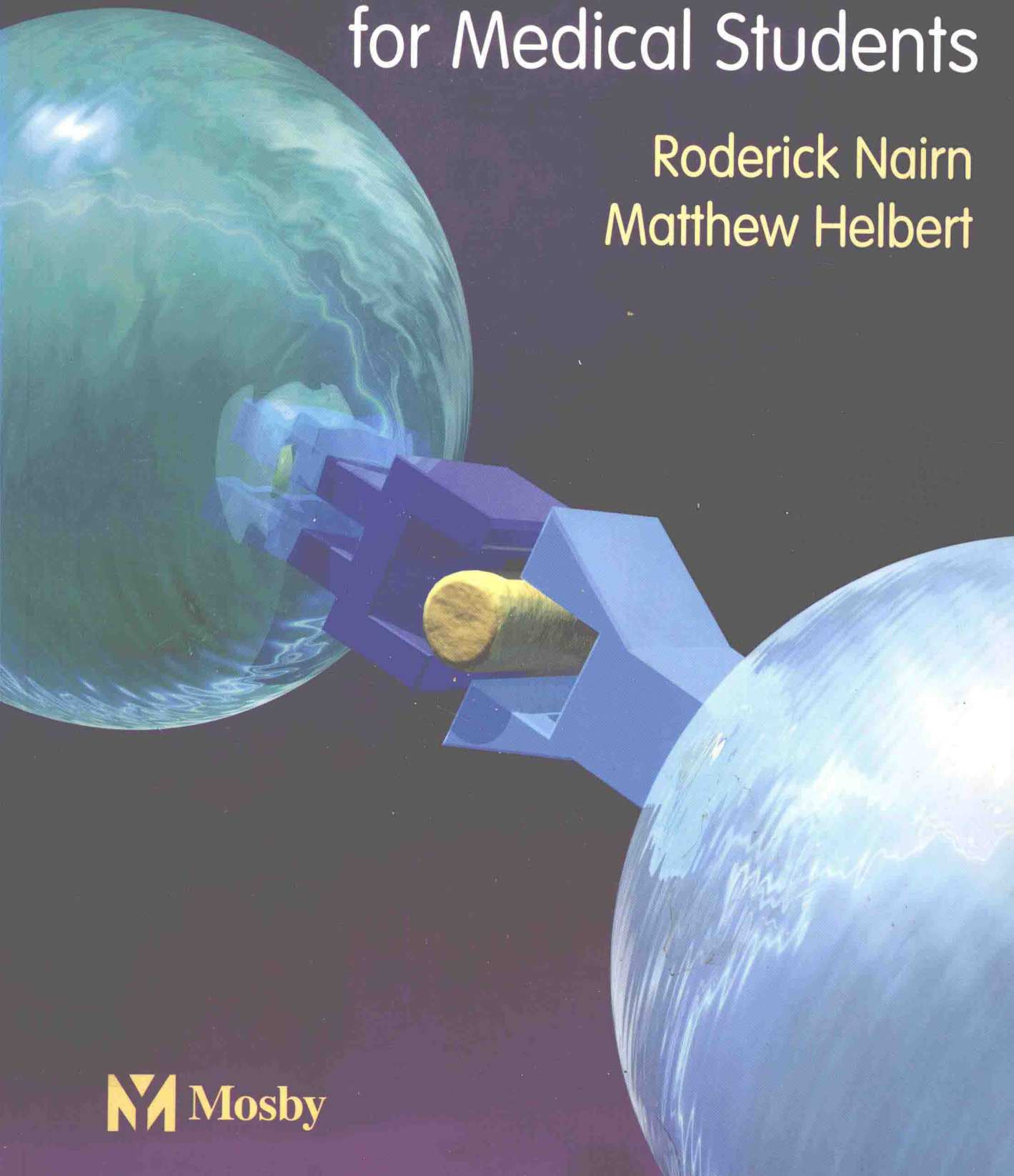
Immunology

for Medical Students

Roderick Nairn
Matthew Helbert



Mosby

Immunology

For Medical Students

Roderick Nairn
PhD
Professor and Chair
Department of Medical Microbiology and Immunology
Senior Associate Dean, Academic Affairs
Creighton University School of Medicine
Omaha
Nebraska, USA

Matthew Helbert
MBChB MRCP MRCPath PhD
Consultant Clinical Immunologist and Honorary Senior Lecturer
St Bartholomew's Hospital
London, UK

Illustrations by Ethan Danielson

Mosby

EDINBURGH LONDON NEW YORK OXFORD PHILADELPHIA ST LOUIS SYDNEY TORONTO 2002

MOSBY
An affiliate of Elsevier Science Limited

First published 2002
Reprinted 2003

ISBN 0-7234-3190-6

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
A catalog record for this book is available from the Library of Congress

Note
Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The authors and the publishers have taken care to ensure that the information given in this text is accurate and up to date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice.

Printed in China
N/02

Immunology

For Medical Students

Commissioning Editor: Louise Crowe
Project Development Manager: Siân Jarman
Project Manager: Frances Affleck
Designers: Judith Wright and George Ajayi
Illustrations Manager: Bruce Hogarth

PREFACE

We have recognized the need for an immunology book that is primarily focused on the needs of medical students for as long as we have been teachers of immunology. This book has been written to fill this need. Immunology can fall into different medical school courses or modules. Often, the immunology is taught in the Host Defense course, which integrates basic and clinical immunology (including allergy, immunopathology, etc.). Some medical schools, however, teach basic immunology and clinical immunology in two separate courses. This book should be useful for either curriculum organization.

We have concentrated on a simple, straightforward treatment of the subject. The book is relatively short and contains the topics we considered important to understand the human immune system and its role in protecting us from disease. This reflects our acknowledgement of the time constraints on today's medical student. With new topics and a growing amount of information considered to be essential, there are increasing demands on students. It is therefore important to have a concise, readable, textbook and that has been our primary aim. Most chapters contain the information needed for a typical 50-minute large class or small-group teaching/learning session. This, of course, means that details dear to the hearts of some immunologists are not covered!!

We are aware of two specific problems that medical students have with immunology. First, the immune system is complex, because it has evolved to respond to the wide range of pathogens. Many students find themselves bogged down in the complexities of the molecules and cells of the immune system, without having an understanding of how these components work together to fight infection. We begin our book with two overview chapters which explain what the immune system does and then how the components fit together. We recommend that students begin by reading these chapters. Further on in the text, there are more short, integrating overview chapters. These are not just for revision, but are there to make sure that the student understands how the material that they have read fits into the overall system. The second problem is that medical students do not always immediately see the relevance of immunology to day-to-day clinical practice. We have included clinical correlations throughout the text, which explain how understanding the science of immunology can translate into understanding real clinical problems.

The book is a concise description of the science of immunology, a topic that defies a final complete description, because there is much still to be learned. Hopefully, we will have succeeded in inducing an interest and appreciation of the relevance of immunology to medical students, to form the basis for a lifetime of learning about the immune system and its potential for use in improving the human condition. Most medical students today could still be practicing medicine in 40–50 years. Approximately, 50 years ago immunology was still in its infancy. For example, we did not know the chemical structure of antibody molecules in any detail, and treatments such as organ transplantation had not been carried out. The next 50 years will likely bring equally important advances in the field. History suggests that we would be foolish to try to predict what they will be. We hope that you enjoy participating in these advances in immunology and their application to human disease as much as we have in those that we have been privileged to observe in our careers.

2002 R.N. & M.H.

ACKNOWLEDGEMENTS

Many thanks to my wife, Morag, for deciphering the many drafts of my chapters, and to my family for their forbearance while this book was being written, to my mentors and colleagues for their insights and guidance, and especially all at Harcourt for their faith in the book and for expertly shepherding the project to completion. The book is dedicated to Morag and Carolyn, Muriel, James and Alastair.

R.N.

I am indebted to Lindsay and Caroline, who have given me tremendous insights to understanding immunology patients. Writing this book would not have been possible without Pat's immense patience.

M.H.

HOW TO USE THIS BOOK

Immunology for Medical Students is organized to be read comprehensively. The flow of the book is from genes and molecules to cells and organs, and finally to the immune system as an integrated system protecting the body from infection and regulating the health of the body.

- Section 1 introduces the basic concepts and is essential for an understanding of the language of immunology.
- Section 2 continues with a discussion of the antigen-recognition molecules, that is, antibodies, T cell receptors and the molecules encoded by the major histocompatibility complex.
- Section 3 deals with immune physiology, the role of the cells and organs of the immune system in the response to a pathogen.
- Section 4 discusses the innate immune system.
- Section 5 considers hypersensitivity, allergy/asthma, autoimmunity, immunodeficiency, transplantation, etc.

Throughout the book the core knowledge objectives are listed as Learning Points at the ends of chapters to aid in review. There are also four integrating overview chapters (e.g., Review of antigen recognition, Review of innate immunity), and these focus the student on the major points. Each section is relatively freestanding. For example, Section 5, Immune system in health and disease, could be used in a clinical correlations course, independent of the remainder of the book. *Immunology for Medical Students* will be most useful in the comprehensive Host Defense type courses growing in popularity in medical schools.

The icons used throughout are illustrated overleaf. You should become familiar with them immediately in order to follow the illustrations. We have selected several pathogens (listed in the figure overleaf) to use throughout the book as examples. As a reminder, some basic aspects of the structure and mechanism of action of these organisms are described. You should reacquaint yourself with these organisms, undoubtedly encountered in microbiology or infectious disease courses, and use the figure as a convenient reference as you encounter these pathogens in the examples in this book.

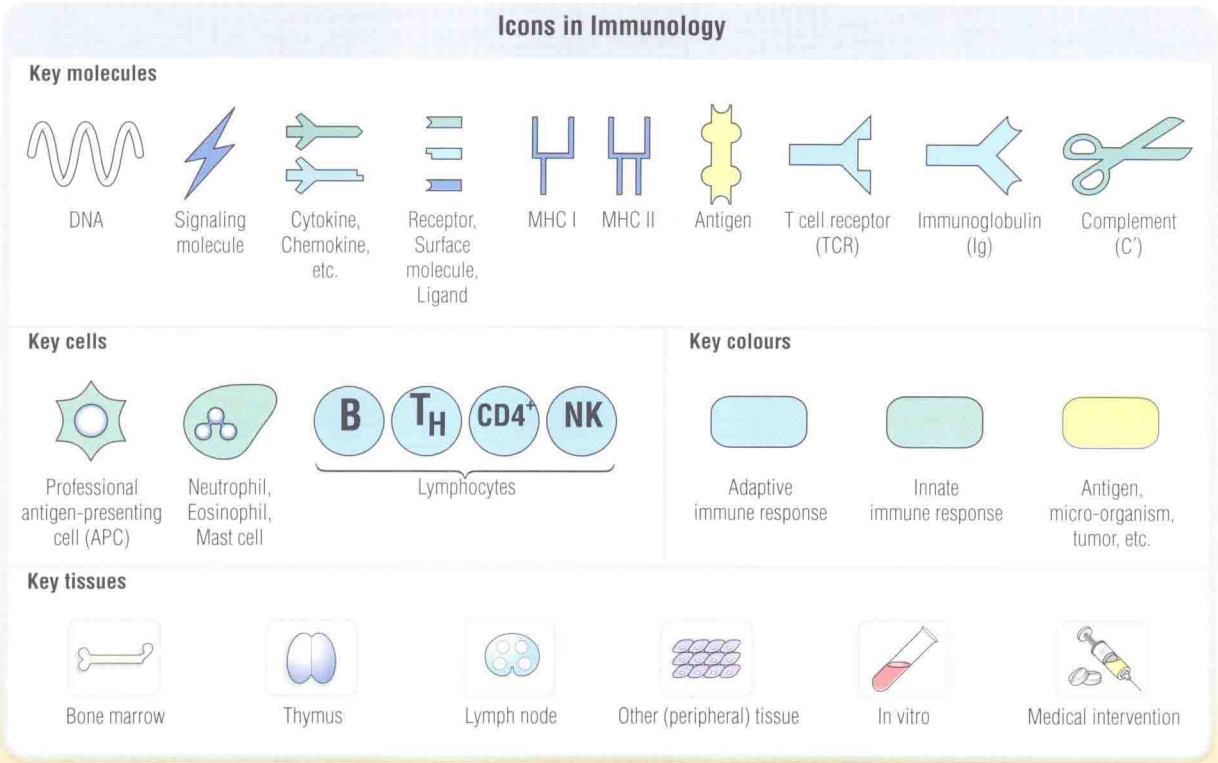
CLINICAL BOX

Clinical boxes, throughout the text, put immunology into a clinical context. The clinical material selected is current and relevant.

TECHNICAL BOX

Technical boxes show how advances in the field have expanded our knowledge of how the immune system works, and provided new means of preventing disease.

ICONS


Icons in Immunology
Key molecules
DNA
Signaling molecule
Cytokine, Chemokine, etc.
Receptor, Surface molecule, Ligand
MHC I
MHC II
Antigen
T cell receptor (TCR)
Immunoglobulin (Ig)
Complement (C')
Key cells
Professional antigen-presenting cell (APC)
Neutrophil, Eosinophil, Mast cell
B
TH
CD4+
NK
Lymphocytes
Key colours
Adaptive immune response
Innate immune response
Antigen, micro-organism, tumor, etc.
Key tissues
Bone marrow
Thymus
Lymph node
Other (peripheral) tissue
In vitro
Medical intervention

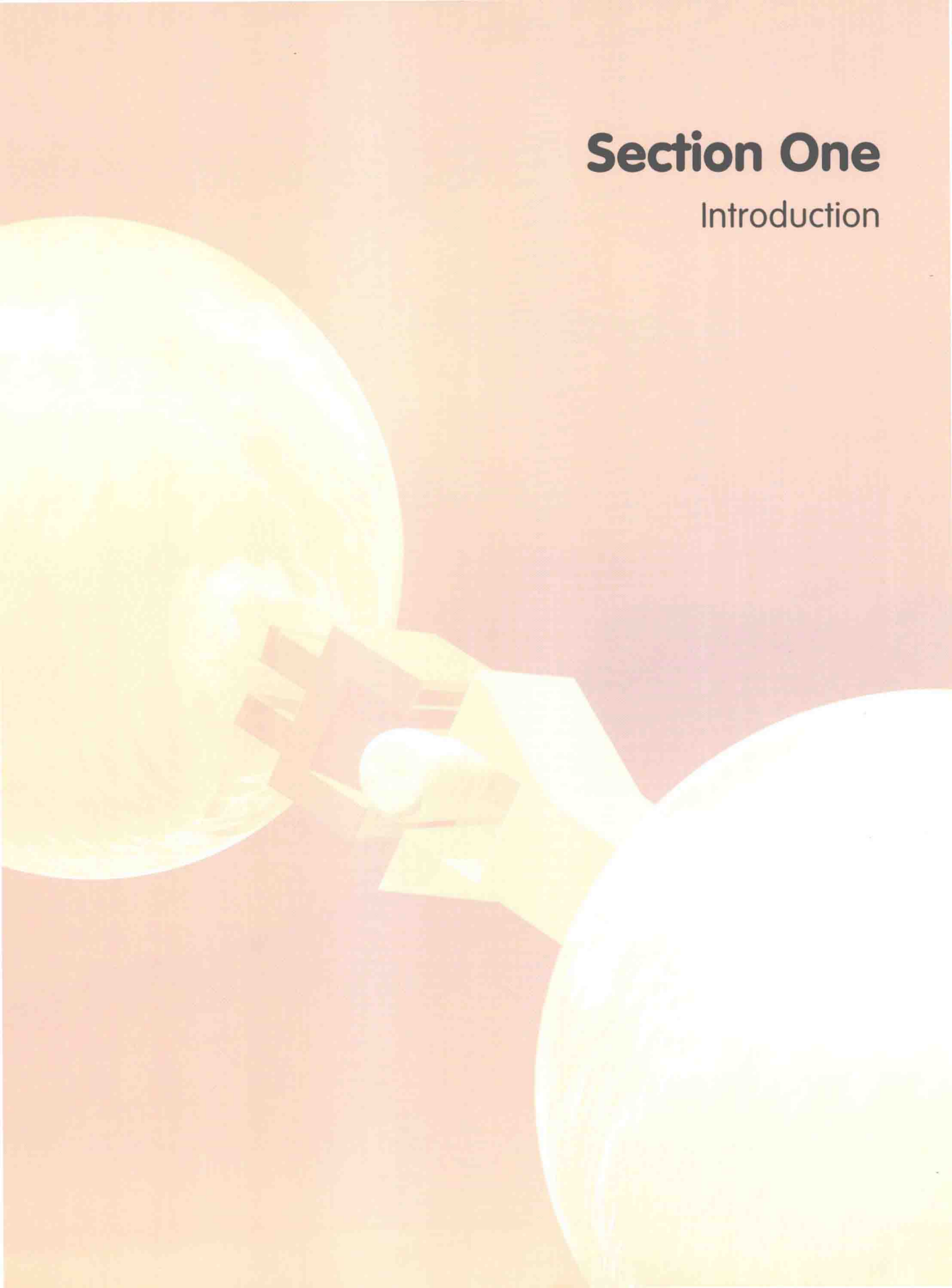
This Figure shows some of the different types of infection the immune system has to cope with. The mechanisms used by the immune system in response to each of these infections is described in detail in different chapters of this book.

Pathogen	Type of organism	
Human immunodeficiency virus (HIV)	RNA virus	HIV infection requires intimate sexual contact or exposure to blood. HIV has a small genome which frequently mutates, allowing escape from the immune response. Most infected individuals do not develop adequate immunity to clear the virus. Infection frequently results in the acquired immunodeficiency syndrome (AIDS). No vaccine exists.
Influenza virus	RNA virus	Influenza causes global epidemics. Casual contact can result in infection of the respiratory tract causing influenza. Influenza is also a small virus and new epidemics reflect the emergence of mutant strains which are not recognized by the populations' immune system. Vaccines exist but have to be changed every year to overcome mutations.
Epstein–Barr virus (EBV)	DNA virus	EBV infects the pharynx causing glandular fever or "infectious mononucleosis". B lymphocytes of the immune system are also infected and their uncontrolled growth can sometimes lead to lymphoma (a type of malignancy). EBV has a large genome which does not mutate frequently. The genome encodes proteins which help EBV evade the immune system.
Hepatitis B virus (HBV)	DNA virus	HBV infects liver cells. In many individuals, there is only transient liver damage. In others, there is chronic, severe liver damage, possibly as a result of the immune response to HBV.
Bordetella pertussis	Bacterium	*B. pertussis* infects the airways and causes whooping cough, which can be life threatening. A very effective vaccine exists and whooping cough has become rare in the developed world.
Escherichia coli	Bacterium	*E. coli* is a normally harmless bacterium living in the colon. If it enters the bloodstream in small numbers, phagocytes usually destroy such bacteria. When *E. coli* survives in the bloodstream, septic shock may occur.
Mycobacterium tuberculosis	Bacterium	*M. tuberculosis* also infects the airways. It is able to survive inside phagocytes. Because of this intracellular site it is difficult for the immune system to clear infection and tuberculosis may result. Tuberculosis is a major threat to global health, in part because patients with AIDS are particularly unable to clear mycobacterial infection.
Schistosoma	Helminth	This worm invades the gut and urinary tract. A special part of the immune system, involving mast cells, has a role in eradicating such infections.

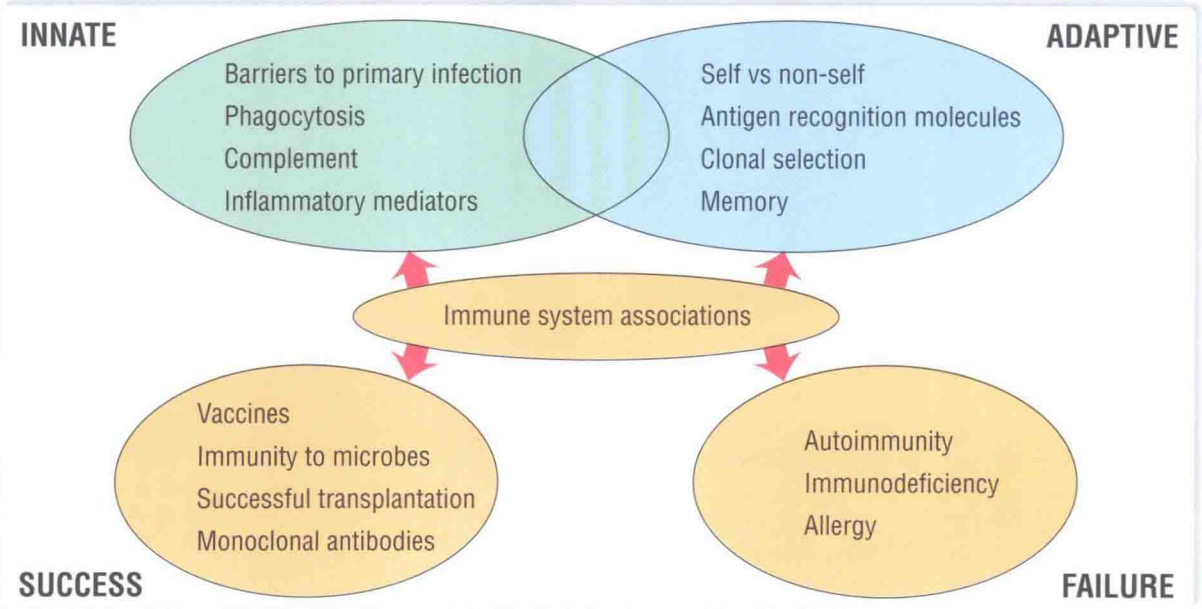
CONTENTS

Section One

Introduction



1 Basic concepts and components of the immune system



This chapter will briefly introduce the major components of the human immune system, what they do and how they accomplish their host defense role. We inhabit a world dominated by microbes, many of which can cause harm. The immune system is the body's primary defense system against invasion by microbes. Studies of the immune system are aimed at answering the following questions.

- How does our body defend itself from pathogenic, i.e. disease-causing microbes?
- How is a pathogen that succeeds in breaching the body's defenses eliminated?
- How does our body remember a prior exposure to a pathogen and respond faster and more effectively when the pathogen is re-encountered?

The human body has evolved in such a way that there are natural barriers to prevent entry by microbes (see also Ch. 2 and Section IV). For example, the skin and mucous membranes are part of the **innate** or **non-adaptive immune system**. However, if these barriers are broken (e.g., after cutting a finger), then microbes, including potential **pathogens** (harmful microbes), can enter the body and then begin to multiply rapidly in the warm, nutrient-rich systems, tissues and organs.

One of the first features of the immune defense system that a foreign organism would encounter after being introduced through a cut in the skin is the **phagocytic white blood cells** (leukocytes, e.g., macrophages), which congregate within minutes, and begin to attack the invading, foreign, microbes (see Chs 2 and 20). Later on, neutrophils (Fig. 1.2) would be recruited into the area of infection. These phagocytic cells bear molecules (pattern-recognition molecules) that detect structures commonly found on the surface of bacteria. Phagocytosis, the ingestion of particulate matter into cells for degradation, is a fundamental mechanism by which many creatures defend themselves against invading foreign organisms (Ch. 20). Various other protein components of serum, including the **complement** components (Ch. 19), may bind to the invader organisms and facilitate their phagocytosis, thereby limiting the source of infection/disease. Other small molecules, known as **interferons**, mediate an early response to viral infection by the innate system.

The innate immune system is often sufficient to destroy invading microbes. If it fails to clear infection rapidly then it activates the **adaptive** or acquired **immune response**, which takes over. The connection between the two systems is mediated by messenger

BOX 1.1
A young baby with her mother in India

Fig. 1.1 A young baby. (With permission from Andy Crump, TDR, WHO and the Science Photo Library.)

This baby was born a few weeks ago. Her mother is able to provide her with food, warmth and shelter. However, she has left the safe environment of the uterus and is now exposed to a wide range of harmful bacteria, viruses, fungi and worms. Her mother is barely able to protect her from these pathogens, particularly in the environment of the developing world where drinking water is often contaminated with human feces. Over the next 5 years she has a 1 in 8 chance of dying from infections. The largest threat is from water-borne infections causing severe diarrhea. Measles virus infects through the respiratory tract and kills up to 1 in 20 children in the developing world. In addition, this child will encounter parasites that are transmitted through insect bites and worms that can burrow through the skin.

What is remarkable is that seven out of eight children born in this hostile environment survive. What is the nature of the systems that protect children from such a wide range of infections?

molecules known as **cytokines**. The interferons are part of the cytokine family.

The effector cells of the adaptive immune defense system are also white blood cells: the **T** and **B lymphocytes** (Chs 2, 12, 14 and 15). The B and T cells of the adaptive immune system are normally at rest, but they become activated (see Chs 2 and 11) on encountering a foreign (non-self) entity referred to as an **antigen**.

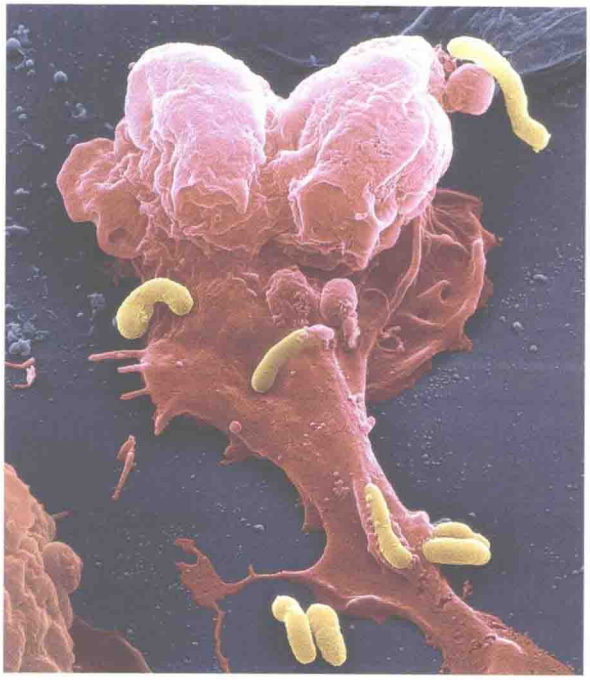


Fig. 1.2 Scanning electron micrograph of a macrophage (red) engulfing bacteria (yellow). (With permission from Juergen Berger, Max-Planck Institute and the Science Photo Library.)

Adaptive immune responses are highly effective but they can take 7–10 days to mobilize completely. A very important aspect of the adaptive immune response is the molecular mechanism used to generate specificity in the response. The immune system as a whole distinguishes *self* from *non-self*. It is able to cope with the great diversity in non-self structures by anticipating these different structures (foreign antigens) and creating a diverse repertoire of antigen receptors or **antigen-recognition molecules**. These receptors bind to small areas of the molecular structures of the non-self entities (e.g., foreign pathogens) called **antigenic determinants** or **epitopes**. The genetic mechanisms used for generation of this diverse range of antigen-recognition molecules are described in Chapters 6–8, 14 and 15. Several versions of these antigen receptors are employed by the immune system; these are **antibodies** (B cell antigen receptors), **T cell antigen receptors** and the protein products of a genetic region referred to as the **major histocompatibilty complex (MHC)**. All vertebrates appear to possess an MHC. The MHC genes of humans are referred to as human leukocyte antigen (HLA) genes and their products as HLA molecules (Ch. 8).

Antibodies are the most highly studied of the antigen-recognition molecules. In addition to being antigen receptors on B cells, they are also found as soluble antigen-recognizing molecules in the blood (**immunoglobulin** or **antibody**). Both the B and T cell