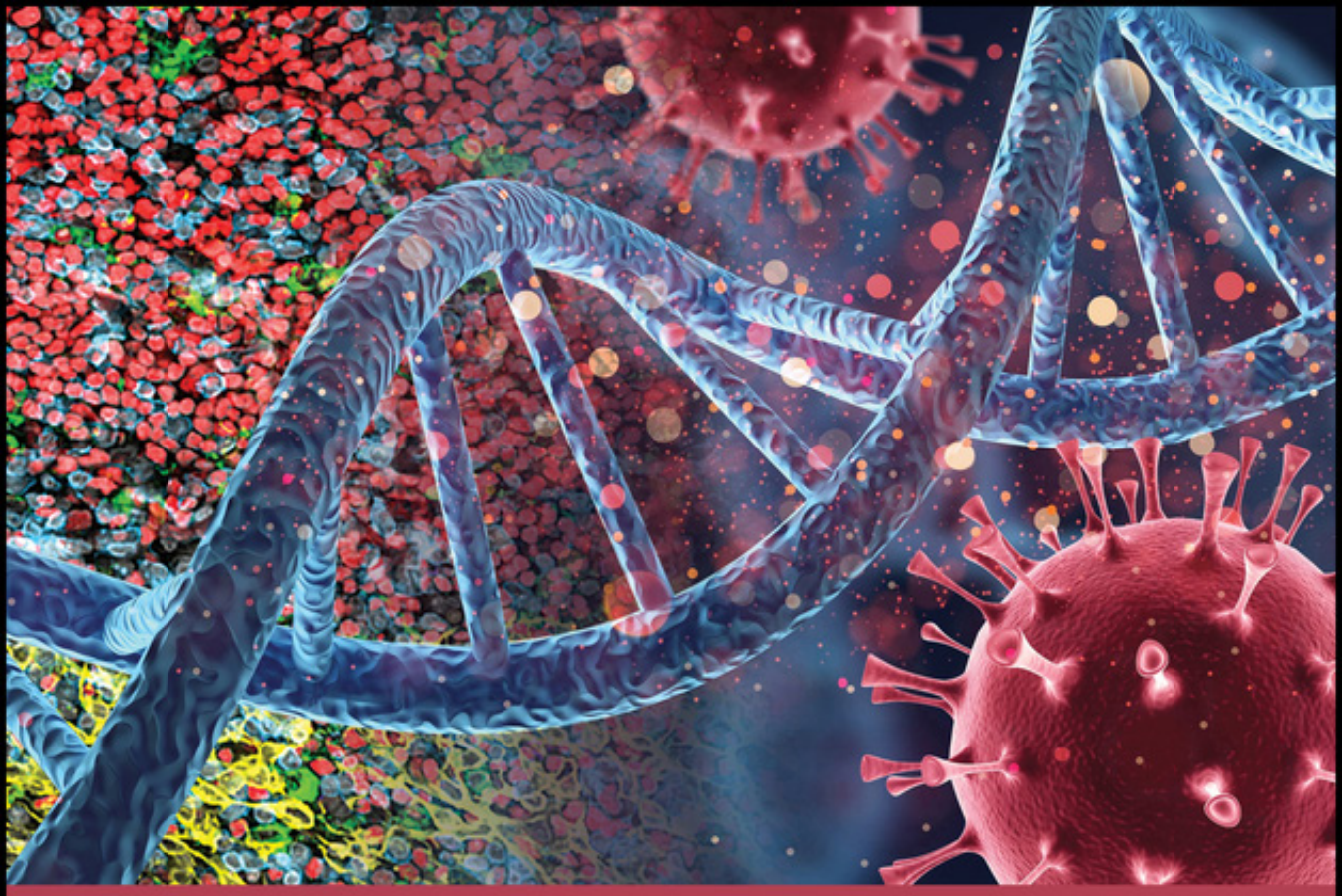

Third Edition

# The Biology of Disease

Edited by
Paul G. Murray • Simon J. Dunmore • Shantha Perera

with website

WILEY

The Biology of Disease

# The Biology of Disease

*Third Edition*

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# Preface to the Third Edition

It is with great pleasure and enthusiasm that we introduce the third edition of *The Biology of Disease*. Since the publication of the second edition over 2 decades ago, the landscape of disease biology has undergone a profound transformation. In parallel, advances in medical science and clinical practice have reshaped our approach to diagnosis and treatment. This new edition reflects these seismic shifts, incorporating the latest insights and discoveries in the field. As such, most of the previous chapters and case studies have undergone extensive modification to ensure that they remain at the cutting edge of current knowledge. Moreover, we have added 34 new case studies, each carefully selected to illuminate the relevance of disease biology within modern day clinical practice.

Notable changes since the second edition reflect the unprecedented challenges that the global community now faces, including the emergence of new and drug resistant pathogens, an increasing recognition of the environmental factors, including climate change, that influence health, and the growing impact of diet and physical inactivity on the development of obesity and related disorders including cancer and type 2 diabetes. Our revamped content addresses these issues, providing readers with a holistic view of the complex interplay between biology, the environment and human health.

For the first time, we are pleased to introduce over 500 new multiple-choice questions, designed to test students' knowledge and understanding of the material, helping them reinforce their learning and prepare for assessments. Among these questions, you will find 'extra challenge' questions that encourage deeper critical thinking and problem-solving, making this edition an invaluable resource for medical students and learners across various health sciences disciplines. These MCQ are available as an online companion to this book.

We would like to express our heartfelt appreciation to all the contributors who have dedicated their expertise to make this edition possible, including those who laid the foundations of the first and second editions. Their collective wisdom and dedication have enriched this book immeasurably. We also extend our gratitude to the previous editors, Jonathan Phillips, Paul Kirk and John Crocker. We particularly acknowledge the contribution of our friend and colleague, Paul Nelson, who passed away soon after proposing this edition but whose vision inspired us to continue with this endeavour. We also thank the production team at Wiley for their expert support and guidance. We are also indebted to Professor Kevin Dunne who carefully reviewed the entire manuscript.

Finally, we acknowledge the unwavering support of our respective families and colleagues. Your encouragement and support have been instrumental in bringing this venture to fruition.

We hope that this third edition of *The Biology of Disease* will continue to serve as an essential companion for students and professionals alike, fostering a deeper understanding of the biology of disease and its clinical applications.

*Paul G. Murray*
*Simon J. Dunmore*
*Shantha Perera*
*July 2024*

## Preface to the Second Edition

We were delighted to be given the opportunity to prepare a second edition of *The Biology of Disease*. Its appearance is timely in that, in the 5 years or so since the first edition, significant advances have been made in the basic sciences of cell biology and immunology, and in our understanding of the molecular mechanisms of disease. These developments are reflected in the relevant chapters. A new edition also offers the opportunity to review the aims of the book, though these still remain to produce a succinct volume with sufficient detail to enable a good understanding of the principles of disease biology.

In planning the second edition, we were keen to build upon the successful aspects of the first, particularly the use of case studies to amplify the points made in the chapters and to show how an understanding of the biology of disease translates into clinical practice. We have expanded the number of case studies to include a greater range of conditions and have reorganized some chapters to reflect this more clinically oriented approach. This is in line with developments in the medical curricula where students are exposed to clinical teaching at an early stage, and there is increased emphasis on clinically oriented problem solving. We anticipate that the revised book will also appeal to students on a range of other courses in the Health Sciences, including biomedical science, physiotherapy and other paramedical subjects, complementary therapies and nursing.

Finally, we would like to express our thanks to the Associate Editor team, to our colleagues in our respective Institutions, to the production team at Blackwell Science and not least to our families. All of these have supported us throughout, demonstrating good humour and patience at difficult times, and made significant contributions to the achievement of our goals.

*Jonathan Phillips*
*Paul G. Murray*
*Paul Kirk*
*June 2000*

# Preface to the First Edition

*The Biology of Disease* aims to present the basic principles of disease processes in a form readily accessible to students trying to assimilate large volumes of information from a variety of sources. In conceiving this book, we recognized a need for a succinct volume that would give a broad yet sufficiently detailed account of the biology of disease. Acknowledging the expertise which lies in our medical and scientific colleagues (some working in education, some in research and others in clinical practice), we have drawn upon the experience and enthusiasm of a wide range of authoritative contributors. We feel that the book has benefited from this diversity of expertise, which has enabled us to cover many of the important topics in medicine today. Equally importantly, we were keen to adopt an accessible style of presentation and a common writing style, and we are grateful to all our contributors for their help in enabling us to achieve this aim.

From the outset, we felt it important to integrate the biological principles of disease processes with their clinical manifestations-the signs and symptoms which enable a diagnosis to be made. We have achieved this by ensuring that the principal chapters are clinically relevant and, where possible, that they bridge any gap between the biological and clinical features of disease. In addition, we have included clinical case studies in all the major sections of the book, each of which emphasizes the link between our current understanding of the basic science of the relevant condition and its clinical presentation. There is inevitable overlap and integration of topics in different sections of the book, so we have indicated cross-references where appropriate.

We anticipate that this book will be of use to a wide range of readers, particularly medical students approaching their clinical studies, students of clinical and biomedical sciences and students of other paramedical subjects. Sections of the book cover major areas of clinical science including epidemiology, immunology, infection, disorders of the blood, genetic diseases, oncology and mental health. Each section is complete in itself, enabling the book to be used selectively for the study of individual topics. We have tried to provide a succinct, yet comprehensive, overview of each topic and we hope that readers will be stimulated to seek out further, more detailed information. For this reason, each chapter concludes with key points and suggestions for further reading.

We are most grateful to all our contributors whose cooperation and expertise has been invaluable in achieving the aims of the book. We also thank our Associate Editor, John Crocker, for his help and guidance in the early stages of the editing process. Finally, we wish to acknowledge the support of our colleagues in the School of Health Sciences, of the editorial team at Blackwell Science and not least, that of our respective families, all of whom have helped us to nurture this venture to fruition.

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## About the Companion Website

*The Biology of Disease* is accompanied by a companion website:

**www.wiley.com/go/murray/biologyofdisease3e**


The website includes:

- Multiple choice questions listed by section and divided into two levels of difficulty.
- The answers to these multiple choice questions, with an explanation.
- The figures as power point slides which may be used, for example, for teaching.

# Part 1

# Basic Principles of Disease and Epidemiology

# 1

# The Nature of Disease

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## Introduction

This chapter considers how disease is defined, what types of factors cause disease and how diseases are classified. It considers why disease classification systems are important and how they are evolving in the era of personalised medicine. The chapter also serves as a foundation for later chapters which are focussed on the biological mechanisms underpinning disease development and progression.

## Definition of Health and Disease

Health and disease can be difficult to define. Health is often described as the absence of disease and an individual may be in good health if there are no impediments to proper functioning or survival. The World Health Organization (WHO) has defined health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'. This latter definition is much broader and it is likely that most people would not be considered 'healthy' on the basis of these criteria.

Nevertheless, the WHO definition is useful since it acknowledges the importance of psychological and social well-being in the maintenance of health. Perhaps, a more realistic definition considers that health is a condition or quality of the human organism which expresses adequate functioning under given genetic and environmental conditions. This definition implies that an individual may be

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Companion website: www.wiley.com/go/murray/biologyofdisease3e

considered healthy even if compromised in some way. An example here would be someone with Down syndrome who might well be considered healthy under the latter definition but not under the former.

Implicit in many definitions of health is the concept that efficient performance of bodily functions takes place in the face of a wide range of changing environmental conditions. Health in this context may be regarded as an expression of adaptability, and disease a failure thereof. Disease can also be defined as a pattern of responses to some form of insult or injury resulting in disturbed function and/or structural alteration.

## Concepts of Normality

Individuals who are free from disease are often described as being 'normal'. It is important to recognise that normality does not always indicate health, but is merely an indication of the frequency of a given condition in a defined population. Some diseases occur with such frequency in the population that they might be considered to be 'normal', e.g. dental caries.

If we examine the distribution of an indicator of health, for example, the level of a particular analyte in the blood (e.g. haemoglobin), we can see it usually follows a *normal distribution* in a population (Fig. 1.1). Applying limits to the distribution curve produces two cut-off points. Below and above these points, haemoglobin levels may be considered abnormal. However, a value within the normal range may be considered pathological in a particular individual or under certain circumstances. Likewise, a small percentage of individuals falling within the abnormal zones will remain healthy and suffer no consequences as a result of their 'abnormally' high or low haemoglobin concentration. Furthermore, in adult females, the total blood haemoglobin concentration tends to be lower than in males, due in part to their monthly menstrual blood loss. Taking another example of blood cholesterol

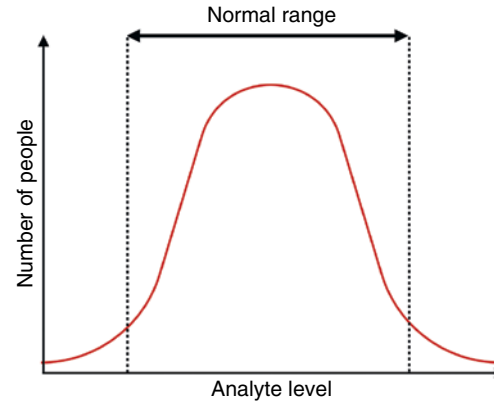


**Figure 1.1** The normal distribution of blood levels of a typical analyte. Reference ranges are used to determine whether a patient's test results fall within the normal range, usually the central 95% of values derived from the results of tests done on a large number of healthy individuals. If blood levels fall outside the normal range, then this could indicate an underlying medical condition. Reference ranges can be influenced by a number of factors, including age and biological sex, and so reference ranges may be reported separately for different patient groups. Moreover, reference ranges may vary between different laboratories. For this reason, the reference ranges used in this book (Appendix 1) are provided only as a guide. *Source:* Created with BioRender.com.

concentration, the normal distribution in Western countries may not reflect levels that are ideal for the maintenance of health. For this reason, the term *reference range* instead of the *normal range* is preferred when defining the desired level of an analyte.

The rigid application of reference ranges can give rise to confusion, depending on how they are interpreted. For example, it is commonplace to show reference ranges for the *differential* white cell count (i.e. the different populations of white blood cells which make up the total leucocyte count) either as a percentage of the total or as the actual (or *absolute*) number in a given volume. When expressed as percentages, it is assumed that the total white cell count is normal. The use of absolute numbers is less ambiguous. For example, a normal lymphocyte count is in the range of $1.5–4.0 \times 10^9$/L or 20–45% when the total white cell count is normal ($4–11 \times 10^9$/L). If

the total white cell count is raised to $15 \times 10^9$/L, a differential count showing lymphocytes as 15% of the total could be interpreted as indicating lymphopenia (reduction in lymphocyte count). In reality, the absolute lymphocyte count is normal (15% of $15 \times 10^9$/L is $2.25 \times 10^9$/L), and the abnormally high cell population here could be neutrophils, for example. Typical reference ranges are given in Appendix 1 of this book, but should only be used as a guide, since reference ranges vary between different populations and even between different laboratories (for example, because of technical differences between different assays).

## Promoting Health

Health promotion refers to the process of taking action to address the social, economic, environmental and behavioural factors that influence health and disease. The goal is to create an environment that encourages healthy behaviours and enables individuals to make informed decisions about their health. This may involve education and the provision of resources to help individuals adopt healthy lifestyles, promoting policies and programmes that support healthy behaviours and creating communities that are designed to support health and well-being. Health promotion activities may include initiatives such as providing access to healthy foods, promoting physical activity, providing resources for smoking cessation and supporting mental health and well-being. Health promotion may also involve efforts to address social determinants of health, such as poverty, lack of education and social isolation.

## Onset of Disease

It can be difficult to be precise about the transition from health to disease because pathological changes with potential to cause disease are present in many apparently healthy people. For example, early *atheromatous* deposits are present in the arteries of a substantial proportion of symptom-free middle-aged adults, increasing their risk of cardiovascular disease. Most patients with coronary heart disease would date the onset of their illness from the first clinical manifestation (e.g. chest pain), rather than from the *hypertension* (increased blood pressure) which may have begun years before and which predisposed them to heart disease.

## Causes of Disease

A great many agents and stimuli are implicated in the causation (*aetiology*) of disease. In the majority of cases, it is not possible to discover a single causative agent which always causes disease when present. For example, exposure to the microorganism *Mycobacterium tuberculosis* does not invariably result in tuberculosis; other factors (e.g. poor diet, reduced immunity, size of the infective dose) are important. However, tuberculosis cannot occur in the absence of the organism. Exposure to *M. tuberculosis* is therefore the *necessary* causal factor and the other factors are *subsidiary* causal factors.

Tuberculosis is an example of a disease for which the causal factors are well known. For other diseases, identification of the causal factors can represent a significant challenge. Often the initial search for a causal factor begins by examining the patterns of disease within human populations. This is *epidemiology* and is the subject of Chapter 2.

## Types of Aetiological Factors

Aetiological factors may be broadly divided into *endogenous* factors (those which create a disturbance or imbalance from within) and *exogenous* factors (factors which threaten existence from the outside). Chromosome abnormalities giving rise to genetic disorders

may be regarded as endogenous factors, whereas environmental insults are examples of exogenous aetiological agents. However, there is an overlap between these two groups. For example, some inherited chromosome abnormalities have been shown to be the result of parental exposure to mutagens in the environment, e.g. ionising radiation. Some genetic disorders then may ultimately be attributed to exposure to exogenous factors. Some disorders do not have a known cause and are often referred to as *idiopathic*. Diseases induced by medical intervention are referred to as *iatrogenic*.

Although modern humans, i.e. *Homo sapiens*, are a single species, they carry with them thousands of species of micro-organisms, including those that routinely inhabit the skin, lungs, saliva, oral mucosa, conjunctiva, biliary tract, gastrointestinal tract and other sites. Collectively, the bacteria, archaea, fungi, protists (single-celled organisms of the kingdom Protista, such as protozoa or simple algae) and viruses, living in or on humans, are known as the *microbiome*. Therefore, it is also important to consider how the microbiome, as an extension of the human organism, influences, and is itself influenced by, disease. The term *human metagenome* is sometimes used to refer to the collective genomes of these resident microorganisms.

## Naming Diseases

With the recognition of new diseases such as COVID-19, it is timely to reflect on what basis diseases are named. Some diseases are given a name according to their symptoms, appearance, or other characteristics. For example, *psoriasis* which is a skin condition characterised by red, scaly patches on the skin (Fig. 1.2) comes from the Greek word 'psora', which means 'itch'. Other diseases are named after the person who first described them or identified their cause. For example, Alzheimer disease is named after Alois Alzheimer. Some diseases are named using

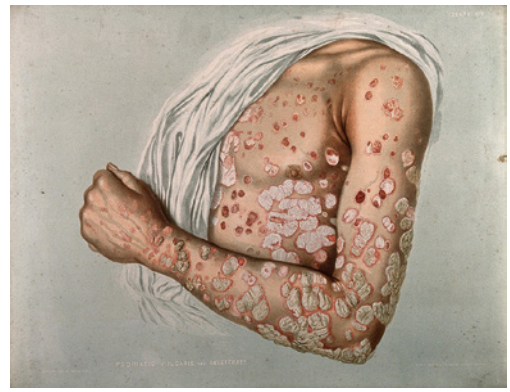

**Figure 1.2** Psoriasis, so named after the Greek word 'psora', meaning 'itch'. This image shows diseased skin on the chest and arm of a man suffering from psoriasis. *Source:* Wellcome Collection/https://wellcomecollection.org/works/z2wkwnf6/images?id=ek5tq6qx / last accessed November 13, 2023.

an acronym that stands for the name of the condition. For example, AIDS is short for *acquired immunodeficiency syndrome*. Other diseases are named after the place where they were first identified or where they are particularly common. For example, Lyme disease is named after the town of Lyme in Connecticut, where it was first identified. Similarly, German measles (also known as rubella) gets its name because it was German physicians who first described this disease in the 1700s.

## Classification of Disease

Diseases are classified either on the basis of the outward signs produced by disease (*manifestations*) or on the existence of a common aetiological agent. Most diseases are classified on manifestational criteria irrespective of the causative agents involved. Thus, a number of causal factors are implicated in the development of various types of carcinoma of the lung, including cigarette smoke, asbestos, coal smoke and other atmospheric pollutants, but patients with the manifestations of lung cancer are grouped together irrespective of the

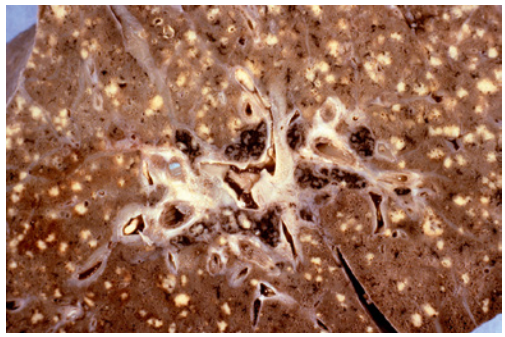

**Figure 1.3** Miliary tuberculosis. This picture shows a close-up of a lung from an adult who was HIV-positive. The parenchyma is studded with 1–4 mm nodules of miliary tuberculosis granulomas. 'Miliary' refers to a form of tuberculosis in which there is widespread dissemination of lesions which have an appearance similar to millet seeds. *Source:* Wellcome Collection/https://wellcomecollection.org/works/wvtqyn8v/items / last accessed November 13, 2023.

involvement of one or more of these agents. Conversely, diseases caused by *M. tuberculosis* may produce different clinical manifestations in different individuals, yet all are classified as forms of tuberculosis (Fig. 1.3).

Classification of disease on the basis of shared aetiology may follow the identification of a new and important aetiological agent, particularly if this offers promise of major therapeutic or preventive advantage. For example, all forms of disease associated with infection with the SARS-CoV-2 virus are referred to as COVID-19. However, not all diseases are classified on the basis of a shared aetiology. For example, the identification of cigarette smoke as the most important cause of lung cancer did not promote a revision of the classification of lung cancer or of other diseases caused by smoking (e.g. emphysema and chronic bronchitis).

The classification of disease into discrete entities enables patients to be assigned to specific groups. The patients may then be treated in a similar fashion to other patients assigned previously to the same group, thus, at least in theory, improving the clinical outcome based on past experience. This is sometimes referred to as *stratified medicine*. This view may be extended on the basis that the development of disease, and its progression and response to treatment, should be regarded as unique to the individual. This has led to the concept of *personalised medicine*, in which an individual's profile, for example their genetics, is used to guide decisions with respect to prevention, diagnosis and treatment. The terms personalised and stratified medicines are often used interchangeably and can be considered under the broader heading of *precision medicine*.

## Identifying Disease

We have seen how diseases are classified but have not yet considered how a particular set of features is first designated as a disease state. Doctors use *signs* (what the doctor sees or feels when carrying out a physical examination), *symptoms* (what the patient complains of) and a range of laboratory and clinical tests to determine whether a patient has a given disease. The taking of a thorough clinical history will determine whether there has been exposure to any potential aetiological agents. The existence of certain predisposing conditions may make the development of a disease more likely. Examples of these risk factors include certain genetic disorders, lifestyle, psychological and personality profile, age and environmental factors such as climate and pollution. Furthermore, the presence of one disease (e.g. type 2 diabetes; T2D) may predispose a patient to the development of a different disease (e.g. atherosclerosis).

One of the early steps in identifying a disease is to establish a range of diagnostic possibilities from which the eventual diagnosis will be selected. This is referred to as the *differential diagnosis*. The final diagnosis may sometimes be established shortly after clinical presentation, in other cases perhaps only after extensive use of laboratory and clinical tests, or occasionally may never be identified during the lifetime of the patient. It must be remembered that disease is a dynamic process and indicators of

disease may vary as the disease progresses. Furthermore, in some patients, particularly those who are elderly, different diseases may co-exist (referred to as *co-morbidities*), thus confusing the diagnostic processes.

The impact of disease on an individual patient or population group may be measured as *morbidity* (i.e. its detrimental effects, such as pain or disability) or as *mortality* (death). *Prognosis* is the likely future for the patient in terms of length and quality of life. Prognosis depends on many factors, including the stage the disease has reached and the likely impact of therapy. Once a disease has been identified, treatment, aimed at relief of symptoms or, where feasible, cure, is usually initiated. The decision on how to manage the patient often involves input from a number of different healthcare professionals in the so-called *multidisciplinary team meetings*. Following treatment, patients may be cured of the disease or may enter *remission* (a symptom-free period) from which they may either *relapse* (when symptoms of the disease return) or be cured. Some diseases are not amenable to cure, but can be controlled, for example, by the administration of drugs. Some patients with advanced disease may receive *palliative* treatment only, with the aim of relieving their symptoms for the remainder of their life.

## The Global Fight Against Disease

Significant progress has been made in reducing the incidence of, or even eradicating, certain diseases. One of the greatest success stories was the eradication of smallpox. This deadly virus had been a scourge on humanity for centuries, causing millions of deaths and leaving many more people permanently scarred or disabled (Fig. 1.4). Edward Jenner, widely regarded as the founder of immunology, was responsible for first showing that his cowpox 'vaccine' conferred specific immunity to smallpox (Fig. 1.5). Since then, a global effort centred upon widespread vaccination, as well as strict disease surveillance,

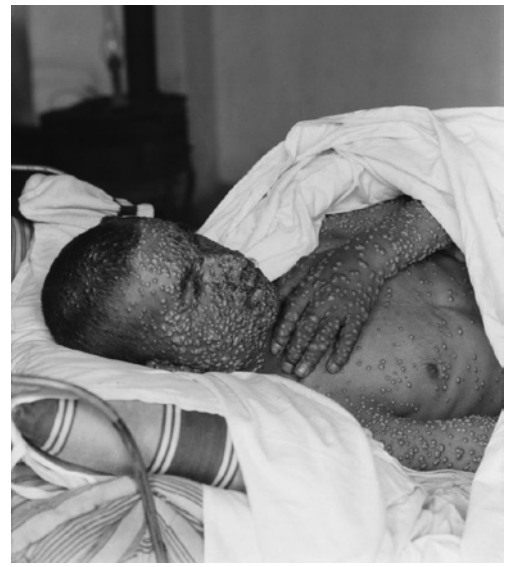

**Figure 1.4** Smallpox, a once deadly disease. The heavily pockmarked face, arms and hands of a smallpox victim in Palestine, c. 1900–1925. By 1980, the disease was finally eradicated by the World Health Organization. *Source:* Everett Collection/Shutterstock.

led to the complete eradication of smallpox in 1980. Similarly, from the 1960s, the widespread use of poliovirus vaccines has prevented an estimated 30 million cases of paralysis. Efforts to eradicate poliovirus globally, initiated in 1988, have reduced the number of reported poliomyelitis cases from 35 000 in 1988 to less than 2100 by 2001. However, recent events such as the declaration of a state of emergency in New York following a reported case of poliomyelitis, the detection of polioviruses in wastewater samples in New York and London, and the resurgence of wild Poliovirus type 1 (WPV1) cases in Pakistan and imported cases in Malawi and Mozambique have highlighted that poliovirus remains a threat. Moreover, newly emergent infectious diseases, for example, Ebola, Zika and, most recently, coronavirus diseases, will continue to pose major challenges to global health in the years to come.

The rising incidence of non-communicable diseases perhaps presents an even a greater