Textbook of Medical Virology

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Preface

The great advances which have taken place in the field of virology during the last two decades have made the subject one of increasing importance to students and practitioners of medicine. Until now, most recent advances in the subject have been available only in the original literature, specialist monographs, review articles, or in advanced texts designed for the professional virologist. This book is designed to meet the needs of students and practitioners of medicine; in it, I have tried to present a simple, readable, and up-to-date account of virology in its relation to medicine. The text is, however, sufficiently comprehensive to make it useful for medical graduates reading for the Membership examination of the College of Pathologists, and for other postgraduate diplomas. Although written primarily for students, the book should prove useful to general practitioners who wish to bring themselves up to date in the subject. Theirs is a particular need, since they are frequently concerned with the diagnosis and prevention of virus diseases.

The book is based on a course of lectures given to students at University College Hospital Medical School, and is divided into three parts. The first part is devoted to general virology, and deals with the principles of technique, structure, nomenclature, and replication, as well as with mechanisms of virus infection and the host's resistance to it. Parts 2 and 3 deal with various aspects of viral and rickettsial infections, respectively. With students in mind, and in the interests of general readability and simplicity, no detailed references have been included but credit is given to those who have made specially important contributions to the subject. Inevitably, many names which no doubt should have been included have been omitted, but I am deeply conscious of my indebtedness to all those whose long, arduous, and often brilliant research has made this book possible. Nearly all the references to original papers which may be

required can be found in the books which are listed in the guide to further reading, and others can easily be traced in the *Index Medicus*. I have not therefore considered it necessary to repeat these references again here.

My choice of arrangement and nomenclature requires a word of explanation. I have adopted, as far as possible, the nomenclature proposed by the Provisional Committee for the Nomenclature of Viruses which is likely to receive international agreement before long. This has not been allowed to prevent my using the more widely known colloquial names for the purpose of achieving greater clarity. In the arrangement of subject matter, the claims of clinical logic have been allowed to outweigh those of virus taxonomy; this is in keeping with the applied nature of clinical virology. Occasionally the superficial and dogmatic treatment of subjects which others may consider controversial has been dictated by the necessity of keeping the book within a reasonable compass.

No textbook can be written without reference to other works on the subject, and I have referred constantly to many classic works on virology. I am particularly indebted to Rivers' famous textbook *Viral and Rickettsial Diseases of Man*, now edited by Horsfall and Tamm. This may be regarded as one of the great classics of medical literature and it has served as my model in preparing this book. Most other works to which I have referred are listed in the guide to further reading, to which those requiring further information may turn.

It is a pleasure to acknowledge, with gratitude, the help and co-operation of many friends and colleagues. I am indebted to Professor G. Belyavin for his generous support and encouragement, and for reading the manuscript. Especial thanks are due to my friend and colleague Dr Peter Higgins who provided me with many tissue culture preparations and other material for illustration. I am also grateful to Professor J. F. Smith for the sections illustrating poliomyelitis, rabies, and zoster infections; and to Dr D. McSwiggan and Dr M. W. N. Nicholls who provided material infected with coxsackie virus.

I am indebted to Mr V. K. Asta for his fine and skilful drawing of Figs 3, 5–8, 15a–17a, 21, 33, 36a, 37, 38, 42, 43, 45, 46, and 49 and to University College Hospital Medical School for permission to

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I am especially grateful to the many authors, editors, and publishers who so readily granted me permission to reproduce figures from their various publications, and most of all to those who supplied me with actual photographs and unpublished material. Their contributions are acknowledged in the appropriate places.

My greatest thanks are due to Miss Diana Wilson who has typed and retyped the manuscript, and has been of invaluable assistance in many different ways. The unfailing patience and courtesy of Mr Per Saugman of Blackwell Scientific Publications Ltd is also gratefully acknowledged.

Finally, I wish to pay tribute to my teachers, the late Professor Wilson Smith F.R.S. with whom I was privileged to work for several years, and to Professor George Belyavin, teacher, friend, and colleague of many years standing. The following pages owe much to their influence.

London A. COHEN

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PART 1

General Virology

CHAPTER 1

Introduction

The classical researches of Pasteur (1822–95) established the germ theory of infective disease beyond doubt, and before the end of the nineteenth century the causative bacteria of many diseases had been isolated and identified. There were some infective diseases, however, from which no causative bacteria could be isolated and whose aetiology remained in doubt. The first clue that another type of micro-organism might be responsible for them was provided by Ivanovsky in 1892. He observed that the mosaic disease of tobacco plants was transmitted by an agent which passed through filters whose pores were small enough to hold back ordinary bacteria. But, it was not until 1899 that Beijerinck seized upon the significance of this observation, and realized that the filterable agent of tobacco mosaic disease was something other than a bacterium, referring to it as a contagium vivum fluidum. Later, the term filterable virus, or virus, was applied to this type of filterable infective agent.

Infective agents similar to that of tobacco mosaic disease were soon recognized as the cause of a number of diseases of man and animals. They were characterized by the specific pathological effects produced in their hosts, their filterability, their failure to grow on ordinary bacteriological media, and by their invisibility in the light microscope. By these criteria, the viral aetiology of foot-and-mouth disease of cattle was proved by Loeffler and Frosch in 1898, that of yellow fever by Walter Reed and his colleagues in 1901, and that of poliomyelitis by Landsteiner and Popper in 1909. A few years later, the independent observations of Twort and d'Herelle showed that even bacteria were susceptible to infection with specialized viruses called bacteriophages.

The numerous unsuccessful attempts by these and other workers to grow viruses on artificial, non-living, media, using the usual bacteriological methods, led to the realization that the most

characteristic property of viruses is their dependence on living host cells for replication. Because of this, the range of viruses studied in the laboratory was for many years limited to those few which were pathogenic for experimental animals. This restriction was partially lifted by the work of Goodpasture, Woodruff, and Buddingh who, in 1931, succeeded in growing the viruses of fowlpox, vaccinia, and herpes simplex on the chorioallantoic membrane of the chick embryo. Since then, the discovery that other parts of the chick embryo are also susceptible to virus infection has led to the extensive use of chick embryos in virus studies. This advance in technique freed the virologist of some of the difficulties inherent in the use of experimental animals, which have to be fed, housed, and protected from extraneous diseases. For the first time, large scale preparation of some viruses for use in vaccines, and the investigation of some aspects of cell–virus interaction became possible.

Although the chick embryo is susceptible to a number of viruses, including those of influenza, mumps, yellow fever, and psittacosis, it is not susceptible to all. Intensive investigation of those viruses, including poliovirus, to which the chick embryo is not susceptible had therefore to wait for some further advance in technique. This was provided in 1949, when Enders, Weller, and Robbins discovered that the virus of poliomyelitis would grow in cells of human and monkey tissues maintained in artificial culture. True, others had previously used tissue cultures for growing viruses, but the difficulty of maintaining sterile conditions without the aid of antibiotics, and the necessity of subinoculation into experimental animals to demonstrate virus growth, prevented the adoption of tissue culture methods for routine use. The achievement of Enders and his colleagues was two-fold: first, they succeeded in growing poliovirus in non-nervous tissue and thereby demonstrated that the tissue tropism of the virus was not as rigidly specific as had previously been thought; secondly, they realized that the degeneration and necrosis of infected cells, which they were able to observe with the low power objective of the light microscope, was sufficient evidence of virus growth, making resort to animal inoculation unnecessary. Neutralization of this cytopathogenic effect by the appropriate antiserum left no doubt that tissue cultures could provide an effec-

tive substitute for experimental animals, with the added advantages of easy manipulation and economy.

It is no exaggeration to say that the introduction of modern tissue culture techniques has revolutionized the study of viruses. Not only have they made the production of poliovirus vaccine possible, but they have provided techniques for the selection of avirulant variants for use in live virus vaccines. Of no less importance, they have led to the isolation of a great number of new viruses, many of which were previously unsuspected. In the research laboratory, they have facilitated the study of viruses at the cellular level, and have thereby increased our understanding of the cell–virus relationship.

Concurrently with the important advances made in the biological study of viruses, exciting progress was made in the elucidation of their physical and chemical characteristics. After Beijerinck's original concept of the virus as a contagium vivum fluidum, it was some years before the particulate nature of viruses came to be generally accepted. Even the early visual demonstration by light microscopy of some of the larger viruses was not always accepted as evidence of the particulate nature of viruses. The issue was, however, settled in the early 1930s by Elford and his colleagues who measured the size of various viruses with collodion membrane filters, which they were able to make to any required pore size. They showed that viruses are not only particulate but that different viruses are characterized by their size, which may vary from 10 to 300 mμ.

The development of the electron microscope in the late 1930s and its application to virus studies in the following decade made the visual demonstration of even the smallest viruses possible. Thereafter, the distinctive size and morphology of various viruses was no longer in doubt. Recently, the introduction of the negative staining technique in electron microscopy has revealed a wealth of detail in the fine structure of viruses, hitherto undreamt of.

The new insight into the physical structure of viruses which has been gained in the last 20 years has been parallelled by the increase in our knowledge of virus chemical structure. A prerequisite for meaningful chemical analyses of viruses is the supply of pure preparations. This was achieved spectacularly by Stanley in 1935 when he succeeded in crystallizing the tobacco mosaic virus (TMV).

Chemically, tobacco mosaic virus proved to be relatively simple consisting of 94·4% protein and 5·6% ribosenucleic acid (RNA). More recently, some of the smaller animal viruses, including the poliovirus, have been crystallized (Fig. 1). The finding that they too are nucleoproteins, consisting solely of RNA and protein, serves to show that there is a fundamentally close relationship between some of the animal and plant viruses. It is now known that all viruses con-

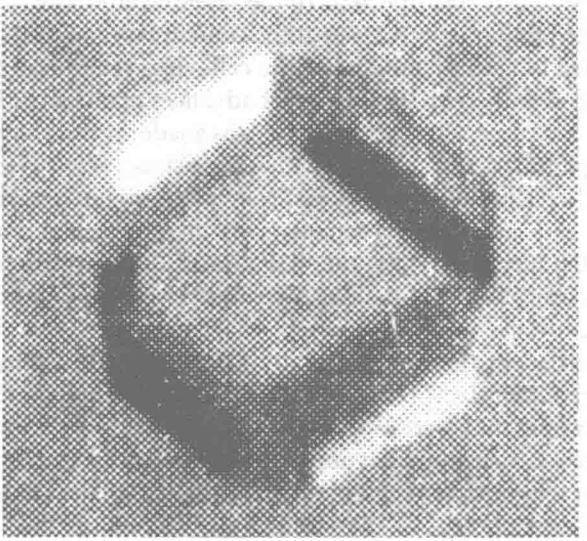

Fig. 1. Crystal of type 1 poliovirus [from Russell L. Steere and Frederick L. Schaffer (1958) *Biochim. et Biophys. Acta* **28**, 241–46 (Elsevier Publishing Co, Amsterdam)].

sist essentially of protein and nucleic acid, of which the latter may be either ribosenucleic acid (RNA) or deoxyribosenucleic acid (DNA), but never both. Although smaller viruses consist of protein and nucleic acid only, larger ones like influenza and vaccinia viruses are structurally more complex and possess, in addition, lipid and carbohydrate components as well as some enzymic activity.

A remarkable relationship between structure and function was established by Hershey and Chase in 1952. They demonstrated that