Topley and Wilson's

Principles of bacteriology, virology and immunity

Seventh edition in four volumes

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Volume 4

Virology

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General Editors' Preface to 7th edition

After the publication of the 6th edition in 1975 we had to decide whether it would be desirable to embark on a further edition and, if so, what form it should take. Except for the single-volume edition of 1936, the book had always appeared in two volumes. We hesitated to alter this arrangement but reflection made us realize that a change would be necessary.

If due attention was to be paid to the increase in knowledge that had occurred during the previous ten years two volumes would no longer be sufficient. Not only had the whole subject of microbiology expanded greatly, but some portions of it had assumed a disciplinary status of their own. Remembering always that our primary concern was with the causation and prevention of microbial disease, we had to select that part of the newer knowledge that was of sufficient relevance to be incorporated in the next edition without substantial enlargement of the book as a whole.

One of the subjects that demanded consideration was virology, which would have to be dealt with more fully than in the 6th edition. Another was immunology. Important as this subject is, much of it is not directly concerned with immunity to infectious disease. Moreover, numerous books, reviews and reports were readily available for the student to consult. What was required by the microbiologist and allied workers was a knowledge of serology, and by the medical and veterinary student a knowledge of the mechanisms by which the body defends itself against attack by bacteria and viruses. We resolved, therefore, to provide a plain straightforward account of these two aspects of immunity similar to but less detailed than that in the 6th edition.

The book we now present consists of four volumes. The first serves as a general introduction to bacteriology including an account of the morphology, physiology, and variability of bacteria, disinfection, antibiotic agents, bacterial genetics and bacteriophages, together with immunity to infections, ecology, the bacteriology of air, water, and milk, and the normal flora of the body. Volume 2 deals entirely with systematic bacteriology, volume 3 with bacterial disease, and volume 4 with virology.

To this last volume we would draw special attention. It contains 27 chapters describing the viruses in detail and the diseases in man and animals to which they give rise, and is a compendium of information suitable alike for the general reader and the specialist virologist.

The first two editions of this book were written by Topley and Wilson, and the third and fourth by Wilson and Miles. For the next two editions a few outside contributors were brought in to bridge the gap that neither of us could fill. For the present edition we enlisted a total of over fifty contributors. With their help every chapter in the book has been either rewritten or extensively revised. This has led to certain innovations. The author's name is given at the head of each chapter; and each chapter is prefaced by a detailed contents list so as to afford the reader a conspectus of the subject matter. This, in turn, has led to a shortening of the index, which is now used principally to show where subjects not obviously related to any particular chapter may be found. A separate but consequently shorter index is provided for each of the first three volumes and a cumulative index for all four volumes at the end of volume 4. Each volume will be on sale separately. As a result of these changes we shall no longer be able to ensure the uniformity of style and presentation for which we have always striven, or to take responsibility for the truth of every factual statement.

We are fortunate in having Dr Parker, who has been associated with the 5th and 6th editions of the book, as the third general editor of all four parts of this edition and as editor of volume 2. Dr Geoffrey Smith with his extensive knowledge of animal disease has greatly assisted us both as a contributor and as editor of volume 3. Dr Fred Brown, formerly of the Animal Virus Research Institute, Pirbright, has organized the production of volume 4, and Professor Heather Dick the immunity section of volume 1.

Two small technical matters may be mentioned. Firstly, in volume 2 we have retained many of the original photomicrographs and added others at similar magnifications because they portray what the student sees when he looks down an ordinary light microscope in the course of identifying bacteria. Elec-

tronmicrographs have been used mainly to illustrate general statements about the structure of the organisms under consideration. Secondly, all temperatures are given in degrees Celsius unless otherwise stated.

Apart from those to whom we have just expressed our thanks, and the authors and revisers of individual chapters, we are grateful to the numerous workers who have generously supplied us with illustrations; to Dr N. S. Galbraith and Mrs Hepner at Colindale for furnishing us with recent epidemiological information; to Dr Dorothy Jones at Leicester for advice on the *Corynebacterium* chapter and Dr Elizabeth Sharpe at Reading for information about *Lactobacillus*; to Dr R. Redfern at Tolworth for his opinion on the value of different rodent baits; to Mr C. J. Webb of the Visual Aids Department of the London School of Hygiene and Tropical Medicine for the reproduction of various photographs and diagrams; and finally to the Library staff at the London School and Miss Betty Whyte, until recently chief librarian of the Central Public Health Laboratory at Colindale, for the continuous and unstinted help they have given us in putting their bibliographical experience at our disposal.

GSW
AAM

Volume Editors' Preface

Our knowledge of virology has grown tremendously during the last 30 years. This has been particularly true for the chemical nature of the agents and is the result of the explosive increase in the knowledge of nucleic acids and proteins and the general acceptance that viruses are essentially nucleoprotein molecules. The single most important event in virology in the thirty year period was the discovery by the groups at the Virus Laboratory in California and the Max Planck Institute in Tübingen that the RNA extracted from tobacco mosaic virus was itself infectious. Following closely on the heels of the discovery by Hershey and Chase in 1952 that only the DNA of the infecting bacteriophage entered the cell and the epoch-making paper by Watson and Crick on the structure of DNA, the two papers on tobacco mosaic virus put virology on the crest of a wave on which it is still riding. Classification is now firmly based on the chemical properties of the viruses and our understanding of the way in which the agents multiply, although far from complete, rests on this fundamental chemical knowledge. Alas, the processes of virus disease are much less well defined but already molecular virologists are turning their attention away from model systems to the study of disease.

After an introduction on the history of virology, the criteria on which viral taxonomy is based, and a list of the seventeen families of viruses affecting vertebrates that are now recognized internationally, there comes a chapter on morphology abundantly illustrated with tables and figures and containing a critical examination of the methods by which the shape and structure of viruses may be determined. This is followed by five more general chapters describing the ways in which different viruses multiply, the genetics of viruses, their pathogenic properties, the epidemiology of viral diseases, and the means by which they may be combated and controlled by vaccines and drugs. The greater part of the volume consists of a detailed account of the individual viruses met with in temperate and tropical regions affecting not only man but also a variety of animals and birds.

The volume aims at giving a balanced view of the subject ranging from molecular aspects of the viruses to their aetiological role in a miscellany of diseases. It is furnished with a plenitude of tables, figures and electronmicrographs with numerous references to papers, reviews, monographs and books in which more detailed information is available. Altogether it is a compendium of knowledge suitable for both the general reader and the expert virologist.

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Virology

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The nature of viruses

Fred Brown

Introductory

Although virus diseases have been known for many centuries, the science of virology only started to emerge during the last decade of the nineteenth century. In 1892 Ivanovski discovered that tobacco mosaic disease was caused by an agent which could pass through a filter that retained the smallest bacteria. However, it was Beijerinck (1898) who introduced the concept of an agent which differed fundamentally from a bacterium. He showed that the agent causing tobacco mosaic would diffuse through agar and concluded that it was liquid or soluble and not corpuscular. Beijerinck introduced the term 'contagium vivum fluidum' for this agent. He also showed that only those organs of the plant that are growing and whose cells are dividing are capable of being infected. Beijerinck postulated that the agent must be incorporated into the living protoplasm of the cell in order to propagate and that it cannot multiply outside the cell.

Independently Loeffler and Frosch (1898) demonstrated that foot-and-mouth disease of cattle could also be transferred by material which could pass through a filter; this was, indeed, the first animal disease shown to be caused by a virus. Many years later Twort (1915) and d'Hérelle (1917) recognized that bacteria also could be infected by filter-passing agents, namely the bacteriophages.

While it was recognized, therefore, before the turn of the century that viruses are different from bacteria, it is only since the mid 1930s that the real nature of viruses has been elucidated. In 1935 Stanley crystallized tobacco mosaic virus (Stanley 1935). This was a major step in reaching our present concept that a virus is not living. However, it was the observations of Schlesinger (1936) with bacteriophage and Bawden *et al.* (1936) with tobacco mosaic virus which established the fact that viruses contain nucleic acid and are in fact nucleoproteins.

Further advances in our concept of viruses had to await the discovery by Hershey and Chase (1952) that only the DNA of bacteriophage T2 entered the cell when it infected its bacterial host and therefore that only the DNA was necessary for infection. Shortly afterwards the experiments of Fraenkel-Conrat (1956) in the USA and Gierer and Schramm (1956) in Germany proved without doubt that all the information necessary for the growth of tobacco mosaic virus is carried in its RNA. From that time there has been an enormous upsurge in our knowledge of the nature of viruses and this has advanced alongside the spectacular advances in molecular biology. Indeed viruses have provided extremely useful model systems for exploring the problems of replication, control mechanisms etc.

Viruses can be distinguished from other living things by five characters (Lwoff and Tournier 1966):

1. Possession of only one type of nucleic acid, either DNA or RNA but not both.
2. Reproduction solely from nucleic acid, whereas other agents grow from the sum of their constituents and reproduce by division.
3. Inability to undergo binary fission.

4. Lack of genetic information for the synthesis of essential cellular systems.
5. Use of ribosomes of their host cells.

These criteria clearly distinguish viruses from other micro-organisms, the most important being that viruses contain only one type of nucleic acid and are completely dependent on the host cell for their reproduction.

Physical structure

Morphology

Viruses occur in many shapes and sizes as can be seen from the diagrams in Chapter 80 taken from Matthews' review (1982) on their classification and nomenclature. Electron microscopy of negatively stained particles (Chapter 81) played a vital role in the characterization of viruses in the 1950s and 1960s and has been indispensable in the study of the details of virus structure. The method has also enabled us to obtain an overall picture of how viruses infect and replicate in the cell.

The size of the vertebrate viruses varies between *ca* 20 nm in diameter for the smallest DNA viruses (the parvoviruses) and *ca* 25 nm for the smallest RNA viruses (the picornaviruses) to 300 nm for the poxviruses. Members of the latter group are thus larger than the smallest micro-organisms, the mycoplasmas. Electron micrographs of members of all the virus groups are shown in Chapter 81. It is interesting to note that the volume of viruses can differ by a factor of 1000 but that despite of this they can be arranged into a relatively small number of groups (see Chapter 80).

Construction of viruses

The principles involved in the construction of viruses were laid down in the early 1960s by Caspar and Klug (Klug and Caspar 1960; Caspar and Klug 1962, Caspar 1965); their papers have remained the basis for our concept of the architecture of viruses. These aspects of virus structure are considered in detail in Chapter 81.

The simple viruses consist of nucleic acid enclosed within or built into a protein coat, the *capsid*. The capsid and its enclosed nucleic acid constitute the *nucleocapsid*. In its simplest form the capsid consists of a single layer of similar protein molecules arranged in an icosahedral shell or a helical tube. Clusters of similar or different structure units form the morphological units or *capsomeres* which are seen in the electron microscope.

Some viruses have an envelope of lipoprotein surrounding the nucleocapsid. The envelope is acquired as the virus passes through or buds from one of the cellular membranes and thus contains host cell components.

Chemical structure

Purification

The chemical composition of viruses could not be determined until they had been obtained in a purified form. Although tobacco mosaic virus and some other plant viruses were obtained in a highly purified state in the 1930s, e.g. Stanley crystallized tobacco mosaic virus in 1935, it was not until the 1950s, with the introduction of more refined methods of purification, that animal viruses were purified sufficiently for their analysis to become meaningful. Another reason for the delay in purifying animal viruses was the small amount of material available, but the advent of tissue culture methods for their cultivation and the large scale production of a poliovaccine from virus grown in tissue culture demonstrated the possibilities of growing sufficient virus for chemical analysis. Schwerdt and Schaffer crystallized poliomyelitis virus in 1955 and showed that it was a nucleoprotein containing 30 per cent RNA and 70 per cent protein. This work by Schwerdt and Schaffer gave great impetus to the purification of other animal viruses, and since that time many of them have been purified and their chemical composition determined.

In the purification of all viruses advantage is taken of the fact that they are much larger than even the largest components of the cell. The application of differential ultracentrifugation leads to considerable purification but probably the most important technique introduced in the last twenty years makes use of the different rates of sedimentation in gradients of sucrose of viruses and cell components. This technique was introduced by Brakke in the 1950s (Brakke 1953) and was used in the purification of poliomyelitis virus referred to above. Since a device for producing continuous gradients was described in 1961, the method has had widespread application.

Another method which has proved of great value makes use of the buoyant density of virus particles in salts such as caesium chloride and potassium tartrate. Density gradients of these salts are prepared and the mixture of virus and host cell components is centrifuged in a high speed centrifuge. The different particles

take positions in the gradient corresponding to their buoyant density.

Criteria of purity

Though these methods remove most host cell components, traces of cell material often adhere to virus particles. Such traces can be removed from non-enveloped viruses by the use of mild detergents because *these* agents do not damage the virus particles. However, enveloped viruses are disrupted by detergents, which cannot therefore be used for the purification of this large group of viruses. Consequently there is often a lingering doubt about the purity of enveloped viruses.

The extent of contamination of viruses with host nucleic acid and protein can be measured by growing the virus in host cells that have been pre-labelled with radio-active precursors of these substances. Provided the purification procedure is satisfactory the 'pure' virus should not contain any radioactivity.

All viruses contain protein and some contain carbohydrate and lipid. However, the most important feature is that they contain DNA or RNA, but not both. These similarities between viruses exist irrespective of whether the host is animal, plant or bacterial.

Viruses can be conveniently divided into those that contain a lipid envelope (enveloped viruses) and those that do not (naked viruses). The envelope consists of lipid and carbohydrate, both of which are derived from the cell in which the virus is grown. The enveloped viruses are readily disrupted by lipid solvents or mild detergents into sub-units, some of which have biological properties distinct from those of the intact viruses. The naked viruses are stable in lipid solvents and even in strong detergents such as sodium dodecyl sulphate. Disruption into their constituents usually requires severe treatment such as heating above 50° or treatment with protein denaturants such as urea or phenol.

Nucleic acid

The virus nucleic acid, which, as mentioned above, may be DNA or RNA, may also be single- or double-stranded and the genome may consist of one or several molecules. In most of the DNA viruses described so far the genomes or genetic information consists of a single molecule of nucleic acid but the genomes of many RNA viruses consist of several different molecules. If the genome consists of a single molecule, this may be linear or have a circular configuration. The way in which the genome of those viruses containing several different segments of nucleic acid is organized in the particles is not known. The molecular weight of the DNA of different viruses varies from 1 to over 200×10^6. However, the range of molecular weights of virus RNA is much less, ranging from *ca* 2 to 15×10^6. The variety of forms in which the genetic material may occur is summarized in Table 79.1 together with examples of the viruses in which they are found.

Table 79.1 Nature of the genetic material of viruses

Nucleic acid	*Examples*
Single-stranded DNA	feline panleucopenia, adeno-associated
Double-stranded DNA—linear	pox, herpes
—circular	Shope papilloma, polyoma
Single-stranded RNA—unsegmented	polio, rubella, measles, rabies
—segmented	influenza, Rift Valley fever, lymphocytic choriomeningitis
Double-stranded RNA—segmented	reo, rota, bluetongue

In viruses whose nucleic acid consists of single-stranded RNA molecules, the virus nucleic acid is either a positive strand, e.g. poliovirus RNA, or a negative strand, e.g. rabies virus RNA. With some RNA viruses, the nucleic acid can be extracted in an infectious form. In others the isolated nucleic acid is not infectious, even though it contains all the necessary genetic information. This is because its transcription depends on a virion-associated transcriptase which is separated from the nucleic acid by the extraction procedure. In viruses whose nucleic acid consists of single-stranded RNA molecules, the virus nucleic acid is either positive-stranded, i.e. one that can function as its own messenger, or negative-stranded, i.e. one that produces mRNA as a first step in its replication. Some viruses with single-stranded DNA contain either the positive or the complementary strand.

Most viruses contain only virus DNA or RNA. However, some viruses contain host cell nucleic acids. For example, some papovaviruses contain host cell DNA and the arenaviruses contain cellular ribosomes.

Proteins

All viruses contain proteins and indeed proteins form the major part of most viruses. Although there are viruses which contain only one species of protein, e.g. the caliciviruses, most contain several. Thus the smallest RNA viruses (the picornaviruses such as poliovirus and foot-and-mouth disease virus) contain four distinct species of protein. The more complex viruses such as herpes virus contain many distinct protein species, the molecular weight of the different species ranging from *ca* 5×10^3 to 150×10^3. Whereas there is normally only one copy of the virus nucleic acid in a virus particle, there are usually many copies of each protein. Thus there are 60 copies of each of the four proteins of poliovirus in each particle. Although the

proteins provide a protective shell for the genome, they have other properties as well. For example, the surface proteins have an affinity for the specific receptors on the surface of susceptible cells and they also contain the antigenic determinants which are responsible for the production of protective antibody in the infected or vaccinated animal. Some virus proteins have enzymic activity. For example, there is a protein in the negative-stranded RNA viruses, e.g. rabies virus, which acts as a transcriptase.

In addition to the proteins of the virus particle, many virus-induced non-structural proteins are found in cells infected with viruses. Indeed, most of the virus genome codes for these non-structural proteins. The functions of these proteins are known in only a few instances although it seems clear that they are required for virus multiplication. This brief outline of the nature of viruses is expanded in subsequent chapters on their classification, morphology, replication and genetics (Chapters 80–83).

Further reading

For further information on general virology the following books may be consulted.

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Classification of viruses

Fred Brown

Classification of viruses

The aim of virus classification is to make an ordered arrangement of viruses that will indicate their similarities and differences. Viruses can be classified on the basis of any of their properties but it is logical to use a system that can be applied to all viruses. Such a scheme has considerable value in identification so that the unknown properties of a virus can be predicted by analogy with the known properties of similar viruses. This enables related viruses to be united into the same category. It also has value in virus taxonomy.

The value of a classification scheme is indisputable but the best method to achieve it led to much debate, some of it acrimonious. A system has emerged which is now fairly well accepted universally and it is interesting to summarize the major steps in its development because it has a firm place in the history of virology.

Historical introduction

Infectious diseases were known before the agents which cause them so it was natural that the agents were named according to the disease. Early efforts to classify viruses arranged them according to host symptoms or type of disease and tissue affinities. For example in 1939 Bennett, on behalf of the Committee for Virus Nomenclature of the Council of the American Phytopathological Society, proposed the following criteria for classification:

Criteria for classification

1. Type of symptoms produced on different species and varieties of susceptible plants.
2. Morphological and cytological disturbances produced.
3. Relation of insect vectors to virus transmission.
4. Antigenic reactions in animals and plants.
5. Chemical and physical properties of the viruses themselves.