Viral Immunology and Immunopathology

edited by
Abner Louis Notkins

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（内部交流）

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Preface

The purpose of this book is to bring together into a single volume the new information that has emerged over the last several years concerning the role of cellular and humoral immunity in viral infections, factors responsible for the persistence and recurrence of viral infections in the presence of immunity, mechanisms of viral immunopathology and new concepts in the development of vaccines.

The authors, all active investigators in their respective fields, have attempted to write brief but critical reviews with emphasis on concepts and mechanisms. The 24 chapters in the book are organized systematically so that the book can serve as a text for advanced students and as an up-to-date review for active workers in the field. It begins with a chapter on the history of viral immunology and proceeds to cover the synthesis and properties of viral antigens, the humoral immune response to viruses, mechanisms of viral neutralization, cellular immunity, the role of inflammatory cells and effector molecules in combating viral infections, and genetic control of resistance.

The emphasis of the book is on mechanisms rather than on description of the immune response to a variety of individual viruses. For illustrative purposes, however, three viruses of considerable current interest (hepatitis virus, leukemia virus, and Epstein–Barr virus) were singled out for in-depth analysis. The book then turns to herd immunity and the latest thinking about vaccines. It concludes with five chapters on viral immunopathology and a chapter on the future of viral immunology and immunopathology.

The appendix contains a summary of a 3-day workshop that deals with many of the problems discussed in the book. The workshop on Viral Immunology and Immunopathology was sponsored by The National Institute of Dental Research on April 7–9, 1975, in Airlie House, Airlie, Virginia.

Abner Louis Notkins

Contents

CHAPTER 1

HISTORY OF VIRAL IMMUNOLOGY

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INTRODUCTION

A history of viral immunology is clearly more concerned with tracing the development of immunological concepts than with an analysis of the history of virology, yet the latter is not unimportant. Viruses obviously differ in important respects from non-living antigens, and they differ fundamentally from living cells, including the pathogenic microorganisms. Viral immunology is a "transdisciplinary" subject, and several of the great figures in its history, Jenner in the eighteenth century, Pasteur in the nineteenth and Burnet in the twentieth century, are honored as pioneers by both virologists and immunologists. Since the immune response is an aspect of resistance to disease that is restricted to vertebrate animals, we shall therefore have to consider only the minority of organisms that are vertebrates, and the minority of viruses that infect vertebrates. Indeed, we are ultimately concerned with the human host and the viruses that infect man, and with model systems that enable us to study problems of human medical relevance experimentally.

The outline of this book illustrates the many-facetted nature of viral immunology, and we cannot hope in this introductory chapter to give a satisfactory history of each of the topics represented by a chapter heading. We shall therefore try first to illustrate the discoveries that have led to our present concepts of what vertebrate viruses are and how they behave, and then illustrate the developing concepts of the host's response to viral infection that have brought biomedical scientists to the stage of writing this book. In this introductory chapter we shall try not just to pay homage to the great historical figures of our subject, but also in a sense to set the stage for the other more technical chapters of the book.

THE CONCEPT OF VIRUS

Animal virology began as a branoh of pathology. Virology as a discipline advanced rapidly only when it freed itself from this association, thanks mainly to the leadership of Delbrück and the phage group (1). The concepts developed with phage were extended into animal virology, and it is now possible for virologists to move back into pathology with a greatly enriched understanding.

The brilliant studies of Pasteur, Koch and their followers had by the end of the nineteenth century established the microbial etiology of many of the infectious diseases of man and his domesticated animals (2). However, there were still a number of common infectious diseases for which neither a bacterium nor a protozoan could be incriminated as the causal agent. In 1898, Loeffler and Frosch (3) demonstrated that the economically important disease of cattle, foot-and-mouth-disease, could be transferred from one animal to another by material which could pass through a filter that retained the smallest bacteria. The same technique produced comparable results with other infectious diseases of unknown etiology. Following these discoveries, such diseases were tentatively ascribed to what were first called "ultramicroscopic filterable viruses", then "ultrafilterable viruses", and ultimately just "viruses". We now know that viruses also occur in all other groups of organisms, from trees to mycoplasmas, and in our present state of knowledge it is not unreasonable to postulate that for every species of organism there will be found to exist one or perhaps many more species of virus (4).

From the practical viewpoint of the plant pathologist and the public health worker, it is convenient to regard the viruses that cause disease as pathogenic microorganisms. Indeed, Burnet entitled his Dunham Lectures, delivered at Harvard University in 1944,"Virus as Organism" (5). However, at about this time the question was repeatedly posed as to whether viruses, whatever their host, might have common properties that distinguished them sharply from microorganisms. There was a great deal of discussion about the nature of the "eclipse period" (6), and at about this time Hershey's demonstration in 1952 of the injection of DNA by bacteriophages (7) opened the way for a proper understanding of viral multiplication. The argument about the differences between viruses and microorganisms was sharpened and focussed by Lwoff (8) whose dictum that "viruses are viruses are viruses," i.e., that all viruses show some properties that distinguish them from any microorganism, is now universally accepted (Table 1). Exceptions to some of Lwoff's generalizations have since been discovered, but three are still valid: (a) unlike even the smallest microorganisms (chlamydiae), viruses contain no

TABLE 1

The essential differences between viruses and microorganisms, e.g., bacteria

Character	Virus	Bacterium
Types of nucleic acid	DNA *or* RNA never both	DNA *and* several species of RNA
Infectious nucleic acid	some viruses, +	0
Growth	0	+
Division	0	+
Enzymes of the energetic metabolism	0	+
Genetic information for these enzymes	0	+
Ribosomes	0	+
Genetic information for ribosomal RNA	0	+

functional ribosomes or other cellular organelles, although some enveloped viruses, notably in the genus *Arenavirus*, contain a few ribosomes derived from the host cell, (b) in RNA viruses the whole of the genetic information is encoded in RNA, a situation unique in biology, and (c) viruses lack enzymes for energy metabolism and they lack genes for such enzymes. Other distinctions apply to some but not all viruses , e.g., the isolated nucleic acid of viruses of several genera is infectious, so that the virus can be generated intracellularly from a single molecule of nucleic acid.

It is impossible to define viruses satisfactorily in a sentence or even a paragraph, bearing in mind both their intracellular states and the extracellular particles. The virus particle or virion consists of a genome of either DNA or RNA enclosed within a protective coat of protein molecules, some of which may be associated with carbohydrates or lipids, usually of cellular origin. In the vegetative state and as "provirus" (see Chapter 2), viruses may be reduced to their constituent genomes, and the simplest "viruses" (the "viroids" of Diener, ref. 9) may be transmitted from one host to another as naked molecules of nucleic acid, possibly associated with certain cellular components. At the other extreme, the largest animal viruses, e.g., the poxviruses and the retraviruses are relatively complex and contain many different polypeptides including several enzymes.

Lwoff's dictum that viruses are generically different from organisms has had important theoretical and practical consequences; on the one hand, it emphasized their similarities irrespective of the nature of the host (animal, plant or bacterium), and, on the other hand, it led to the establishment of an international body that works in parallel with the international committees of botany, zoology and bacteriology and is charged with the responsibility of classifying and naming viruses (10, 11). However, the operational division of viruses made according to type of host continues to be used by the majority of virologists most of the time. For example, all the contributors to this book are concerned only with viruses of vertebrates, on which we shall henceforth concentrate our attention.

THE CLASSIFICATION OF VIRUSES OF VERTEBRATES

Since the rest of this book will be concerned almost exclusively with immunology, albeit with immunological aspects of viral infection, we shall begin by reviewing briefly the range and nature of the viruses that infect vertebrates. Viruses can be subdivided according to the nature and amount of their nucleic acid, and the shape and size of the virion, into some twenty groups, some of which currently have the status of families, others of genera. Virologists have so far refrained from making any taxa higher than family, reflecting the belief that viruses are polyphyletic and that each family or genus now recognized probably arose independently of each other one, and that all were derived ultimately from cells. The size and shape of representative members of the various groups of viruses of vertebrates are illustrated diagrammatically in Figure 1.

Many of the features of viruses that fascinate virologists, such as the nature of their genomes (whether double or single-stranded, cyclic or linear, single molecules or fragmented, messenger or complementary strand), and the mode of replication of their genome and the translation of its message, are to a large extent irrelevant to viral immunologists. What is important to them is the way that viruses affect cells (Table 2) and by their effects on cells affect organs and the organism (Tables 3 and 4). While we can state the molecular virologist's interests fairly easily, it is much more difficult to generalize about

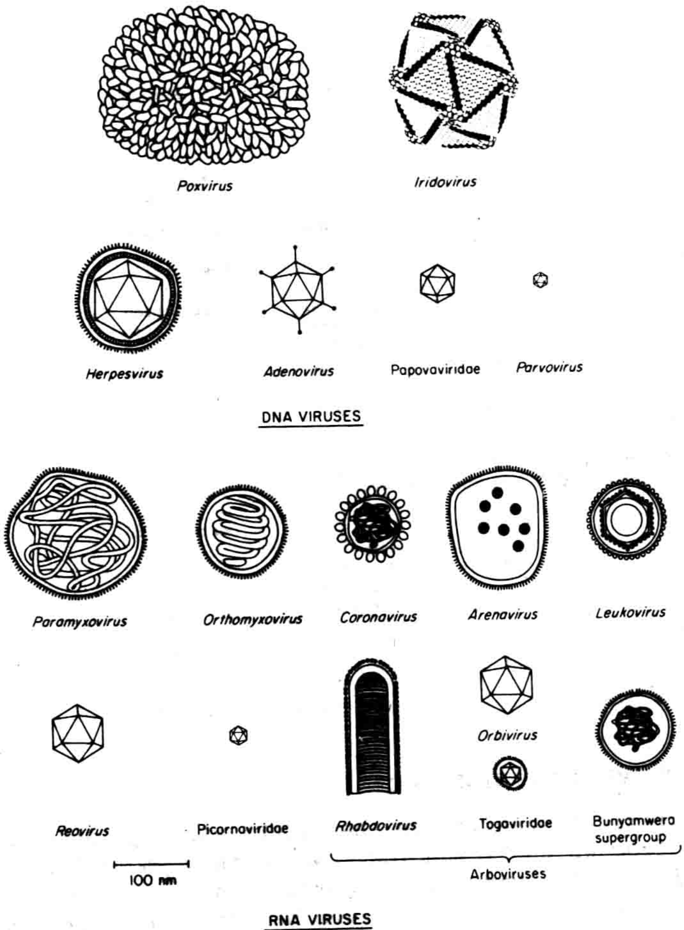

Fig. 1. Diagram illustrating the shapes and relative sizes of animal viruses of the major taxonomic groups (bar = 100 nm). (12)

the effects of viruses of particular families or genera on cells and organs of particular species of host animal, since these interactions depend upon both the cells affected and the virus involved. Nevertheless, some generalizations are possible and may be valuable as a frame of reference. Tables 3 and 4 have been constructed with this in mind.

TABLE 2

Different kinds of virus-cell interaction

Virus	Cell	Interaction	Effect on Cell	Yield of infectious virus
Poliovirus	HeLa	Cytocidal	Destruction	+
	Mouse	Nil	Nil	-
Poliovirus RNA	Mouse	Cytocidal	Destruction	+ (single cycle)
Rabbitpox	Chick	Cytocidal	Destruction	+
	PK	Cytocidal	Destruction	+
Rabbitpox PK-[a]	Chick	Cytocidal	Destruction	+
	PK	Cytocidal	Destruction	-
Lymphocytic choriomeningitis	Mouse	Steady-state	Nil	+
Avian Oncornavirus C	Chick	Steady-state	Nil	+
Avian oncornavirus RSV[b]	Chick	Noncytocidal	Transformation	-
Polyoma	Mouse	Cytocidal (most cells)	Destruction	+
	Mouse	Noncytocidal (few cells)	Transformation	-
	Hamster	Noncytocidal	Transformation	-

[a] PK negative mutant of rabbitpox virus

[b] RSV, Rous sarcoma virus - a mutant avian oncornavirus C

PROTECTION AGAINST REINFECTION

The critical observation that links virology and immunology, and from which "immunology" was both etymologically and scientifically derived, was an observation that goes back to antiquity, namely, that persons who had recovered from smallpox or measles would not get a second attack - they were *immune*. This observation was put to practical use by the Chinese, and later the Turks, and through Lady Wortley Montagu, the English, by the practice of variolation as a method of preventing smallpox (see Voltaire, 1733; ref. 13). However, variolation, i.e., the deliberate inoculation of virulent smallpox virus, was a hazardous practice, for some subjects so treated died or were permanently disfigured, and such patients also constituted a source of natural virulent smallpox to their contacts. People living in the countryside had long been aware that persons who tended cows (which also suffered from "the pox") did not catch smallpox from them, but merely got blisters on the hands. However, these milkmaids did not get smallpox when this disease hit the rest of the community. Edward Jenner took up this piece of