Textbook of HUMAN VIROLOGY

EDITED BY

ROBERT B. BELSHE

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FOREWORD

Recognition of clinical virology as a discipline with its own body of knowledge evolved only within the last two decades. This discipline provided the conceptual link between fundamental virology research and its application in the practice of medicine. The surge of discoveries in virology during the 1950s and 1960s opened the door to a myriad of clinical applications that were to involve physicians in the prevention, diagnosis, and treatment of viral diseases that previously were not preventable or untreatable. En passant, the practicing physician became a clinical virologist.

Among the viruses that were isolated and identified for the first time since the early 1950s were the parainfluenza viruses, respiratory syncytial virus, adenoviruses, rhinoviruses, coronaviruses, rubella virus and Epstein-Barr virus. These successes encouraged virologists to intensify the search for hepatitis viruses, the slow viruses infecting the human central nervous system and human cancer viruses, several of which have been found. The discovery of a spectrum of new viruses and recognition of the diseases they cause encouraged the development of diagnostic procedures, the critical tools of clinical medicine. However, the prospect of establishing specific diagnoses seemed impractical considering the lack of effective modalities for prevention or treatment of virus diseases.

Eventually the development of effective vaccines for poliovirus, the communicable exanthematous diseases, and mumps virus, not only provided the basis for control of those serious virus infections of childhood, but also signaled the beginning of an era of practical applications of basic advances in virology. More so, when vaccines were followed by the introduction of the first potent antiviral drugs for the treatment of serious herpesvirus infections, and of a vaccine effective against hepatitis B virus.

We have arrived at a point when the complex knowledge base of virology has been translated into many major clinical advances. The new information on virus nomenclature, epidemiology of virus infections, host immune responses and their measurement, delineation of clinical syndromes and rapid diagnostic tests facilitate the rational approach to the diagnosis and treatment of viral diseases. Vaccines and antiviral drugs, however limited in number and scope at this time, provide opportunities for preventive and therapeutic intervention previously only available for the treatment of bacterial infections. The prospects seem bright for the development of other vaccines utilizing virus mutants and gene engineering and for the synthesis of new antiviral drugs.

This seems an appropriate juncture to document the body of knowledge of human virology both to promote its clinical applications and to enumerate areas for further research. This *Textbook of Human Virology* aims for this goal. It bridges the gap between virologist and practicing physician by encompassing those aspects of basic virology relevant to clinical medicine. As a compendium of current information, it provides a resource for virologists, physicians, medical students and residents that can facilitate clinical care and stimulate further investigative inquiry.

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INTRODUCTION

The objective of developing a new textbook in virology is to assemble and synthesize information in a single reference for use by physicians, medical and other graduate students, and infection control officers. Rapid growth in the field of infectious diseases, particularly the sub-field of clinical virology, has resulted in a specialized scientific discipline that is not addressed in detail by other textbooks of infectious diseases. The clinician and especially the infectious disease subspecialist of today need a fundamental understanding of viral replication and transmission, so that appropriate measures may be instituted which are aimed at prevention of viral transmission and treatment of infection. This text includes an introduction to the biology of viruses and the clinical and laboratory diagnosis of viral infections. In addition, a comprehensive description of the clinical features of human viral infections is presented.

The Marshall University School of Medicine afforded a unique opportunity to develop this textbook. While working in a community-based medical school, I observed that many of the diseases seen in clinical practice were viral infections for which the availability of diagnostic testing was limited. As diagnostic virology services became available, an interest was generated to develop a detailed text combining aspects of basic and applied virology. Furthermore, advances in basic virology have resulted in a need for a resource that ties together clinical facets of viral infections with molecular virology. As a result, the development of this text was initiated. A fundamental understanding of virus biology is emphasized to enable the reader to interpret the ongoing medical literature as new viruses are discovered and diseases of hitherto uncertain etiology are explained on the basis of viral infection. For example, investigations to identify the cause of the acquired immune deficiency syndrome in male homosexuals and other groups may lead to further understanding of the RNA tumor viruses as they relate to human biology. I have assembled an international group of authors who are active investigators in the fields encompassed by their respective chapters. They have presented fresh approaches to the description of various aspects of viral diseases.

This textbook has been extensively referenced in order to encourage the reader to return to original articles for more detailed discussion of methodology and clinical observations. Immunology of viral diseases, diagnosis of viral infections, antiviral drugs and RNA tumor viruses are covered in separate introductory chapters. DNA tumor viruses are discussed in individual sections according to virus type. Viruses and, in certain cases, groups of viruses are covered separately in individual chapters and in general are organized by nucleic acid content. The text concludes with discussions of suspected viral infections including Kawasaki syndrome and Reye syndrome.

I am indebted to Mrs Judy Hayes for coordinating the development of the manuscript. I gratefully acknowledge the assistance and encouragement of my colleagues and staff, the continued stimulation of my students, and the challenges placed before me by my mentor, Maurice A. Mufson, MD, and other teachers.

ROBERT B. BELSHE, MD

CONTENTS

CHAPTER 1

Structure and Classification of Viruses

Joseph L. Melnick

Until about 1950, little was known about viruses other than their pathogenic effect in causing diseases; therefore, any efforts at classification tended to focus on host responses rather than on properties of the virus particle. At present, the end of an important phase of discovery and characterization of animal viruses is approaching. The knowledge gained in recent years concerning the molecular biology of viruses and their biophysical and biochemical properties has made it possible to establish and broadly define groupings for these agents. It appears that most of the major groups of viruses of vertebrates – at least, most of those affecting man and the animals of direct importance to man – have been recognized and described. Many of these virus groupings, initially established on tentative and provisional bases, now appear to form "real" families and genera, in which the members are indeed related in fundamental ways. For example, the validity of the original grouping of the enteroviruses based on an enteric habitat and small size is being borne out by current studies that utilize sophisticated techniques of modern molecular virology to compare the genetic makeup of different members of the group and their mode of replication.

The shift from sketching broad outlines of the virus kingdom (based in large part on disease causation and ecological setting) to defining group relationships on the basis of properties of the viruses themselves is reflected in the name of the committee responsible for these matters. The original name, International Committee on Nomenclature of Viruses (ICNV), was changed in 1974 to International Committee on Taxonomy of Viruses (ICTV). The ICNV was established in 1966 at a historic meeting in Moscow, the very city where viruses were first discovered by Ivanovski three quarters of a century earlier. Four reports of the ICNV/ICTV have been published.[1-4] Work of specialized study groups of the ICTV has also proceeded, and these groups report regularly in *Intervirology*, the journal of the Virology Division of the International Union of Microbiological Societies. Figures 1-1 and 1-2 serve as useful reference points in the following discussion of classification based on properties of the virus particles. Comparison of these two figures also gives some indication of the rapid accumulation of knowledge about virus composition and structure. Figure 1-1 is taken from a text[5] first published about 15 years ago; it remains fundamentally applicable. However, Figure 1-2 not only includes additional information that has been gained about viruses but also illustrates the wide variety of size and structure that is found among the viruses of vertebrates.[4]

In addition to the ICTV and its study groups, the student is referred to the review in the *American Society for Microbiology Manual of Clinical Microbiology*, third edition,[6] and to the annual reviews in *Progress in Medical Virology* since 1966,[7] to follow the developments in taxonomy.

Tables 1-1, 1-2, 1-4, 1-5, and 1-7 show separation of viruses of vertebrates into 17 families.[7] Table 1-1 includes viruses having a DNA genome, cubic symmetry, and a naked nucleocapsid, and Table 1-2 depicts DNA-containing viruses having envelopes or complex coats. RNA-containing viruses are presented in three tables: Table 1-4, those with cubic capsid symmetry; Table 1-5, those with capsids having helical symmetry; and Table 1-7, those with capsid architecture that is either asymmetric or unknown. Commentaries follow concerning these families, their properties, and their subgroups and individual members. Some important viruses not yet placed taxonomically are also discussed, along with some viruses and virus-like agents presenting taxonomic

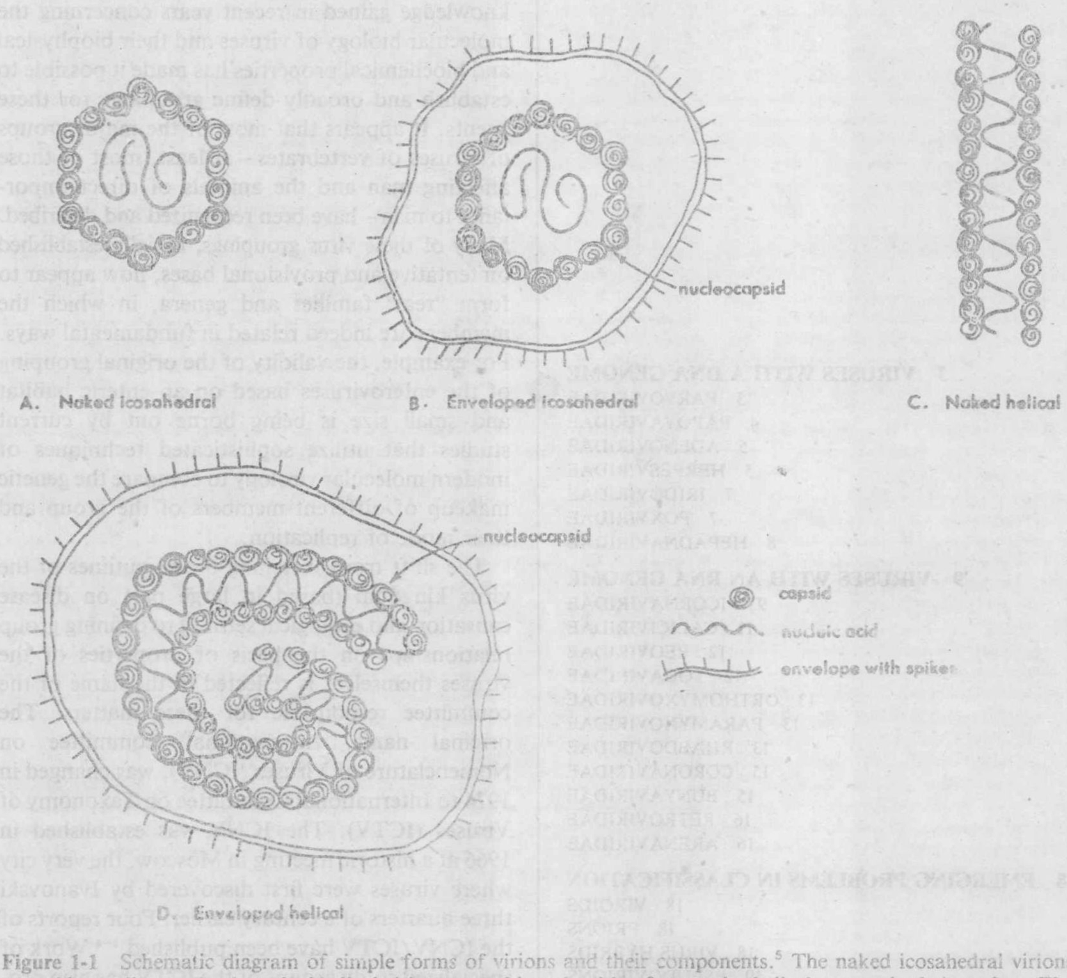

Figure 1-1 Schematic diagram of simple forms of virions and their components.[5] The naked icosahedral virions resemble small crystals; the naked helical virions resemble rods with a fine regular helical pattern in their surface. The enveloped icosahedral virions are made up of icosahedral nucleocapsids surrounded by the envelope; the enveloped helical virions are helical nucleocapsides bent to form a coarse, often irregular, coil within the envelope. Reproduced with permission from Davis BD, et al: *Microbiology*. New York, Hoeber Medical Division, Harper & Row, 1967.

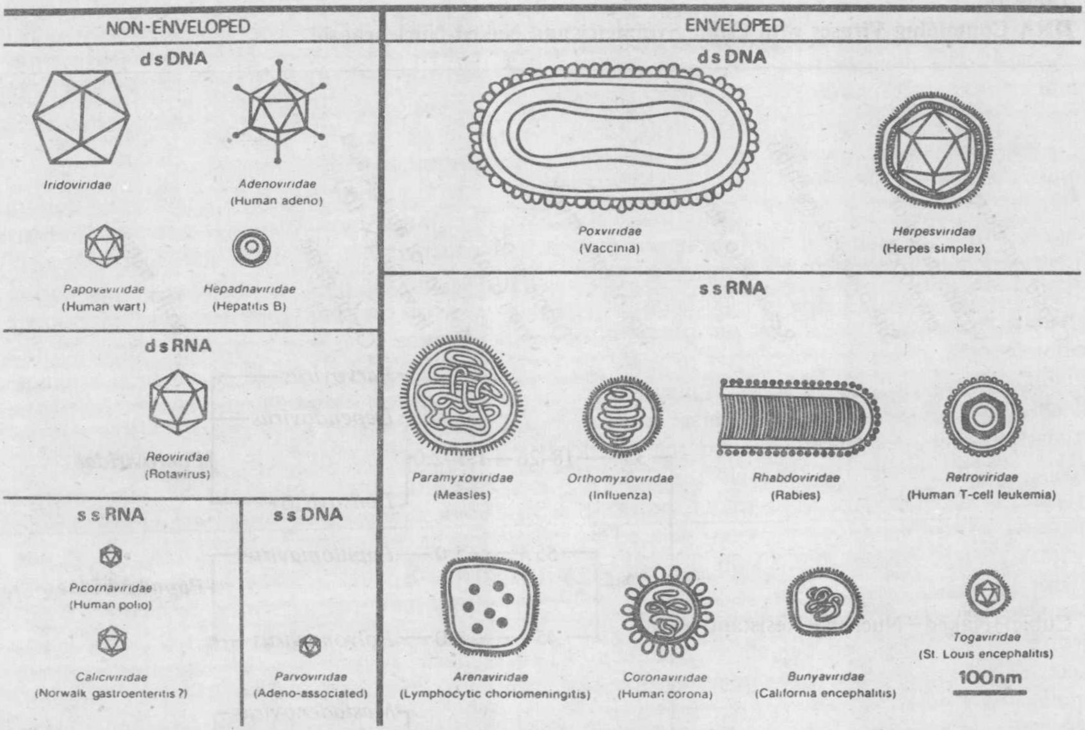

Figure 1-2 Diagram illustrating the shapes and relative sizes of animal viruses of the major families (bar = 100 nm). Representative members that infect humans are listed in parentheses. Iridoviridae are not known to infect humans.

problems that need to be resolved. Finally, in an Appendix at the end of the chapter, there is a tabulation of some members of the families of vertebrate viruses. This is not meant to be an exhaustive list, but it should be useful to the reader wishing to survey the taxonomic placement of many viruses that infect vertebrates or to have an overview of the nature of some of the virus families as illustrated by their commonly known members.

VIRUSES WITH A DNA GENOME

Parvoviridae[4,8,9]

Originally named picodnaviruses to reflect their small size and DNA genome,[10] the family *Parvoviridae* now includes three genera, *Parvovirus*, *Densovirus*, and *Dependovirus*. A typical dependovirus is adeno-associated satellite virus, several serotypes of which are indigenous to man, although with no known association with human disease. As shown in Table 1-1, these are viruses with a DNA genome, cubic symmetry, and a naked (unenveloped) nucleocapsid. Infectivity is resistant to ether and other lipid solvents; the capsid has 32 capsomeres; and the diameter of the virus particle is 18 to 26 nm. (The capsomeres that form the outer layers of the nucleocapsid are each 2 to 4 nm in diameter.) The molecular weight of the nucleic acid is between 1.5 and 2.0 × 10^6.

The genus *Parvovirus* includes autonomously replicating agents that infect vertebrates: Kilham's rat virus (the type species) and other viruses of mammals and birds, and Aleutian mink disease virus. Of special note recently has been the discovery of a new parvovirus that infects dogs—an agent distinct from the minute virus of canines. (The latter agent, described in 1970, is antigenically distinct from all recognized parvoviruses. Because of the lack of a susceptible cell line, this longer-known minute virus of canines has been difficult to characterize and usually is considered only as a "possible member" of the genus *Parvovirus*.) The newly recognized and widespread agent that has attacked so many household pets in recent years is a true parvovirus, now being called canine parvovirus (CPV). It is a host-range mutant (subspecies) of feline parvovirus, the best-known subspecies of which is the feline panleukopenia virus. The new canine virus induces acute enteritis with leukopenia in young and adult dogs as well as myocarditis in puppies. Infections with CPV have reached enzootic proportions around the world.

Table 1-1
DNA-Containing Viruses with Cubic Symmetry and Naked Nucleocapsid

Capsid symmetry	Virion: naked or enveloped	Site of capsid assembly	Reaction to ether	No. of capsomeres	Diameter of virion (nm)	Mol. wt. of nucleic acid in virion ($\times 10^6$)	Genus name	Family name
Cubic	Naked	Nucleus	Resistant	32	18–26	1.5–2.0	*Parvovirus*	*Parvoviridae*
							Dependovirus	
							Densovirus	
				72	55	5.0	*Papillomavirus*	*Papovaviridae*
					45	3.0	*Polyomavirus*	
				252	70–90	20–30	*Mastadenovirus*	*Adenoviridae*
							Aviadenovirus	

The members of the *Densovirus* genus are the densonucleosis viruses of insects, but they are also capable of producing cytopathic effects in L cells (of vertebrates); they replicate autonomously. Adeno-associated satellite viruses (genus *Dependovirus*), however, are defective and cannot multiply in the absence of a replicating adenovirus that serves as a "helper virus." Herpesvirus can act as a partial helper; in cells coinfected with herpesvirus, infectious satellite DNA and capsid proteins are produced, but they are not assembled into satellite virions.

Members of the family *Parvoviridae* are the only DNA-containing viruses of vertebrates whose DNA genome is single-stranded within the virion; all the others have double-stranded DNA. In adeno-associated viruses and densoviruses, separate virions contain single strands of positive or negative DNA (see Chapter 3); these strands are complementary, and, when isolated from the virion shells, they come together to form a double strand. However, in members of the genus *Parvovirus*, the DNA in the virion is a negative strand only. Members of this genus show preference for actively dividing cells, have been shown to be transmissible transplacentally, and are receiving attention for their special disease potential in fetuses and neonates.

Papovaviridae[3,4,11]

These relatively small, ether-resistant viruses contain double-stranded DNA in circular form. Many are unusually heat-stable, surviving temperatures that inactivate most viruses. Representative members that infect human beings are the papilloma or wart virus and SV40-like viruses.

These viruses have relatively slow growth cycles characterized by replication within the nucleus. Papovaviruses produce latent and chronic infections in their natural hosts; all are tumorigenic in at least some animal species. The genome integrates into cellular chromosomes of transformed cells.

Two genera have been established. One genus, *Papillomavirus*, has as its type species the well-known rabbit (Shope) papillomavirus. Other members are known for man (nine types) and other vertebrate species. Each virus species contains a distinct surface antigen, but all members of the genus share a common antigen revealed by