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VIRAL CHEMOTHERAPY

Volume 1

SECTION EDITOR

D. SHUGAR

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PREFACE

SINCE viruses are obligate intracellular parasites, fully dependent on the host cells, which furnish the necessary apparatus required for the transformation of the genetic information of the viral nucleic acid into progeny viral particles, considerable scepticism existed up to only a few years ago as to the feasibility of developing antiviral agents sufficiently specific to readily traverse the host cell membrane and to inhibit such processes as viral uncoating, replication and assembly without adversely affecting the normal metabolic functions of the cell.

The early, frequently vociferous and even vituperative, opposition to viral chemotherapy came largely from some of the proponents of immunization. The successes achieved by vaccination are indisputable, and include virtual eradication of smallpox, and effective control of such diseases as poliomyelitis. However, both the development and subsequent production of vaccines are by no means free of problems, some of them rather formidable. The recent FDA approval of a vaccine for hepatitis B, prepared by isolation of hepatitis B surface antigen (HBsAg) from viral particles collected from the blood of human carriers, represents a significant new achievement in this field. But it should not be overlooked that it is "the first completely new viral vaccine in 10 years", while its use is to be limited only to those considered at high risk of developing the disease. Furthermore, development of vaccines against, for example, herpes, influenza and rhino viruses poses even more formidable theoretical and practical problems. One of the new approaches, involving the use of chemically synthesized peptides, and exemplified by the recent report of an effective vaccine against foot-and-mouth disease in guinea pigs and rabbits, holds out considerable promise for further advances, particularly when considered with the possible applications of recombination techniques. Meanwhile, it would appear obvious that chemotherapy offers the only alternative, in those instances where a fully effective vaccine is not already available, and, in those instances where it is by itself sufficiently effective, may be preferable to immunization.

During the past 10 years, scepticism regarding the possibilities of viral chemotherapy have been largely dispelled, in large part by practical demonstrations which have already resulted in official approval, in a number of countries, of several compounds for clinical use. As in the case of many other drugs, initial potential candidates for viral chemotherapy were uncovered during the course of *in vitro* random screening programs, with attempts at subsequent improvements based on structure-activity studies, i.e. evaluations of relative activities and cytotoxicities of various synthetically modified analogues of the parent compound with proven activity. The number of promising new agents is presently increasing at an impressive rate, and an appreciable number of these have attained the stage of being subjected to preclinical trials. One of the impressive recent achievements is the FDA approval for use of Acyclovir (or Acycloguanosine) in treatment of primary genital herpes less than 5 years following the initial report on the discovery of this compound and its *in vitro* activity against herpes viruses types 1 and 2.

Concurrently with the foregoing, remarkable progress has been achieved during the 1970s in the elucidation of the molecular biology of viral replication. This has led to the pinpointing of a variety of 'targets', especially viral-encoded enzymes and proteins, with specificities frequently sufficiently different from the corresponding constituents of the host cells to provide a reasonably solid basis for further, and more fundamental, research in this field. As a result of this, one of the interesting features of a number of new antiviral agents, currently in course of development, has been the success achieved in delineating their

mode(s) of action. It is to be anticipated that this will significantly contribute to the design of more effective compounds. An important result of the foregoing is the gradual introduction of so-called more 'rational' approaches in the search for new, and more effective, agents, which is esthetically more satisfying and stimulating to the organic chemists who participate in the necessary synthetic programs and to the virologists, biochemists, enzymologists, pharmacologists, clinicians (and physical chemists and theoretical chemists involved in structure-activity relationships), all of whose collaborative efforts contribute to the eventual introduction of a useful compound into the clinic. Current progress is now such as to envisage the use of combination therapy, based on employment of two or more agents, each of which may affect a different step in viral replication, a field as yet relatively little explored.

With the foregoing in mind, contributors to this volume and to succeeding ones have been asked to concentrate as much as possible on fundamental aspects of their respective fields, so that these will prove useful in further research, and, wherever possible, to present as much detail as possible regarding the mechanism(s) of action of the agents described. I am indebted to most of the contributors for their assistance in attempts to attain this objective. I am also grateful to friends and colleagues who have been kind enough to offer suggestions and advice as to the nature and scope of the contributions required in such a volume and, particularly, to Dr. Ernest C. Herrmann, Jr., and Dr. William H. Prusoff, both well-known pioneers in the development and application of antiviral agents, and to Dr. Alan Sartorelli and Dr. Barbara Z. Renkin, whose assistance in dealing and processing of contributions has been invaluable.

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CHAPTER 1

THE NATURE AND CLASSIFICATION OF VIRUSES OF MAN

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CONTENTS

1.1. INTRODUCTORY REMARKS

Studies on viral chemotherapy begin with experiments on virus-infected cultured cells, then move to viral infections in intact experimental animals, and finally, in the few cases where the earlier experiments are sufficiently promising, to clinical trials in man. The initial investigations are usually carried out with particular 'model' viruses that lend themselves to experimental manipulation. In order to appreciate the significance of discoveries made with such model systems it is necessary to understand how generally any discovered effect may extend among viruses pathogenic for man. This involves a knowledge of viral classification; if a chemotherapeutic effect is discovered which operates through its effect on a particular viral enzyme, for example, it can be expected to behave similarly in other viruses that possess that enzyme, but not in viruses of other families that do not.

This review begins with a description of the chemical composition and physical structure of the virions of the viruses that affect vertebrate animals. There follows a brief account of each of the twenty families of viruses that encompass almost all the viruses that affect man and other vertebrates.

1.2. INTRODUCTION

Virology began as a branch of pathology. At the end of the nineteenth century, when the microbial etiology of many infectious diseases had been established, pathologists recognized that there were a number of common infectious diseases of man and his domesticated animals for which neither a bacterium nor a protozoan could be incriminated as the causal agent. In 1898 Loeffler and Frosch demonstrated that 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. Following this discovery such diseases were tentatively ascribed to what were first called 'ultramicroscopic filterable viruses', then 'ultrafilterable viruses', and, ultimately, just 'viruses'. The word 'virus' itself, originally meaning a disease-producing

poison, was appropriated to this particular class of agents because of the currency that Jenner had given to the term in describing cowpox and smallpox viruses a hundred years earlier.

1.3. THE NATURE OF VIRUSES

Unicellular microorganisms can be arranged in order of decreasing size and complexity: protozoa, yeasts and certain fungi, bacteria, mycoplasmas, rickettsiae and chlamydiae. Then there is a major discontinuity, for in one sense the viruses cannot be regarded as microorganisms at all. True microorganisms, however small and simple, are cells. They always contain DNA as the repository of their genetic information, and they also have their own machinery for producing energy and macromolecules. Microorganisms grow by synthesizing their own macromolecular constituents (nucleic acid, protein, carbohydrate and lipid), and they multiply by binary fission.

Viruses, on the other hand, contain only one type of nucleic acid, which may be either DNA or RNA, double-stranded or single-stranded. Furthermore, since viruses have no ribosomes or other organelles, they are completely dependent upon their cellular hosts for the machinery of protein synthesis, energy production, and so on. Unlike any of the microorganisms, many viruses can, in suitable cells, reproduce themselves from a single nucleic acid molecule. The key differences between viruses and microorganisms are listed in Table 1.

TABLE 1. *Properties of Microorganisms and Viruses**

	Growth on nonliving media	Binary fission	DNA and RNA	Ribosomes	Sensitivity to antibiotics	Sensitivity to interferon
Bacteria	+	+	+	+	+	−
Mycoplasmas	+	+	+	+	+	−
Rickettsiae	−	+	+	+	+	−
Chlamydiae	−	+	+	+	+	+
Viruses	−	−	−	−	−	+

* From Fenner and White (1976).

Viruses differ from cellular microorganisms in that they exist in two or sometimes three physically and functionally different states. Firstly, they exist as viral particles, or virions, which are the inert form that carries the viral genome from one host cell and/or one host organism to another one. Commonly, but incorrectly, the word 'virus' is often used as a synonym for 'virion'. The second functional state is 'vegetative virus', in which the viral genome undergoes replication, directs the formation of polypeptides and controls the assembly and often the release of progeny virions. In this state the 'virus' is part of the host cell that it infects; the unit is the virus-infected cell. Finally, with a few families of viruses, including lysogenic bacteriophages, papovaviruses and retroviruses, the viral genome, in whole or in part, is at times integrated into the host cell DNA as a 'provirus'. In the case of retroviruses, the provirus is a DNA copy of the RNA genome of the virion.

Virions consist of a genome of either DNA or RNA enclosed within a protective coat of virus-specified protein molecules, some of which may be associated with carbohydrates or lipids specified by the viral or more commonly the host cell genome. In the vegetative state and as 'provirus', viruses are reduced to their constituent genomes. The simplest 'viruses' (viroids) (Diener, 1979) may be transmitted from one host to another and exist only as naked molecules of nucleic acid, possibly associated with certain cellular components. At the other extreme, the virions of the larger animal viruses, e.g. the poxviruses and the retroviruses, have a relatively complex structure.

Viruses parasitize every kind of organism; possibly, indeed, every individual organism, prokaryote and eukaryote, is infected with one or more viruses. For our purposes we need consider only the viruses of vertebrate animals—mainly those of man, but also some viruses that infect domestic or experimental animals and are important in experimental virology, including viral chemotherapy.

1.4. THE CHEMICAL COMPOSITION OF ANIMAL VIRUSES

The virions of the simpler viruses consist solely of nucleic acid and a few virus-specified polypeptides. More complex viruses usually also contain lipids and carbohydrates; in the great majority of viral families these chemical components are not specified by the viral genome but are derived from the cells in which the viruses multiply. In exceptional situations, cellular nucleic acids or polypeptides may be incorporated in viral particles.

1.4.1. Nucleic Acids

Viruses, unlike microorganisms, contain only a single species of nucleic acid, which may be DNA or RNA. In different families of viruses the nucleic acid is single- or double-stranded, a single molecule or several, and if a single molecule either linear or cyclic. About 20 per cent of the cytosine residues in the ranavirus FV3 are methylated, but neither 5-methyl cytosine nor novel bases of the type encountered in some bacterial viruses have been found in other vertebrate viral nucleic acids. However, the nucleic acids of some viruses contain oligonucleotides rich in adenylate, of unknown function. The base composition of DNA from animal viruses covers a far wider range than that of the vertebrates, for the guanine plus cytosine (G + C) content of different viruses varies from 35 to 74 per cent, compared with 40 to 44 per cent for all chordates. Indeed, the G + C content of the DNA of viruses of one family (Herpesviridae) ranges from 46 to 74 per cent.

The molecular weights of the DNAs of different animal viruses vary from 1.5 to 185 million; the range of molecular weights of viral RNAs is much less, from just over about 2.5 to 15 million. The nucleic acid can be extracted from viral particles with detergents or phenol. The released molecules are often easily degraded but if kept intact the isolated nucleic acid of viruses belonging to certain families is infectious. In other cases, the isolated nucleic acid is not infectious even though it contains all the necessary genetic information, for its transcription depends upon a virion-associated transcriptase without which multiplication cannot proceed.

The genomes of all DNA viruses consist of a single molecule of nucleic acid, but the genomes of many RNA viruses consist of several different molecules, which are probably loosely linked together in the virion. In viruses whose genome consists of single-stranded nucleic acid, the viral nucleic acid is either the 'positive' strand (in RNA viruses, equivalent to messenger RNA) or the 'negative' (complementary) strand. Preparations of some Parvoviridae, which have genomes of single-stranded DNA, consist of particles that contain either the positive or the complementary strand.

Viral preparations often contain some particles with an atypical content of nucleic acid. Host-cell DNA is found in some papovaviruses, and what appear to be cellular ribosomes in some arenaviruses. Several copies of the complete viral genome may be enclosed within a single particle (as in paramyxoviruses) or viral particles may be formed that contain no nucleic acid ('empty' particles) or that have an incomplete genome ('defective interfering' particles), lacking part of the nucleic acid that is needed for infectivity.

Terminal repetition occurs in the DNA of some vertebrate viruses and the genome of retroviruses consists of two or three identical single-stranded RNA molecules linked end to end, but most sequences are unique. The largest viral genomes contain several hundred genes, while the smallest carry only sufficient information to code for about three proteins.

1.4.2. Proteins

The major constituent of the virion is protein, whose primary role is to provide the viral nucleic acid with a protective coat. The protein shells of the simpler viruses consist of repeating protein subunits. Sometimes the capsid protein consists of only one sort of polypeptide; more commonly there are two or three different polypeptides in the protein shell. Often certain of these surface polypeptides have a special affinity for complementary 'receptors' present on the surface of susceptible cells. They also contain the antigenic determinants that are responsible for the production of protective antibodies by the infected animal. Viral polypeptides are quite large, with molecular weights in the range

10,000–150,000 daltons. The smaller polypeptides are often, but not always, internal; the larger ones often, but not always, external. There are no distinctive features about the amino acid composition of the structural polypeptides of the virion, except that those intimately associated with viral nucleic acid in the 'core' of some icosahedral viruses are often relatively rich in arginine.

Viral envelopes usually originate from the cellular plasma membrane from which the original cellular proteins have been totally displaced by viral peplomers and a viral "membrane protein" (see Fig. 1). The peplomers consist of repeating units of one or two glycoproteins, the polypeptide moiety of which is virus-specified while the carbohydrate is added by cellular transferases. In many but not all enveloped viruses, the inside of the viral envelope is lined by a viral protein called the membrane or matrix protein.

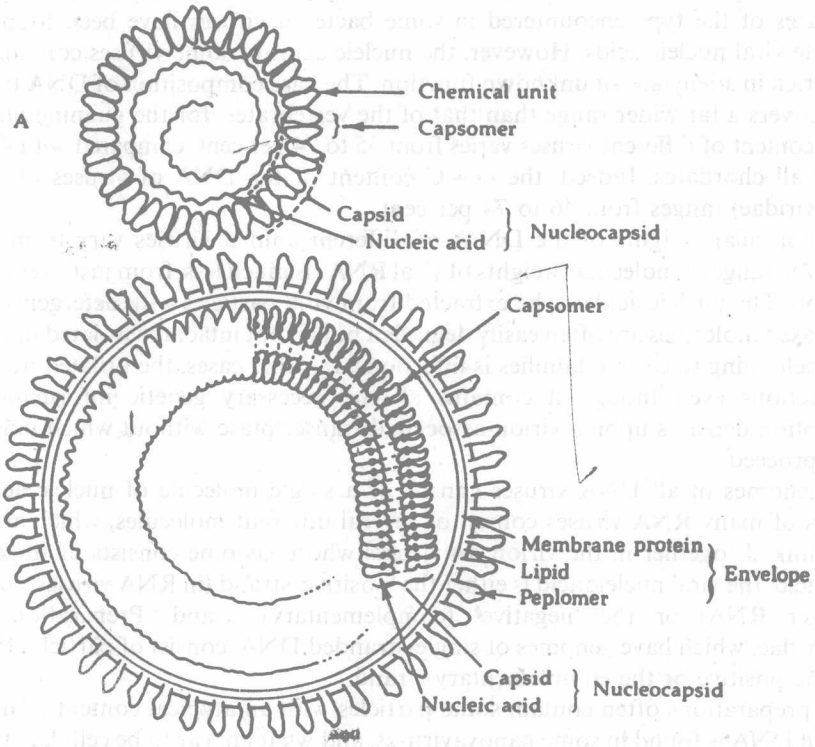

FIG. 1. Schematic diagrams of the structure of a simple non-enveloped virion with an icosahedral capsid (A) and an enveloped virion with a tubular nucleocapsid with helical symmetry (B). The capsids consist of morphological subunits called capsomers, which are in turn composed of structural subunits that consist of one or more chemical subunits (polypeptide chains). Many icosahedral viruses have a 'core' (not illustrated), which consists of protein(s) directly associated with the nucleic acid, inside the icosahedral capsid. In viruses of type B the envelope is a complex structure consisting of an inner virus-specified protein shell (membrane protein, made up of structural subunits), a lipid layer derived from cellular lipids, and one or more types of morphological subunits (peplomers), each of which consists of one or more virus-specified glycoproteins (from Fenner and White, 1976).

Not all structural viral proteins are primary gene products, since in viruses of several families the viral mRNA is translated into a large polypeptide that is enzymatically cleaved to yield two or more smaller virion proteins. Cleavage is often one of the terminal events in the assembly of the virion and it can occur on the virion after most of the proteins are already in place.

Although most virion polypeptides have a structural role, some have enzymatic activity. Many viruses contain a few molecules of an internal protein that functions as a transcriptase, one of the two kinds of peplomers in the envelope of orthomyxoviruses has neuraminidase activity, and several other enzymes are found in the virions of the larger, more complex viruses.

In addition to polypeptides that occur as part of the virion, part of the viral genome codes for polypeptides that have a functional role during viral multiplication but are not incorporated into viral particles. Few of these 'nonstructural viral proteins' have been characterized.

1.4.3. Lipid and Carbohydrate

Lipids and to a large extent carbohydrates are usually found only in viral envelopes except in the virions of poxviruses and some iridoviruses, where they occur in the outer membrane as well as the envelope. The lipids of viral envelopes are characteristic of the cell of origin, though minor differences may be demonstrable. About 50–60 per cent of the lipid is phospholipid and most of the remainder (20–30 per cent) is cholesterol. Some of the viral carbohydrate occurs in the envelope as glycolipid characteristic of the cell of origin, but most of it is part of the glycoprotein peplomers that project from the viral envelope.

1.5. THE STRUCTURE OF ANIMAL VIRUSES

Three structural classes of viruses of vertebrates can be distinguished: isometric particles, which are usually 'naked' but in some families are enclosed within a lipoprotein envelope; long tubular nucleoprotein structures, always surrounded by a lipoprotein envelope; and in a few groups, a more complex structure.

1.5.1. Terminology

Virion (plural, virions) is used as a synonym for 'virus particle'. The protein coat of an isometric particle, or the elongated protein tube of viruses with helical symmetry, is called the *capsid* (Fig. 1). It may be 'naked', or it may be enclosed within a lipoprotein *envelope* (peplos) which is derived from cellular membranes as the virus matures by budding. Where the capsids directly enclose the viral nucleic acid, as is usual with tubular capsids but less common with isometric capsids, the complex is called the *nucleocapsid*. With most isometric particles, and in all complex virions, the capsid encloses another protein structure containing the viral genome, called the *core*.

Capsids consist of repeating units of one or a small number of protein molecules. Three levels of complexity can be distinguished. *Chemical units*, the ultimate gene products, are single polypeptides that may themselves constitute the *structural units*, or several polypeptides may form homo- or heteropolymers which constitute structural units. The structural units, or groups of them, may be visualized in the electron micrographs as *morphological units*. Morphological units that form part of a capsid are called *capsomers*; those projecting from the envelope are the *peplomers* (sometimes called 'spikes', an unsatisfactory term since they are never pointed and may, indeed, have knob-shaped ends).

The chemical units are sometimes held together by disulfide bonds to form the structural units, hence the practice of using reducing agents in polyacrylamide gel electrophoresis when analyzing viral proteins to determine their constituent polypeptides. The structural units are held together to form the capsid by noncovalent bonds, which may be polar (salt and hydrogen bonds) or nonpolar (van der Waals and hydrophobic bonds). The capsids of some viruses are readily disrupted in molar calcium or sodium chloride, suggesting electrovalent bonds between the structural units; others are unaffected by salt and can only be disrupted by detergents, suggesting that they are hydrophobically bonded.

1.5.2. Isometric Viruses

The capsomers of isometric viruses are arranged with icosahedral symmetry, because the icosahedron is that polyhedron with cubic symmetry which, if constructed of identical subunits, would least distort the subunits or the bonds between them.

An icosahedron (Fig. 2) has twenty equilateral triangular faces, twelve vertices, where the corners of five triangles meet, and thirty edges, where the sides of adjacent pairs of triangles meet. It shows two-fold symmetry about an axis through the center of each edge (Fig. 2A), three-fold symmetry when rotated around an axis through the center of each triangular face (Fig. 2B), and five-fold symmetry about an axis through each vertex (Fig. 2C). Each triangular face may be thought of as containing, and being defined by, three asymmetric units (i.e. units that have no regular symmetry axes themselves) so that a minimum of sixty asymmetric units are required to construct an icosahedron.

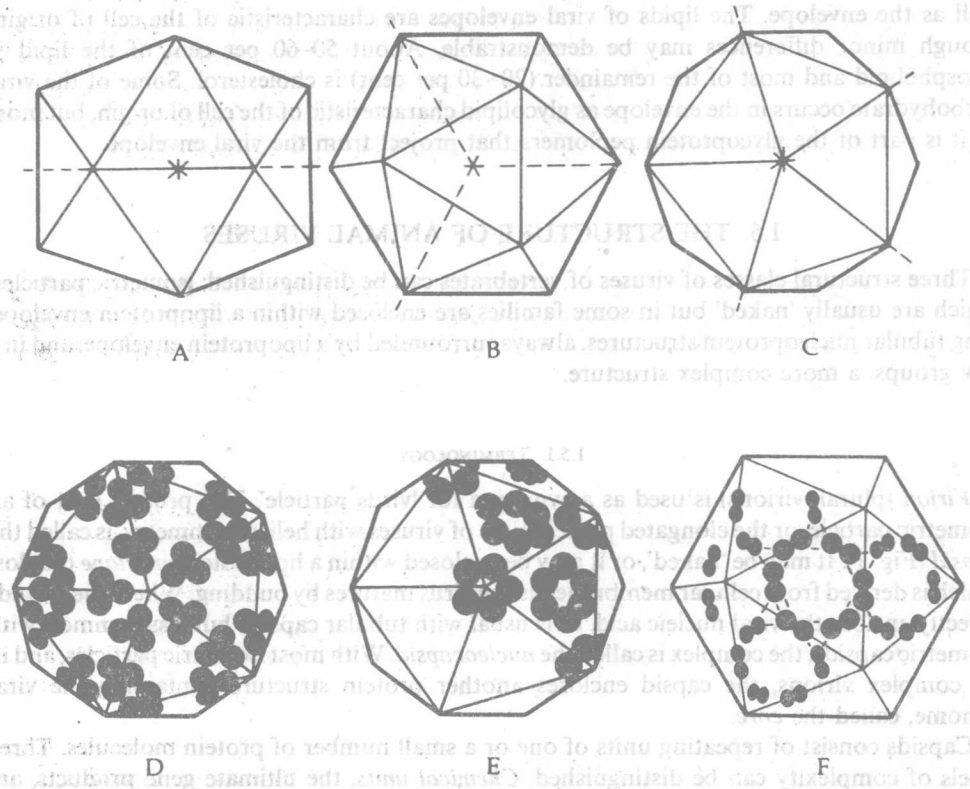

FIG. 2. Features of icosahedral structure. Above: Regular icosahedron viewed along two-fold (A), three-fold (B), and five-fold (C) axes. Various clusterings of structural subunits give characteristic appearances of capsomers in electron micrographs. With $T = 3$ the structural subunits may be arranged as 20T trimers (D), capsomers are then difficult to define, as in poliovirus; or they may be grouped as 12 pentamers and 20 hexamers (E) which form bulky capsomers as in *Parvovirus*, or as dimers on the faces and edges of the triangular facets (F), producing an appearance of a bulky capsomer on each face, as in *Calicivirus* (from Fenner and White, 1976).

The pattern seen on the surface of the virion need not reflect the way in which the structural units are bonded together, and gives no clue as to whether the structural units are constituted by single chemical units or are homo- or heteropolymers of the chemical units. However, the number of structural units in each capsomer can be guessed at from the arrangement and size of the capsomers (Fig. 2).

All animal viruses whose genome is DNA have isometric (or complex) capsids, as do those whose genome is double-stranded RNA (Reoviridae) and the viruses of two large families (Picornaviridae and Togaviridae) whose genome consists of a single molecule of single-stranded RNA.

1.5.3. Viruses with Tubular Nucleocapsids

Tubular nucleocapsids are found in many families of viruses of vertebrates, but only among those whose genome consists of single-stranded RNA. None of these occurs 'naked';