VIRUS INFECTIONS

Modern Concepts and Status

Edited by Lloyd C. Olson

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The Children's Mercy Hospital
University of Missouri–Kansas City
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Preface

At the midpoint of this century, viruses were invisible organisms which were responsible for certain acute human disease, which killed laboratory mice, and which parasitized bacteria. Conceptually they were elemental parasites which invaded, wreaked their consequences, and were in turn eliminated. Now that is all changed, not only as a consequence of a more thorough understanding of what viruses are, but also because of our more complete appreciation of the nature of the host cells themselves. Numerous viruses have been isolated and characterized, and each has been classified according to its genome, virion structure, relation to its hosts and host cells, and antigenic composition. As knowledge of each becomes more complete, that knowledge becomes more complex and extensively documented.

The techniques employed by investigators to pursue this knowledge have also become more sophisticated, innovative, and ingenious and borrow not only from cellular and molecular biology but also biophysics and electronic engineering. As a result, the interpretation of much of experimental virology has passed outside the immediate concerns of many of those with at least a passing interest in viruses. This is particularly unfortunate in that new viruses continue to be isolated, and the biology of virus infections continues to expand.

To be sure, virology is periodically reviewed. Such reviews, however, tend to be exhaustive and heavily referenced compendia appropriate to a current analysis of the subject. As such, on the other hand, they tend to lack the elements of broad interpretations or speculations necessary to a reasonably durable perspective of the topic. The present volume attempts to provide these elements. An overview of viruses, their relationships with the host cell and the molecular pathogenesis of their effects, is presented first. Next is analyzed the host immune response and how this may lead to an immunopathologic process. One part of this immune response is interferon production, which forms the subject of a detailed review. Finally, our current understanding of the new hepatitis viruses, of the fascinating agents best designated as unconventional viruses, and of the two major groups of tumor viruses, each receive detailed consideration. All discussions are intended to be informative and interpretive rather than a technical reference source. The authors have intended their efforts to provide insight into the intriguing relationships between cell and virus in an entertaining manner. We hope the reader will find it so.

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chapter 1

Virus Replication and the Pathogenesis of Disease

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Eukaryotic cells represent the culmination of an immense evolutionary effort directed toward the successful perpetuation of complex life forms Central to this success is the development of nucleic acid-based systems for storage of information necessary to the proper construction and function of organisms. Perhaps even more remarkable, however, are the systems ensuring coordinated expression of this information in a manner that best serves the individual cell and the total organism. This is especially true when one considers the enormity of the task of starting with an individual array of data to construct such complex multicellular organisms as dinosaurs or elephants. The regulatory mechanisms responsible for expression of information at the proper time, in the proper sequence, and in the proper proportion are complex and exquisitely controlled.

This elegant biosynthetic machinery is also susceptible to expropriation by viruses. That this is a common event in the natural biology of the cell is attested to by the myriad successful schemes pursued by viruses for their own purposes, and by the fact that few if any cells are exempt from virus predations. Intracellular competitions between invading viruses and the host cell represent the fundamental element of the virus-cell relationship. In fact, viruses represent the most basic form of parasitism; they are in essence genetic interlopers. Some viruses interject in place of the cellular chromosome their own DNA message, which, once innocently processed by the cell, provides all the elements necessary to the construction of virus progeny. Other kinds of viruses accomplish the same goal by representing themselves to the cell as the intermediate messenger normally employed for information transfer.

As with all life forms, the sole purpose of a virus is to ensure reproduction in kind. To do so, however, has required that viruses be constructed in a manner that allows progeny virions to escape from the host cell, pass through a hostile extracellular and extraorganismic environment, successfully encounter new host cells and fresh hosts, and recognize and then enter such cells as are capable of supporting renewed replication. The adaptive strategies various viruses have developed for each step of the infectious cycle are diverse; many are fascinating; and were viruses granted the attribute of conscious intent many would best be described as exceptionally ingenious.

In actual fact viruses do not merely provide the genome for the cell's synthesizing machinery without themselves exerting controls over gene expression. Many viruses possess means to precisely regulate the rate at which the cell manufactures virus-specific products, the order in which gene products are expressed, and also provide some of their own enzymes necessary to replication. The extent and means of regulating gene expression are as diverse as the kinds of virus, and each has developed to meet the needs of a particular virus within the constraints imposed by the host cell. For it must be borne in mind that eukaryotic cells have not remained totally passive victims to the self-serving strategies of virus replication. Politicians do not provide a free lunch; neither does nature. In many instances it seems likely that certain viruses have been made to be of some use to the host. For others, the cell possesses a number of retaliatory mechanisms for minimizing the deleterious effects of virus infections. In many instances the cell has in effect learned to accommodate, or at least to tolerate, the presence of virus. Finally, multicellular organisms have perfected an organ system specifically for the purpose of recognizing and destroying harmful microorganisms.

This chapter will discuss the state of our current understanding of what viruses are, how they replicate, and how they affect their host cell. More importantly, an attempt will be made to relate the molecular biology of the virus replication process to the impact that such events have on the whole organism—the pathogenesis of virus diseases. For the most part the discussion will concentrate on viruses of eukaryotic cells, with an especial effort to consider animal viruses. Other virus systems will be referred to only when they offer a particularly interesting example of the subject under consideration.

VIRUS STRUCTURE AND FUNCTION

The essential feature of the intracellular phase of most viruses is that the nucleic acid core is constructed and organized to allow full expression of the genetic information. In some instances it appears that certain viruses function intracellularly as isolated nucleic acid free of other virus components. Usually, however, other proteins remain associated with the genome for purposes of protecting the nucleic acid from digestion by cellular enzymes, or because the proteins are necessary to appropriate expression of the genetic message.

The extracellular phase of a virus (the virion), on the other hand, reflects a much more complicated structure. Elements necessary to protect the genome from the various hazards encountered in extracellular fluids and in the outside world are ordinarily required. An exception are the viroids, thought to be small pieces of naked RNA but which are capable of infecting, then multiplying and damaging certain kinds of plants (potato spindle tuber viroid, chrysanthemum stunt viroid, and other exotica). No such examples are known for animal hosts, however.

The simplest virions are those consisting of a protein shell tightly surrounding the nucleic acid core. A number of features can be quickly inferred from such a structure. First, the shell or coat must be complete and tightly constructed. As the structural materials for the shell are virus specified, only a few species of proteins at most are available, so that, second, the subunit structures must be regularly repeating entities (capsids) held together by intermolecular forces. Third, this endows upon the structure the quality of symmetry, and much has been made of the kinds of the icosahedral or helical symmetries possessed by such virions. Fourth, assembly of the virion must be a relatively simple process rather than requiring elaborate schemes involving complex regulation; the simplest of these is "self-assembly," in which virus components naturally come together as a compact entity. Otherwise, it presumably would require more energy to keep dispersed molecules intrinsically destined to interact. Fifth, such self-associating structures must be compactly constructed; as such, many are extraordinarily stable to such forces as chemicals and heat. Simple shelled structures are characteristic of viruses which infect via the gastrointestinal tract. Presumably, the stability endowed by this form enables them to survive passage through the acid environment of the stomach.

The need to form compact and stable structures presumably limits the feasible size attainable in terms of dimension and genetic information. The adenoviruses are large enough that their genome consists of 30 to 40 genes, but other of these viruses are limited to approximately 10 genes. Finally, these viruses encounter a barrier in terms of release from the host cell. It appears the only way to get from the intracellular site of assembly to the extracellular space is by disrupting the cell membrane. In general this is accomplished by destruction of the membrane, brought about by severely impairing cellular metabolism and causing cell death. As a consequence such viruses generally tend to be cytocidal.

Perhaps as a means to avoid this outcome, and in recognition of the fact that it is undesirable for the parasite to kill an accommodating host, many viruses use a mechanism of *envelopment* as a means of egress from the host cell. This process adds an additional element to the final structure of the virion, an element, moreover, which as a rule is critical to infectivity of the virion. The reason for the latter will become obvious when virus-cell interactions are discussed; the formation of the envelope will be considered in detail in the next section.

Appropriately, viruses with envelopes are referred to as "enveloped" viruses. Those without are designated "naked" viruses. A desire to avoid destroying the cell is actually not the sole reason for envelopment, apparently, as a third group of viruses, the complex animal viruses known as poxviruses, can independently direct the manufacture of their own envelopes. Be that as it may, the envelope thus becomes the surface barrier presented to the environment. This appears to relax the critical relationship of internal structures to each other so that additional elements may be present in enveloped virions. Arenaviruses, for example, incorporate host cell ribosomes, and cellular genetic elements are frequently included in other viruses. Many virions may contain more than one genome copy (multiploidy). The relationship of protein to nucleic acid is usually not as rigid as with the naked viruses, so that the protein in many instances does not completely enclose the nucleic acid. The envelope contains lipid and protein in an arrangement characteristic of any cellular membranous structure, and is not nearly as resistant to destruction as are the icosahedral shells of naked viruses. Enveloped viruses are thus forced to be more cautious in their environmental exposures, and tend to prefer transit from host to host by direct contact. Spread via respiratory tract secretions is apparently also tolerable, as many of the viruses transmitted in this manner are enveloped.

The nucleic acid genome of viruses may be composed of DNA or RNA. All families of DNA viruses but one possess DNA as a double-stranded (ds) molecule; the exception is parvovirus, which contains single-stranded(ss) DNA (hepatitis B virus seems to possess dsDNA containing a long stretch of ssDNA). Conversely, all RNA virus families possess ssRNA genomes except the reoviruses, which carry their genetic information in the form of dsRNA. As far as is known all DNAs are one continuous molecule. Presumably this reflects the fact that eukaryote cells are familiar with this form of DNA and routinely are able to select only those portions needed at the moment. This is, of course, not the case with RNA; cell experience is limited to interpreting discrete individual messages on ss molecules. Reflecting this fact, many of the genomes of RNA viruses are segmented, each segment being monocistronic in the same manner as the cell's mRNA. Other RNA viruses, however, do not contain segmented RNA, but the molecule is continuous and polycistronic.

For the segmented RNA viruses, the virion RNA may be directly translatable to virus polypeptides, or a complementary copy (cRNA) must first be synthesized and the cRNA is translated to authentic virus polypeptides. This feature necessitates the assignment of polarity to RNA genomes; those in which virus RNA is directly used as messenger are said to be of messenger or plus-strand polarity. Viruses containing RNA which must be transcribed to cRNA to form functional message are, by convention, designated as negative-strand viruses and the RNA is said to be of antimessage polarity. The segmented ssRNA viruses are all negative stranded, with the exception of Nodamura virus (a virus containing two segments of (+) strand RNA, which along with a black beetle virus probably represents a unique group of RNA viruses). Nonsegmented ssRNA viruses may be plus or negative stranded. All known dsRNA viruses contain segmented genomes, almost certainly because nature is otherwise very naive in being able to interpret dsRNA information.

For all viruses the nucleic acid has a very specific configuration in the virion, usually with associated proteins which may have various functions. The DNA in viruses such as adenovirus, papovavirus, and herpesvirus are maintained in nucleosome-like structures, the DNA being wrapped around either virus-specified polypeptides or histones requisitioned from the host cell. Numerous other proteins are also associated with the nucleic acid core of viruses, which may function as enzymes, structural components, or regulatory molecules.

Naked viruses complete their structure, as previously mentioned, by aggregating a shell (or shells, in the case of reovirus), around the core (Fig. 1). The completed shell is the *capsid*, subunits of the shell are called *capsomeres*, and the structural polypeptides thereof are *capsid* (or coat) *proteins*. More than one species of capsid protein may be present in some viruses, but as a rule economy is effected by most in that only one or a very few different proteins compose the capsid. Further, many capsid proteins serve additional functions other than structural. As they form the exterior surface of the virion certain capsid proteins are of vital importance to virus-host cell interactions and to the early events during infection. However important a stable and nonyielding capsid is to the virion, it must also be readily removable once infection has been initiated.

Enveloped viruses (Fig. 2) generally do not have as rigid a nucleocapsid structure since the external protective structure is the envelope. The latter is derived from the membrane of the infected cell and consists of the lipid bilayer synthesized by the cell plus polypeptides which have, for the most part, been specified by the viral genome. Envelope polypeptides are of two classes: surface proteins which are almost always glycosylated by host cell enzymes with carbohydrate moieties, and an underlying protein layer called M (matrix or membrane) protein

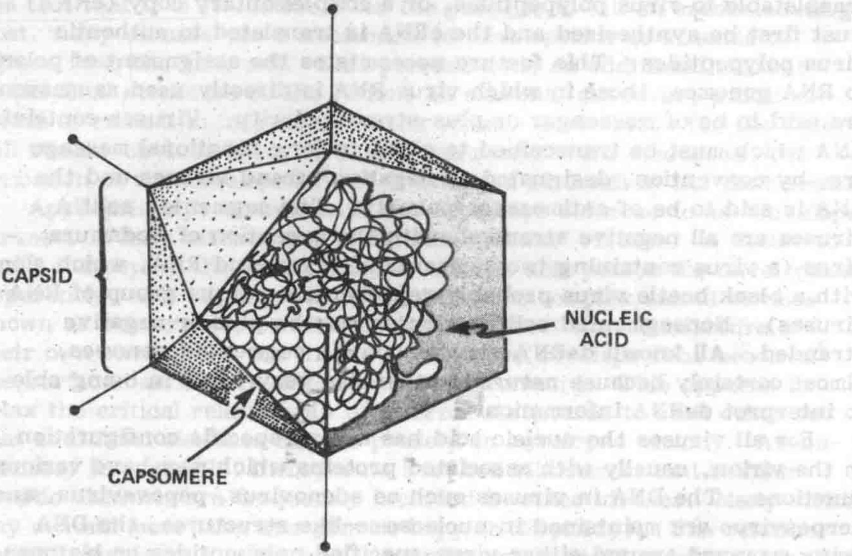

Figure 1 A naked virus, here illustrated with icosahedral symmetry.

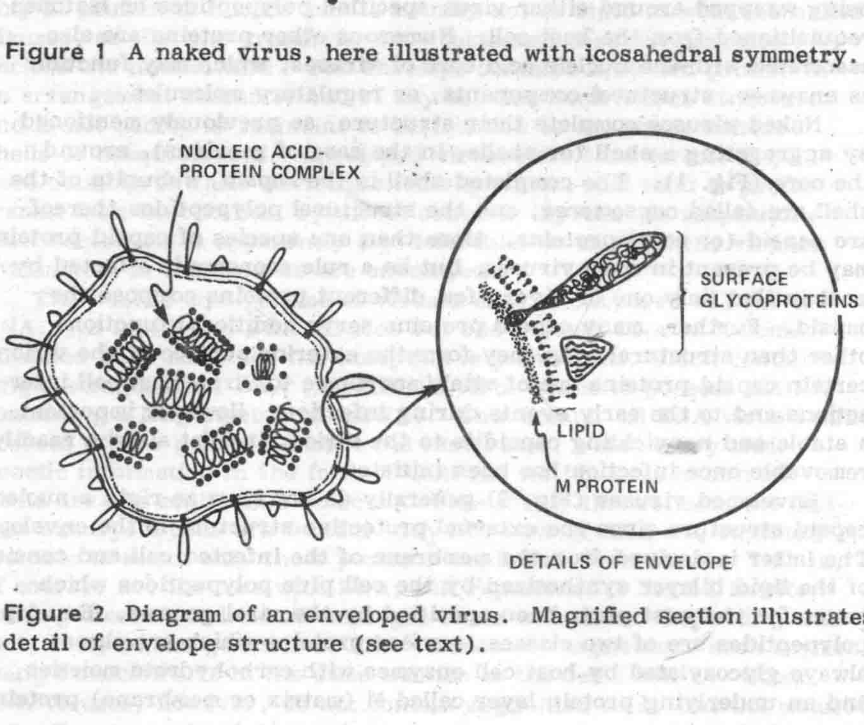

Figure 2 Diagram of an enveloped virus. Magnified section illustrates detail of envelope structure (see text).

Table 1 Virus Families: Features and Common Examples

Family	Genus	Genome	Envelope	Examples
Adenovirus		dsDNA		Human adenoviruses types 1-34; canine hepatitis virus
Arenavirus		ssRNA, segmented, -	+	Lymphocytic choriomeningitis, Bolivian hemorrhagic fever, Lassa
Astrovirus		?		? Human diarrhea viruses
Bunyavirus		ssRNA, segmented, -	+	California encephalitis, LaCrosse, snowshoe hare
Calicivirus		ssRNA, +		? Human diarrhea viruses (e.g., Norwalk, Montgomery County, etc.), vesicular exanthem of swine
Coronavirus		ssRNA, +	+	Human respiratory and diarrhea (?) viruses, mouse hepatitis
Herpesvirus		dsDNA	+	Herpes simplex, varicella zoster, cytomegalovirus, Epstein-Barr virus; pseudorabies, Marek's disease virus
Orthomyxovirus		ssRNA, segmented, -	+	Influenza viruses of humans, swine, ducks, horses
Papovavirus		dsDNA		BK, JC viruses of humans; SV40 polyoma virus
Paramyxovirus		ssRNA, -	+	Parainfluenza viruses, mumps, measles
Parvovirus		ssDNA		Adeno-associated virus

(continued)

(Table 1 continued)

Family	Genus	Genome	Envelope	Examples
Picornavirus	*Rhinovirus*	ssRNA, +		Human rhinoviruses, foot-and-mouth disease virus
	Enterovirus			Poliovirus, coxackie A and B virus, echovirus, enterovirus types 68-71, ? human hepatitis A
Poxvirus		dsDNA	+	Smallpox, monkey pox, vaccinia, orf, rabbit myxoma, canary pox
Reovirus	*Reovirus*	dsRNA, segmented		Human reoviruses
	Orbivirus			Bluetongue virus, African horsesickness virus
	Rotavirus			Human diarrhea viruses
Retrovirus		ssRNA, +	+	Visna, maedi, Zwoegerziekte; mammalian, avian tumor viruses
Rhabdovirus		ssRNA, -	+	Rabies, vesicular stomatitis virus
Togavirus	*Alphavirus*	ssRNA, +	+	Eastern, Western, Venezuelan encephalitis viruses; Sindbis virus, Chikungunya virus
	Flavivirus	ssRNA, +		St. Louis, Japanese B encephalitis viruses; dengue virus, yellow fever virus
Unknown: hepatitis viruses (human B, ground squirrel, woodchuck); Marburg-Ebola viruses; Nodamura and black beetle viruses.				