THE HUMAN HERPESVIRUSES

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The Human Herpesviruses

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Preface

The first herpesvirus was discovered in the first quarter of this century. The exact year is uncertain, since in the World War I years publication did not immediately follow discovery. For many years, herpesviruses were considered to be responsible for a few nuisance diseases of children, the afflictions of a few unfortunate individuals who became infected under circumstances they would rather not disclose, benign infections of old world monkeys contrasted with lethal consequences of humans who let themselves be bitten by them, and for several diseases of pigs. The assessment that the consequences of herpesvirus infection are trivial was not a strong inducement for recruitment of workers in the field. At the time when polioviruses were understood well enough to be purified and crystallized, herpes virologists were still not sure of the size and nature of its genome. Not surprisingly, herpes virologists of that period received little recognition for the research done on viruses whose hour was yet to come.

Three significant events propelled the blossoming of herpesvirus research. Foremost, it has finally dawned on the infectious disease community that herpesviruses are significant pathogens responsible for diseases ranging from relatively trivial to those posing a significant threat to life. A close second, was the discovery that herpesviruses have evolved a variety of sophisticated mechanisms by which they maintain themselves in their hosts for the life of the host. Third, and perhaps no less important, was the realization that members of the herpesvirus family differ from other virus families with respect to the evolutionary diversity of its members. What other family of viruses can boast of a twofold variability in both size and G + C content of their genome? Whereas some members of the herpesvirus family splice the mRNAs sparingly, others do so overwhelmingly. Herpesviruses are in their age of discovery. Among the discoveries of the past few years, are two human herpesviruses and arrays of viral genes which shed light on both viral and cellular functions.

Herpesviruses have been discovered in all higher eukaryotes investigated to date. Notwithstanding their diversity, all of the features that make herpesviruses exciting targets of intensive research are also shared by the herpesviruses which infect humans. This volume is about human herpesviruses.

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The editors owe the authors of this volume special recognition for an extraordinary effort to publish up-to-date assessments of their fields of interest. The editors are also grateful to Raven Press for just the right amount of pressure to get this endeavor completed.

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The Human Herpesviruses, edited by
B. Roizman, R.J. Whitley, and C. Lopez.
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CHAPTER 1

The Family Herpesviridae

A Brief Introduction

Bernard Roizman

Who made the world I cannot tell;
'Tis made, and here I am in hell.
My hand, though now my knuckles bleed,
I never soiled with such a deed.

A. E. Housman, No. XIX in *More Poems*

DEFINITION

Inclusion in the Family Herpesviridae

Membership in the family *Herpesviridae* is based on the architecture of the virion (Fig. 1). A typical herpesvirion consists of a core containing a linear double-stranded DNA, an icosadeltahedral capsid approximately 100 to 110 nm in diameter containing 162 capsomeres with a hole running down the long axis, an amorphous, sometimes asymmetric material surrounding the capsid designated as the tegument, and an envelope containing viral glycoprotein spikes on its surface.

Distribution in Nature

Herpesviruses are highly disseminated in nature, and most animal species have yielded at least one herpesvirus on examination. Of nearly 100 herpesviruses that have been at least partially characterized, 7 have been isolated so far from humans [herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human cytomegalovirus (HCMV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and human herpesvirus 6 and 7 (HHV6 and HHV7)], 5 from horses, at least 4 from cattle, 2 from pigs [pseudorabies virus (PSV) and porcine cytomegalovirus], and 3 from chickens (infectious laryngotracheitis virus and 2 viruses associated with Marek's disease). The known herpesviruses are listed in Table 1. References to the individual viruses comprising the family Herpesviridae are found in the current description of the family.

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ARCHITECTURE

Structural Components

The Core. The core of the mature virion contains the viral DNA in the form of a torus (13,26). In some herpesvirions, the torus appears to be suspended by a proteinaceous spindle consisting of fibrils embedded in the underside of the capsid and passing through the hole of the torus. The precise arrangement of the DNA in the toroid is not known.

The Capsid. The structural features of the capsid, that is, its 100 nm diameter and 162 capsomeres, are characteristic of all herpesviruses. The pentameric capsomeres at the vertices have not been well characterized. The hexameric capsomeres are 9.5 × 12.5 nm in longitudinal section. A channel 4 nm in diameter runs from the surface along the long axis (37).

The Tegument. The tegument, a term introduced by Roizman and Furlong (31) to describe the structures between the capsid and envelope, has no distinctive features in thin sections but may appear to be fibrous on negative staining (14,24,25,37). The thickness of tegument may vary depending on the location of the virion within the infected cell. When the amount is variable, there is more of it in virions accumulating in cytoplasmic vacuoles than in those accumulating in the perinuclear space (13). The available evidence suggests that the amount of tegument is more likely to be determined by the virus than by the host (21). The tegument frequently is distributed asymmetrically.

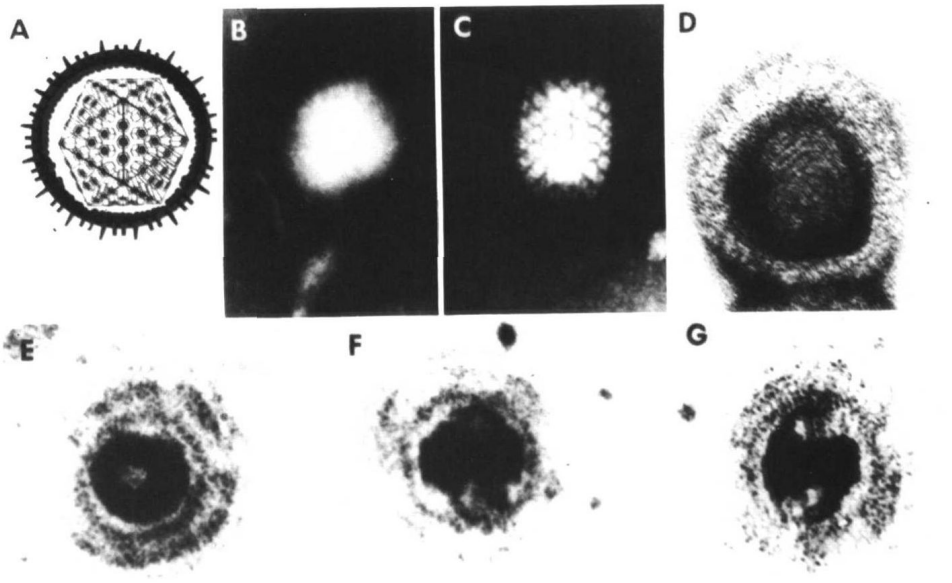

FIG. 1. The morphology of herpesviruses. **A:** Schematic representation of the herpesvirion seen through a cross-section of the envelope with spikes projecting from its surface. The sides of the icosadeltahedron forming the capsid show a twofold symmetry. The irregular inner perimeter of the envelope is meant to represent the occasional asymmetric arrangement of the tegument. **B:** An intact, negatively stained HSV-1 virion. The intact envelope is not permeable to negative stain. The diameter of the virion is approximately 120 nm. **C:** An HSV-1 capsid exposed to negative stain and showing twofold symmetry matching the diagrammatic representation of the capsid in **A. D:** HSV-1 capsid containing DNA permeated with uranyl acetate. The electron micrograph shows the presence of threadlike structures 4 to 5 nm wide on the surface of the core. **E, F, G:** Electron micrographs of thin sections of HSV-1 virions showing the core cut at different angles. The preparation was stained with uranyl acetate and counterstained with lead citrate. The DNA core preferentially takes up the stain and appears as a toroid with an outer diameter of 70 nm and an inner diameter of 18 nm. The toroid appears to be suspended by a fibrous cylindrical structure. The micrographs show the toroid seen looking down the hole (**E**), in cross-section (**F**), and from the side (**G**). (**D, E, F, G,** from ref. 14.)

The Envelope. Electron microscopic studies on thin sections have shown that the outer covering, the envelope, of the virus has a typical trilaminar appearance (12). It appears to be derived from patches of altered cellular membranes (1,13,25). The presence of lipids was demonstrated by analyses of virions (2,4) and by sensitivity of the virions to lipid solvents and detergents (17,34,35). The herpesvirus envelope contains numerous protrusions of spikes, which are more numerous and shorter than those appearing on the surface of many other enveloped viruses. Wildy and Watson (37) estimated that the spikes on HSV virions are approximately 8 nm long. The spikes consist of glycoproteins. The number and relative amounts of viral glycoproteins vary. HSV specifies at least 11 glycoproteins (see the chapter, "The Herpes Simplex Viruses and Their Replication," by Roizman and Sears).

The Virion. The size of herpesvirions has been reported to vary from 120 nm to nearly 300 nm (reviewed in ref. 31). The difference is due in part to variability in the thickness of tegument. Another major source of variability is the state of the envelope. Intact envelopes are impermeable and generally retain the quasi-spherical shape of the virion. Damaged envelopes are permeable to negative stains, and permeated virions have a sunny-side-up egg appearance, with a diameter much larger than that of an intact virion.

The precise number of polypeptide species contained in the herpes virions is not known and may vary from one virus to another. The estimates generally range from 30 to 35 polypeptides.

Herpesvirus DNAs

Size, Conformation, and Base Composition. The herpesvirus DNAs extracted from virions and characterized to date are linear and double stranded, but they circularize immediately on release from capsids into the nuclei of infected cells.

The variable features of the herpesvirus DNAs are their molecular weight and base composition. The molecular weight of herpesvirus DNAs varies from approximately 80 million to 150 million, or approximately 120 to 230 Kbp (Table 1). The variability in the size of herpesvirus DNAs does not reflect polymorphism in the size of DNAs of individual viruses. The variation in the size

TABLE 1. *Viruses comprising the family Herpesviridae*[a]

Designation	Common name (synonyms)	Subfamily	G + C (mole %)	Group[b]	Size Kbp
Viruses of humans					
Human herpesvirus 1	Herpes simplex virus 1	α	68.3	E	152
Human herpesvirus 2	Herpes simplex virus 2	α	69	E	152
Human herpesvirus 3	Varicella-zoster virus	α	46	D	125
Human herpesvirus 4	Epstein-Barr virus	γ	60	C	172
Human herpesvirus 5	Cytomegalovirus	β	57	E	229
Human herpesvirus 6		β	42	A	162
Human herpesvirus 7		β			
Viruses of nonhuman primates[c]					
Aotine herpesvirus 1	HV aotus type 1	β	55	E	220
Aotine herpesvirus 3	HV aotus type 3	β	56	D	219
Cercopithecine herpesvirus 1	B virus, HV simiae	α	75	E	160
Cercopithecine herpesvirus 2	SA8	α	67	E	150
Cercopithecine herpesvirus 3	SA6	β	51		
Cercopithecine herpesvirus 4	SA15	β			
Cercopithecine herpesvirus 5	African green monkey cytomegalovirus	β			
Cercopithecine herpesvirus 6	Liverpool vervet monkey virus	α	52		
Cercopithecine herpesvirus 7	Patas monkey HV; MMV or PHV delta HV	α			
Cercopithecine herpesvirus 8	Rhesus monkey cytomegalovirus	β	52		
Cercopithecine herpesvirus 9	Medical Lake macaque HV; simian varicella HV	α			
Cercopithecine herpesvirus 10	Rhesus leukocyte associated HV strain I				
Cercopithecine herpesvirus 12	HV papio, baboon HV	γ	—	C	170
Cercopithecine herpesvirus 13	Herpesvirus cyclopis				
Cercopithecine herpesvirus 14	African green monkey EBV-like virus	γ			
Cercopithecine herpesvirus 15	Rhesus EBV-like HV	γ			
Ateline herpesvirus 1	Spider monkey HV	α	72		
Ateline herpesvirus 2	HV ateles	γ	48	B	135
Callitrichine herpesvirus 1	HV saguinus				
Callitrichine herpesvirus 2	SSG, marmoset cytomegalovirus	β			
Cebine herpesvirus 1	Capuchin HV (AL-5)	β			
Cebine herpesvirus 2	Capuchin HV (AP-18)	β			
Pongine herpesvirus 1	Chimpanzee HV; pan HV	γ	—	C	170
Pongine herpesvirus 2	Orangutan HV	γ			
Pongine herpesvirus 3	Gorilla HV	γ			
Saimiriine herpesvirus 1	Marmoset HV; herpes T, HV tamarinus, HV platyrrhinae type	α	67	D	152
Saimiriine herpesvirus 2	Squirrel monkey HV, HV saimiri	γ	46	B	155
Viruses of other mammals					
Bovidae[d]					
Bovine herpesvirus 1	Infectious bovine rhinotracheitis HV	α	72	D	140
Bovine herpesvirus 2	Bovine mammillitis virus; Allerton virus, pseudolumpy skin disease HV	α	64	E	133
Bovine herpesvirus 4	Movar HV	γ	50	B	145
Bovine herpesvirus 5	Bovine encephalitis HV	α	72	D	140
Ovine herpesvirus 1	Sheep pulmonary adenomatosis associated HV			D	137
Ovine herpesvirus 2	Sheep associated malignant catarrhal fever of cattle HV	γ		B	
Caprine herpesvirus 1	Goat HV	α			
Alcelaphine herpesvirus 1	Wildebeest HV, malignant catarrhal fever HV of European cattle	γ	61	B	160

continued

TABLE 1. *Continued.*

Designation	Common name (synonyms)	Subfamily	G + C (mole %)	Group[b]	Size Kbp
Alcelaphine herpesvirus 2	Hartebeest HV	γ	—	B	
Cervid herpesvirus 1	Red deer HV	α	—	D	
Cervid herpesvirus 2	Reindeer (*Rangifer tarandus*) HV	α	—	D	
Canidae					
Canid herpesvirus 1	*Canine HV*	α	32		
Caviidae					
Caviid herpesvirus 1	Guinea pig HV 1, Hsiung-Kaplow virus, GPHLV	γ	60		
Caviid herpesvirus 2	Guinea pig cytomegalovirus	β	57		
Caviid herpesvirus 3	Guinea pig HV 3, GPXV				
Cricetidae					
Cricetid herpesvirus	Hamster HV	β			
Elephanitidae					
Elephantid herpesvirus	Elephant (loxodontal) HV				
Equid herpesvirus 1	Equine HV 1; equine abortion HV	α	57	D	142
Equid herpesvirus 2	Equine HV 2; equine cytomegalovirus	β	57	A	192
Equid herpesvirus 3	Equine HV 3; equine coital exanthema virus	α	66	D	148
Equid herpesvirus 4	Equine HV 4; equine rhinopneumonitis virus	α	56	D	148
Equid herpesvirus 5	*Equine HV 5*	β			150
Equid herpesvirus 6	Asinine HV 1	α			
Equid herpesvirus 7	Asinine HV 2	β			
Equid herpesvirus 8	Asinine HV 3				
Erinaceidae					
Erinaceid herpesvirus 1[e]	European hedgehog HV				
Felidae					
Felid herpesvirus 1	Feline HV 1; feline rhinotracheitis HV	α	46	D	134
Leporidae					
Leporid herpesvirus 1	Cottontail HV, HV sylvilagus	γ	33	B	145
Leporid herpesvirus 2	HV cuniculi, virus III				
Lorisidae					
Lorisine herpesvirus 1	Kinkajou HV, herpes pottos				
Macropodidae					
Macropodid herpesvirus 1	Parma wallaby HV	α	53	D	
Macropodid herpesvirus 2	Dorcopsis wallaby HV	α	50	E	135
Marmodidae					
Marmodid herpesvirus 1	Woodchuck HV, HV marmota 1	γ	—	B	160
Muridae					
Murid herpesvirus 1	*Mouse cytomegalovirus*	β	59	F	235
Murid herpesvirus 2	Rat cytomegalovirus	β	47		
Murid herpesvirus 3	Mouse thymic HV				
Murid herpesvirus 4	Mouse HV strain 68	γ		B	135
Murid herpesvirus 5	Field mouse HV; *Microtus pennsylvanicus* HV				
Murid herpesvirus 6	Sand rat nuclear inclusion agents				
Murid herpesvirus 7[f]	Murine HV				
Phocidae					
Phocid herpesvirus 1	Harbor seal HV				
Sciuridae					
Sciurid herpesvirus 1	European ground squirrel cytomegalovirus; American ground squirrel HV	β			
Sciurid herpesvirus 2					
Suidae					
Suid herpesvirus 1	Pseudorabies virus, Aujeszky's disease	α	74	D	140
Suid herpesvirus 2	Inclusion-body rhinitis virus, pig cytomegalovirus	β			
Tupaiidae					
Tupaiid herpesvirus 1	Tree shrew HV		66	F	200

TABLE 1. *Continued.*

Designation	Common name (synonyms)	Subfamily	G + C (mole %)	Group[b]	Size Kbp
Viruses of Birds					
Anatidae					
Anatid herpesvirus 1	*Duck plague HV*	α			
Accipitriae					
Accipitrid herpesvirus 1	Bald eagle HV				
Ciconiidae					
Ciconiid herpesvirus 1	Black stork HV				
Columbidae					
Columbid herpesvirus 1	Pigeon HV-1		59		
Falconidae					
Falconid herpesvirus 1	Falcon inclusion body				
Gallidae					
Gallid herpesvirus 1	*Infectious laryngotracheitis virus*	α	46	D	165
Gallid herpesvirus 2	Marek's disease HV 1		47	E	180
Gallid herpesvirus 3	Marek's disease HV 2				
Gruidae					
Gruid herpesvirus 1	Crane HV				
Meleagrid herpesvirus 1	Turkey HV 1		48	E	150
Perdicid					
Perdicid herpesvirus 1	Bobwhite quail HV				
Phalacrocoracidae					
Phalacrocoracid herpesvirus 1	Cormorant HV; Lake Victoria, cormorant HV		58		
Psittacidae					
Psittacid herpesvirus 1	Parrot HV; recently rediscovered *Pacheco's disease virus*				
Sphenicidae					
Sphenicid herpesvirus 1	Black-footed penguin HV				
Stricidae					
Strigid herpesvirus 1	Owl hepatosplenitis		61		
Viruses of amphibia and reptiles					
Boidae					
Boid herpesvirus 1[e]	Boa herpesvirus				
Chelonidae					
Chelonid herpesvirus 1[e]	Gray patch disease agent of green sea turtles				
Chelonid herpesvirus 2[e]	Pacific pond turtle HV				
Chelonid herpesvirus 3[e]	Painted turtle HV, map turtle HV				
Chelonid herpesvirus 1[d]	*Geochelone chilensis* HV, *Geochelone carbonaria* HV, Argentine turtle HV				
Elapidae					
Elapid herpesvirus	Indian cobra HV, banded krait, siamese cobra HV				
Iguanidae					
Iguanid herpesvirus 1	Green iguana HV				
Lacertidae					
Lacertid herpesvirus 1	Green lizard HV				
Ranidae					
Ranid herpesvirus 1	Lucke frog HV		46		
Ranid herpesvirus 2	Frog HV 4		56		
Viruses of bony fishes					
Cyprinidae					
Cyprinid herpesvirus	Carp pox HV				
Esocidae					
Esocid herpesvirus[e]	Northern pike HV				
Ictaluridae					
Ictalurid herpesvirus 1	Channel catfish HV	α	56	A	130
Percidae					
Percid herpesvirus 1	Walleye epidermal hyperplasia virus				
Pleuronectidae					
Pleuronectid herpesvirus	HV scophthalmus, turbot HV				

continued

TABLE 1. *Continued.*

Designation	Common name (synonyms)	Subfamily	G + C (mole %)	Group[b]	Size Kbp
Salmonidae					
Salmonid herpesvirus 1	HV salmonis				
Salmonid herpesvirus 2	*Oncorhynchus masou* HV				

[a] Table compiled by the Herpesvirus Study Group of ICTV. For details see ref. 30.
[b] Letters A–F identify genome arrangements described in the text.
[c] Aotine herpesvirus 2 and feline herpesvirus 2 have been identified as BHV4. In accordance with the rules, this number cannot be assigned to another herpesvirus.
[d] Bovine herpesvirus 3, sometimes referred to as bovine herpesvirus 4, does not now exist. These designations were applied to the virus acquired by cattle from the wildebeest in which it causes malignant catarrhal fever. The wildebeest virus is now called alcelaphine herpesvirus 1.
[e] Indicates reports of herpesvirus-like particles in tissues, but virus was not isolated in cell culture.
[f] Inclusion of this virus in the list is provisional and subject to verification of lack of identity with other murine herpesviruses.

of the genome of any one herpesvirus appears to be minimal but not insignificant. Thus, many viral DNAs contain terminal and internal reiterated sequences. Because of variability in the number of these reiterations, the size of individual genomes may vary by >10 Kbp. Spontaneous deletions also occur. They have been noted in both HSV and EBV strains passaged outside the human host (e.g., EBV strain P3HR1, HSV strain HFEM).

The base composition of herpesvirus DNAs varies from 31 to 75 G+C mole % (Table 1). Furthermore, herpesvirus DNAs vary with respect to the extent of homogeneity of base sequence distribution across the length of the genome. The extent of inhomogeneity in the base composition varies from minimal (e.g., HSV) to very extensive (e.g., the DNAs of herpes saimiri and herpes ateles) (5).

Sequence Arrangements in Herpesvirus DNAs. Probably the most interesting feature of herpesvirus DNAs is their sequence arrangement. The sequence arrangement shown in Fig. 2 emphasizes the presence and location of reiterations of terminal sequences greater than 100 bp. According to this scheme, the herpesviruses can be divided into six groups designated by the letters A, B, C, D, E, and F. In the genomes of viruses comprising group A and exemplified by the channel catfish herpesvirus, a large sequence from one terminus is directly repeated at the other terminus. In the group B genomes, exemplified by herpes saimiri virus, the terminal sequence is directly repeated numerous times at both termini, and furthermore, the number of reiterations at both termini may vary. In the group C genomes, exemplified by EBV, the number of direct terminal reiterations is smaller, but there may be other, unrelated sequences greater than 100 bp that are directly repeated and that subdivide the unique (or quasi-unique) sequences of genome into several well-delineated stretches. In group D genomes, ex-

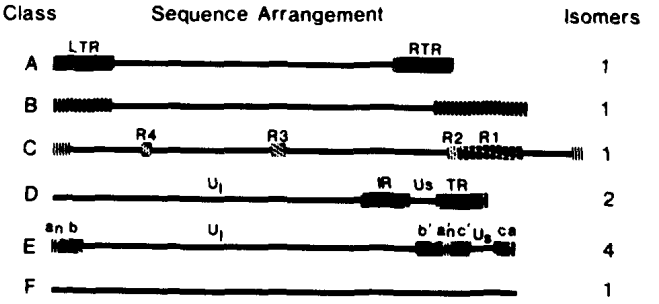

FIG. 2. A schematic diagram of the sequence arrangements in the six classes of genomes of the viruses comprising the family Herpesviridae. The genomes A, B, C, D, E, and F are exemplified by the channel catfish herpesvirus, herpesvirus saimiri, Epstein-Barr virus, varicella-zoster virus, herpes simplex viruses, and tupaia herpesvirus, respectively. In the schematic diagram, the horizontal lines represent unique or quasi-unique regions. The reiterated domains are shown as rectangles and are designated as left and right terminal repeats (LTR and RTR) for group A, repeats R1 to R4 for internal repeats of group C, and internal and terminal repeats (IR and TR) of group D. The termini of group E (e.g., HSV) consist of two elements. One terminus contains *n* copies of sequence *a* next to a larger sequence designated as *b*. The other terminus has one directly repeated *a* sequence next to a sequence designated as *c*. The terminal *ab* and *ca* sequences are inserted in an inverted orientation (denoted by primes) separating the unique sequences into long (U_L) and short (U_S) domains. Terminal reiterations in the genomes of group F have not been described. In group B, the terminal sequences are reiterated numerous times at both termini. The number of reiterations at each terminus may vary. The components of the genomes in classes D and E invert. In class D, the short component inverts relative to the long. Although rarely the long component may also invert, most of the DNA forms two populations differing in the orientation of the short component. In the class E genomes, both the short and long components can invert, and viral DNA consists of four equimolar isomers.

emplified by VZV, the sequence from one terminus is repeated in an inverted orientation internally. In these genomes, the domain consisting of the stretch of unique sequences flanked by inverted repeats (small or S component) can invert relative to the remaining sequences (large or L component) such that the DNA extracted from virions or infected cells consists of two equimolar populations differing solely in the relative orientation of the S component relative to the L component. In group E viral genomes, exemplified by those of HSV and HCMV, sequences from both termini are repeated in an inverted orientation and juxtaposed internally, dividing the genomes into two components, each of which consists of unique sequences flanked by inverted repeats. In this instance, both components can invert relative to each other, and DNA extracted from virions or infected cells consists of four equimolar populations differing in the relative orientation of the two components. The genomes comprising the F group, exemplified by that of the tupaia herpesvirus, the sequences at the two termini are not identical and are not repeated directly or in an inverted orientation.

BIOLOGIC PROPERTIES

The known herpesvirus appear to share four significant biologic properties.

1. All herpesviruses specify a large array of enzymes involved in nucleic acid metabolism (e.g., thymidine kinase, thymidylate synthetase, dUTPase, ribonucleotide reductase), DNA synthesis (e.g., DNA polymerase helicase, primase), and possibly processing of proteins (e.g., protein kinase), although the exact array of enzymes may vary somewhat from one herpesvirus to another.
2. The synthesis of viral DNAs and assembly of capsids occur in the nucleus. In the case of some herpesviruses, it has been claimed that the virus may be de-enveloped and re-enveloped as it transits through the cytoplasm. Irrespective of the merits of these conclusions, envelopment of the capsid as it transits through the nuclear membrane is obligatory.
3. Production of infectious progeny virus invariably is accompanied by the irreversible destruction of the infected cell.
4. The herpesviruses examined to date are able to remain latent in their natural hosts. In cells harboring latent virus, the viral genomes take the form of closed circular molecules, and only a small subset of viral genes is expressed.

Herpesviruses also vary greatly in their biologic properties. Some have a wide cell host range, multiply efficiently, and rapidly destroy the cells that they infect (e.g., HSV-1, HSV-2). Others have a narrow cell host range (e.g., EBV, HHV6). The multiplication of some herpesviruses appears to be slow (HCMV). Although all herpesviruses remain latent in a specific set of cells, the exact cell in which they remain latent varies from one virus to another. For example, whereas latent HSV is recovered from sensory neurons, latent EBV is recovered from B lymphocytes. Herpesviruses differ with respect to the clinical manifestations of diseases they cause.

NOMENCLATURE AND CLASSIFICATION

Current Classification

The purpose of classifying viruses into subfamilies and genera is multifold. A classification scheme often is used to depict evolutionary relatedness, but it also serves the practical purpose of enabling the laboratory worker to predict the properties and identity of a new isolate. The members of the family Herpesviridae have been classified by the Herpesvirus Study Group of the International Committee on the Taxonomy of Viruses (ICTV) into three subfamilies, the Alphaherpesvirinae, the Betaherpesvirinae, and the Gammaherpesvirinae, on the basis of biologic properties (29). The same Study Group classified a small number of herpesviruses into genera based on DNA sequence homology, similarities in genome sequence arrangement, and relatedness of important viral proteins demonstrable by immunologic methods. Although a few genes [e.g., homologs of glycoprotein B of HSV-1 (28,36) or of glycoprotein H (16)] are conserved among members of different subfamilies, nucleic acid and protein sequence homologies are particularly useful for the classification of viruses that are closely related (genera).

A formal binomial nomenclature currently is not applied. The recommendations of the ICTV Study Group is that herpesviruses be designated by serial arabic number and the family (most cases) or subfamily (for primates and some animals) in which the natural host of the virus is classified (e.g., human herpesvirus 6, cercopithecine herpesvirus 1) (Table 1).

Alphaherpesvirinae. The members of this subfamily are classified on the basis of a variable host range, relatively short reproductive cycle, rapid spread in culture, efficient destruction of infected cells, and capacity to establish latent infections primarily but not exclusively in sensory ganglia. This subfamily contains the genera *Simplexvirus* (HSV-1, HSV-2, circopithecine herpesvirus 1, bovine mammillitis virus) and *Varicellovirus* (VZV, pseudorabies virus, and equine herpesvirus 1).

Betaherpesvirinae. A nonexclusive characteristic of the members of this subfamily is a restricted host range. The reproductive cycle is long, and the infection pro-

gresses slowly in culture. The infected cells frequently become enlarged (cytomegalia), and carrier cultures are readily established. The virus can be maintained in latent form in secretory glands, lymphoreticular cells, kidneys, and other tissues. This subfamily contains the genera *Cytomegalovirus* (HCMV) and *Muromegalovirus* (murine cytomegalovirus).

Gammaherpesvirinae. The experimental host range of the members of this subfamily is limited to the family or order to which the natural host belongs. *In vitro,* all members replicate in lymphoblastoid cells, and some also cause lytic infections in some types of epithelioid and fibroblastic cells. Viruses in this group are specific for either T or B lymphocytes. In the lymphocyte, infection is frequently either at a prelytic or lytic stage but without production of infectious progeny. Latent virus frequently is demonstrated in lymphoid tissue. This subfamily contains two genera, *Lymphocryptovirus* (e.g., EBV) and *Rhadinovirus* (herpesvirus ateles and herpesvirus saimiri).

Issues and Trends in Herpesvirus Nomenclature and Classification

Current classification of herpesviruses faces two highly relevant problems.

The first issue is the definition of species. The problem arises from the observation that herpesviruses exhibit considerable genomic polymorphism. The central and vexing question is the differentiation of polymorphic variants from species. The problem is not significant in the case of viruses that differ with respect to a small number of restriction endonuclease cleavage sites or even several genes (e.g., EBV variants A and B) (19) or, at the other extreme, that differ in genome size, gene content, and biologic properties (e.g., HSV-1 and HCMV). The former do not as a rule occupy different biologic and epidemiologic niches, whereas the latter are readily differentiated in these respects. The problem is particularly significant in the case of viruses that share considerable DNA homology and some antigenic determinant sites but that are readily differentiated by unambiguous tests and differ in biologic properties. An example of the problem is the definition of the two prototype strains of HHV6, U1102 and Z29 (21,32). All of the isolates grouped as HHV6 cluster with either U1102 or Z29 (33, N. Frenkel, personal communication). Although each exhibits the polymorphism common to all herpesviruses, the clusters of viruses differ with respect to overall patterns of restriction endonuclease cleavage sites, antigenic specificity, and biologic properties even though they probably are closely related with respect to DNA homology. Although strains in both groups have been isolated from AIDS patients, most isolates from patients with roseola infantum are type Z29 rather than type U1102. The unambiguous differentiation of the two groups with respect to nucleotide sequence and biologic and epidemiologic properties suggests that they could be classified as distinct human herpesviruses (33).

The second issue concerns the classification of herpesviruses. The current classification of herpesviruses has been reviewed in detail recently (30). As it currently stands, it is at once simple, fortuitously appropriate, and defective. Its defect is that it is not based on objective criteria that serve a useful function in defining evolutionary relatedness. The availability of the complete nucleotide sequence of several herpesviruses (3,9,23) has provided a powerful incentive to review this classification. The objective criteria that are available or have been proposed for the classification of herpesvirus subfamilies are (a) conservation of genes and gene clusters (e.g., DNA polymerase, glycoproteins B, C, and H, single-strand DNA binding protein, major capsid protein) and arrangement of gene clusters relative to each other, (b) the arrangement of the terminal sequences involved in packaging of the viral genome, and (c) the presence and distribution of nucleotides that are subject to methylation (7,8,10,11,15,18,20,27). Fortuitously, most herpesviruses assigned to the three subfamilies would have been assigned to these subfamilies by most of the objective criteria. The major exceptions are the Marek's disease herpesviruses, which share biologic properties with members of the Gammaherpesvirinae but by some objective criteria (conservation and colinearity of gene clusters) would end up among the Alphaherpesvirinae (6). HHV6 is another example of a virus that should be classified by biologic criteria into the Gammaherpesvirinae and by objective criteria into the Betaherpesvirinae.

The correlation between the biologic and molecular criteria that can be applied to produce a similar clustering of viruses into subfamilies is gratifying but not necessarily reassuring. The quandary associated with the classification of Marek's disease viruses and of HHV6 is a portent of problems to come. The emphasis solely on the known genes and their conservation and relative arrangement, however, may be misplaced. The key issue is that the three subfamilies differ from each other in fundamental biologic properties, and the objective criteria that should be used to describe them should reflect these properties. In the case of Marek's disease virus, the genes conserved and colinear with those of VZV (6) are not the domains expressed during latency or in transformed cells. Delineation and evolutionary relatedness of genes responsible for biologic properties may be a more significant criterion for both evolutionary relatedness and classification than the arrangement and evolution of genes conserved throughout the family Herpesviridae, but these are not yet known. Regardless of the criteria used, evolutionary trees will inevitably grace the herpesvirus texts in the not too distant future.