

## Introduction to Virology

Scott M. Hammer, M.D.

## 'Virus'

Latin for 'slimy liquid' or 'poison'

## Landmarks in Virology

- Introduction of concept of 'filterable agents' for plant pathogens (Mayer, Ivanofsky, Beijerinck in late 1880's)
- First filterable agent from animals described – foot and mouth disease virus (Loeffler and Frosch in 1898)
- First human filterable agent described - yellow fever virus (Reed in 1901)
- Linkage of viruses with cancer (Ellerman, Bang 1908; Rous 1911)

## Definitions

- **Virus particle or virion**
  - Infectious agent composed of nucleic acid (RNA or DNA), a protein shell (capsid) and, in some cases, a lipid envelope
- **Capsid**
  - Protein coat that surrounds the viral nucleic acid
  - Composed of repeating subunits called capsomeres
  - Have either icosahedral or helical symmetry
- **Nucleocapsid**
  - Complete protein-nucleic acid complex

## Landmarks in Virology

- Description of bacteriophages (Twort and D'Herelle in 1915)
- Visualization of viruses by EM and x-ray crystallography (1939, 1941)
- Development of tissue culture systems (Sanford, Enders, Gay, Eagle 1948-1955); growth of poliovirus in culture
- Discovery of many agents; explosion in molecular biology (past 45-50 years)

## Definitions

- **Satellite or defective viruses**
  - Viruses which require a second (helper) virus for replication
    - » Example: hepatitis delta virus requires hepatitis B
- **Viroids**
  - Small, autonomously replicating molecules
  - Single stranded circular RNA, 240-375 residues in length
  - Plant pathogens
- **Prions**
  - Not viruses
  - Infectious protein molecules responsible for transmissible and familial spongiform encephalopathies
    - » e.g., Creutzfeldt-Jakob disease, bovine spongiform encephalopathy (vCJD in humans)
  - Pathogenic prion protein PrP<sup>Sc</sup> formed from normal human protein, PrP<sup>C</sup>, through post-translational processing

## Virus Classification

- Older based on
  - Host, target organ or vector
- Modern based on
  - Type of viral nucleic acid
    - » RNA or DNA
    - » Single stranded (SS) or double stranded (DS)
  - Replication strategy
  - Capsid symmetry
    - » Icosahedral or helical
  - Presence or absence of lipid envelope
- Governed by International Committee on Taxonomy of Viruses

## Virus Classification

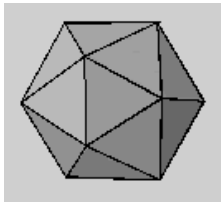
TABLE 119-3 Classification of Viruses

Family	Example	Type of Nucleic Acid	Genome Size (Kilobase or Kilobase Pairs)	Envelope	Capsid Symmetry
<b>RNA-containing viruses</b>					
Flaviviridae	Poliovirus	SS (+) RNA	7.2-8.4	No	I
Caliciviridae	Norwalk virus	SS (+) RNA	7.6-7.7	No	I
Adenoviridae	Adenovirus	SS (+) RNA	12.5-19	No	I
Togaviridae	Rubella virus	SS (+) RNA	10-17	Yes	I
Flaviviridae	Yellow fever virus	SS (+) RNA	10.2-12	Yes	Icub
Coronaviridae	Coronavirus	SS (+) RNA	26-30	Yes	Hel
Rotaviridae	Rotavirus	SS (+) RNA	11-16	Yes	Hel
Flaviviridae	DENV virus	SS (+) RNA	11	Yes	Hel
Papillomaviridae	Measles virus	SS (-) RNA	16-20	Yes	Hel
Orthomyxoviridae	Influenza virus	8 SS (-) RNA segments*	10-14	Yes	Hel
Retroviridae	California encephalitis virus	3 circular SS (ambisense) RNA segments	11-21	Yes	Hel
Herpesviridae	Epstein-Barr virus	2 circular SS (ambisense) RNA segments	10-14	Yes	Hel
Retroviridae	HIV-1	2 identical SS (+) RNA segments†	8-10	No	I
Retroviridae	Human immunodeficiency virus type 1	2 identical SS (+) RNA segments	7-11	Yes	Liquid Helicoscaped
<b>DNA-containing viruses</b>					
Herpesviridae	Hepatitis B virus	Circular DS DNA with SS proteins	3.2	Yes	I
Papillomaviridae	Human papilloma virus B-19	SS (+) or (-) DNA	5	No	I
Papillomaviridae	Human papilloma virus	Circular DS DNA	8-8	No	I
Adenoviridae	Adenovirus	Linear DS DNA	36-36	No	I
Herpesviridae	Herpes simplex virus	Linear DS DNA	130-240	Yes	I
Poixviridae	Vaccinia virus	Linear DS DNA with covalently closed ends	130-260	Yes	Complex

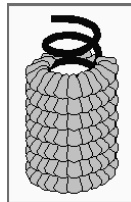
\*Includes 6' capsid proteins.  
 †Reverse transcriptase-mediated and reverse transcriptase-mediated.  
 ‡Includes 6' capsid proteins and reverse transcriptase.  
 ††Includes 6' capsid proteins and reverse transcriptase.  
 †††Includes 6' capsid proteins and reverse transcriptase.  
 ††††Includes 6' capsid proteins and reverse transcriptase.  
 †††††Includes 6' capsid proteins and reverse transcriptase.

From Principles and Practice of Infectious Diseases

## Capsid Symmetry

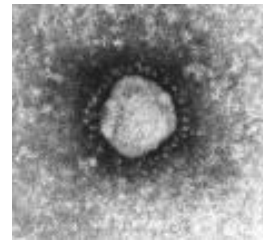


Icosahedral



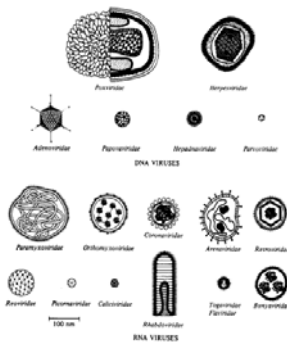
Helical

## Coronavirus



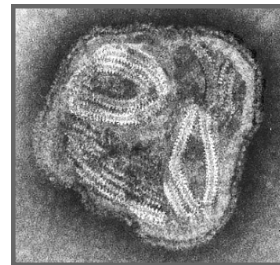
Family: Coronaviridae  
 (+) SS RNA, enveloped, helical

## Virion Morphology



From Principles and Practice of Infectious Diseases

## Paramyxovirus

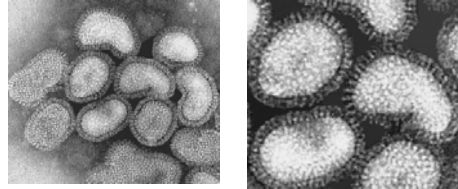


Family: Paramyxoviridae  
 (-) SS RNA, enveloped, helical

## Measles

- Measles virus is a member of the Paramyxoviridae family, genus Morbillivirus
  - Primates are the only natural hosts
- Classically a childhood illness, spread by the respiratory route
  - Primary and secondary viremia
- Incubation period is 10-14 days, followed by 2-3 day prodrome of fever, cough, coryza and conjunctivitis
  - Koplik spots in pharynx may appear
- Maculopapular rash follows
  - Temporally associated with beginning of viral clearance
  - Starts on face and behind ears; moves centrifugally
  - Typically, clinical improvement as rash resolves

## Influenza Virus



Family: Orthomyxoviridae  
(-) SS RNA segmented, enveloped, helical

## Measles

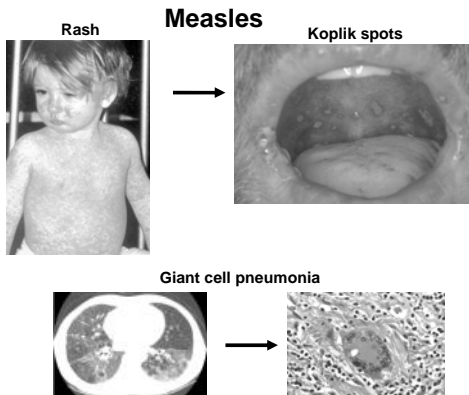
- Complications
  - Pneumonia (giant cell)
  - Encephalitis
  - Subacute sclerosing panencephalitis (SSPE)
    - Rare in vaccine era, but seen years after measles acquired at an early age (<2)
    - High titers of anti-measles Ab
  - Ocular
  - Atypical measles
    - Seen in persons exposed to natural measles virus following vaccination with killed vaccine years earlier
- Mortality can be high in malnourished and immuno-compromised populations
- Despite presence of an effective vaccine, 30 million cases reported worldwide in 2003 with 530,000 deaths
  - >95% in countries with per capita income <\$1000/yr
  - Seen in US by importation
- Vaccine preventable
  - Live attenuated vaccine

## Ebola Virus

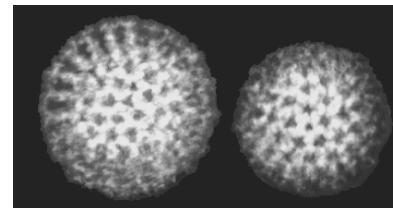


FIG. 1. Ebola virus. Unfixed diagnostic specimen from West Africa, left passage of that human blood specimen examined in the 1970s epidemic. Filamentous virus approximately 100,000 x 20,000 and parallel bundles, x400,000 by negative contrast method (London photographic).

Family: Filoviridae  
(-) SS RNA, enveloped, helical



## Rotavirus



Double Capsid      Inner Capsid

Family: Reoviridae  
DS RNA segmented, nonenveloped, icosahedral

### Retroviruses

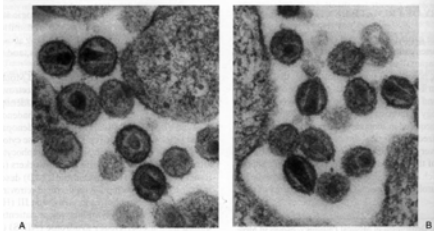
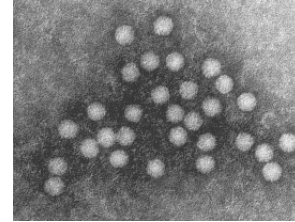


FIG. 1. Ultrastructure of primate lentiviruses. Electron microscopy of extracellular particles of HIV-1 (A) and SIVmac (B) reveals virions, about 110 nm in diameter, with a cone-shaped nucleoid surrounded by a lipid bilayer membrane, which contains envelope glycoprotein spikes ( $\times 100,000$ ).

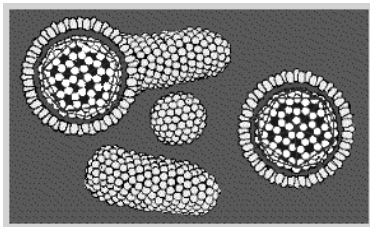
Family: Retroviridae  
2 identical (+) RNA strands, enveloped,  
icosahedral capsid, helical nucleoprotein

### Parvovirus



Family: Parvoviridae  
SS DNA, nonenveloped, icosahedral

### Hepatitis B Virus



Family: Hepadnaviridae  
Circular DS DNA with SS portions,  
enveloped, icosahedral

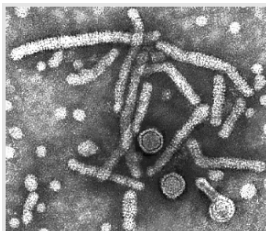
### B19 Parvovirus: Erythema Infectiosum



Plate 8-14

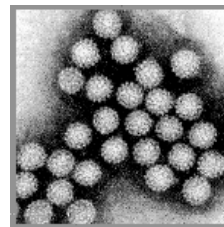
From *Clinical Virology*

### Hepatitis B Virus



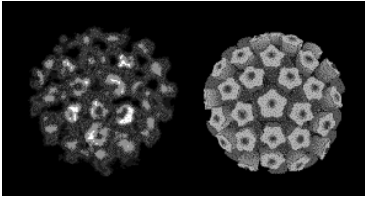
Family: Hepadnaviridae  
Circular DS DNA with SS portions,  
enveloped, icosahedral

### Papillomavirus



Family: Papovaviridae  
Circular DS DNA, nonenveloped, icosahedral

### Papillomavirus



Family: Papovaviridae  
Circular DS DNA, nonenveloped, icosahedral

### Genital Warts



Plate 8-1

From *Clinical Virology*

### Cutaneous Wart

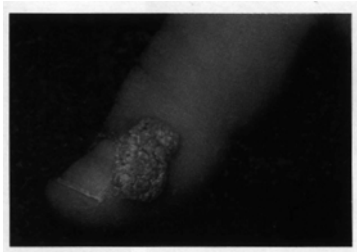
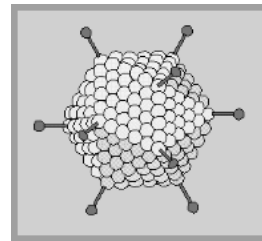


Plate 27-2

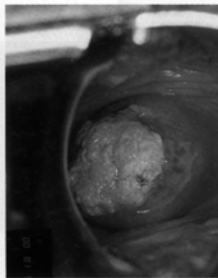
From *Clinical Virology*

### Adenovirus



Family: Adenoviridae  
Linear DS DNA, nonenveloped, icosahedral

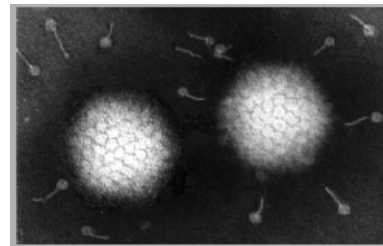
### Cervical Wart



From *Clinical Virology*

Plate 27-8

### Adenovirus



Family: Adenoviridae  
Linear DS DNA, nonenveloped, icosahedral

### Adenovirus Conjunctivitis

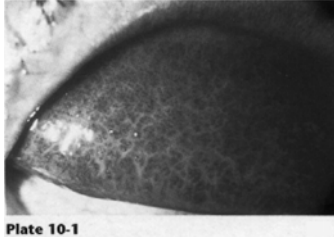


Plate 10-1

From *Clinical Virology*

### Herpes Simplex Virus Keratitis

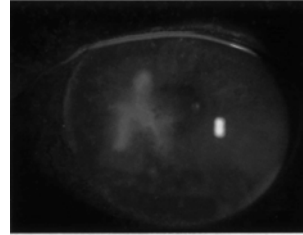


Plate 10-4

From *Clinical Virology*

### Adenovirus Tonsillitis



Plate 25-1

From *Clinical Virology*

### Cytomegalovirus Retinitis

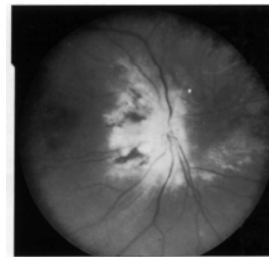
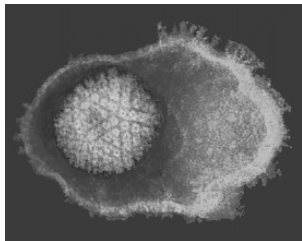


Plate 10-7

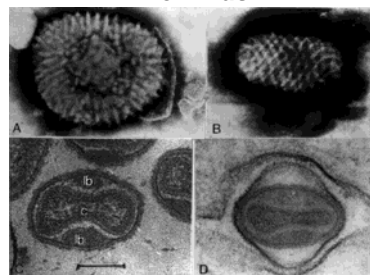
From *Clinical Virology*

### Herpesvirus



Family: **Herpesviridae**  
Linear DS DNA, enveloped, icosahedral

### Poxvirus



A and C: Fowl pox. Negative stains and thin sections  
B and D: Orf virus  
Courtesy of F. Fenner

Family: **Poxviridae**  
Linear DS DNA, enveloped, complex

### Smallpox



### Pathogenetic Steps in Human Viral Infection

- Virus may enter through skin, mucous membranes, respiratory tract, GI tract, via transfusion, needle-stick, or maternal-fetal transmission
- Local replication at site of inoculation
  - Certain agents may cause pathology here
- Neurotropic agents may travel along nerve routes or reach CNS by viremic spread

### Viral Pathogenesis: Elements of Virus-Host Interaction

- Viral strain
- Inoculum size
- Route of exposure
- Susceptibility of host
  - Is there pre-existent immunity from past exposure or vaccination?
  - Host genetic factors
- Immune status and age of host

### Pathogenetic Steps in Human Viral Infection

- For many agents, there is replication in regional lymph nodes with subsequent viremia and spread to target organs
  - Some travel free in plasma (e.g., picornaviruses); some are cell associated (e.g., cytomegalovirus)
- Replication in target organs may lead to local damage and further viremia
- Non-specific and virus-specific host immune responses come into play to downregulate viral replication

### Viral Pathogenesis: Net Result of Virus-Host Interaction

- No infection
- Abortive infection with limited viral replication
- Asymptomatic infection
- Symptomatic infection
- Persistent, latent or self-limited infection
  - Depending upon the agent and immune competence of host
- Influenced by availability of effective prophylaxis or therapy

### Immune Response to Viral Infections

- Non-specific immunity
  - Phagocytic cells (neutrophils and monocyte-macrophages)
  - Cytokines (e.g., interferons) and chemokines
  - Natural killer cells
  - Other 'antiviral' factors
- Specific immunity
  - Antigen specific B and T cell responses
    - » Antibodies
    - » Cytotoxic T cells
    - » Antibody dependent cellular cytotoxicity
- Immunopathologic injury

### Viral Persistence

- **Viruses may cause chronic, persistent infection in the face of an immune response**
  - HIV, hepatitis B, hepatitis C
- **Immune compromise may result in persistent infection where latency or elimination may have otherwise occurred**
  - Herpesviruses, papillomaviruses, rubella virus

### Viral Persistence

- **Sites**
  - Nervous system
    - » Herpes simplex virus, varicella-zoster virus
    - » JC virus
    - » Measles virus
  - Liver
    - » Hepatitis B virus, hepatitis C virus, hepatitis D virus
  - Leukocytes
    - » HIV, cytomegalovirus, Epstein-Barr virus
  - Epithelial tissue
    - » Papillomaviruses

### Viral Persistence

- **Some viruses cause latent infection**
- **Latency is characterized by a quiescent or minimally transcriptionally active viral genome with potential periods of reactivation**
  - Herpesviruses
  - Human retroviruses
  - Human papillomaviruses
- **Viruses which exhibit latency may also exhibit chronic, persistent infection in the setting of immune compromise**

### Oncogenesis: Associations

- Epstein-Barr virus with lymphoma, nasopharyngeal carcinoma and leiomyosarcoma
- Herpesvirus 8 with Kaposi's sarcoma and body cavity B-cell lymphoma
- Hepatitis B and C viruses with hepatocellular carcinoma
- Human papillomavirus with cervical cancer and anogenital carcinoma
- HIV with Kaposi's sarcoma and lymphoma via immunosuppression

### Viral Persistence

- **Mechanisms**
  - **Persistent/chronic infection**
    - » Antigenic variation to escape antibody or CTL responses
    - » Downregulation of class I major histocompatibility antigens
    - » Modulation of apoptosis
    - » Privileged sites
  - **Latency**
    - » Decreased viral antigen expression and presentation to the immune system

### Diagnosis of Viral Infections

- **Clinical suspicion**
  - Is syndrome diagnostic of a specific entity?
  - Is viral disease in the differential diagnosis of a presenting syndrome?
- **Knowledge of appropriate specimen(s) to send**
  - Blood
  - Body fluids
  - Lesion scraping
  - Tissue
  - Proper transport is essential

### **Diagnosis of Viral Infections**

- Isolation of virus in tissue culture, animals, embryonated eggs
- Antigen detection in body fluids, blood, lesion scrapings, or tissue
- Nucleic acid detection in body fluids, blood or tissues
- Antibody detection
  - Presence of IgM or 4-fold rise in IgG titer
- Tissue biopsy for light microscopy supplemented by antigen and/or nucleic acid detection
- Electron microscopy of body fluids or tissues

### **Viral Infections: Prevention and Therapy**

- Vaccines
  - One of the most significant advances in human health
    - » Eradication of smallpox is prime example
  - Effective vaccines exist for polio, mumps, measles, rubella, influenza, hepatitis A, hepatitis B, varicella-zoster, rabies, adenovirus, Japanese B encephalitis, yellow fever, smallpox
- Immune globulin for prevention or amelioration of clinical disease
  - Varicella-zoster immune globulin, rabies immune globulin, cytomegalovirus immune globulin, respiratory syncytial virus immune globulin (and monoclonal Ab), immune serum globulin for hepatitis A

### **Viral Infections: Prevention and Therapy**

- Blood screening
  - HIV, hepatitis B, hepatitis C, CMV (in certain settings)
- Safe sexual practices
  - HIV, hepatitis B, HSV, and human papillomavirus infections
- Specific antiviral therapy
  - Herpes simplex virus, varicella-zoster virus, cytomegalovirus, HIV, influenza virus, respiratory syncytial virus, hepatitis B and hepatitis C