Introduction to Virology

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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)

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 50+ years)

'Virus'

Latin for 'slimy liquid' or 'poison'

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

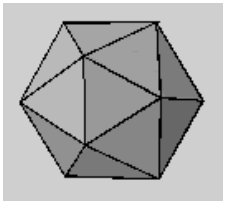
Definitions

- 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^{Sc} formed from normal human protein, PrP^{C}, through post-translational processing

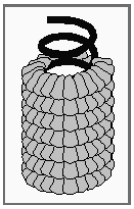
Virus Classification

- **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 symmety**
    - » **Icosahedral or helical**
  - **Presence or absence of lipid envelope**
- **Governed by International Committee on Taxonomy of Viruses**

Capsid Symmetry

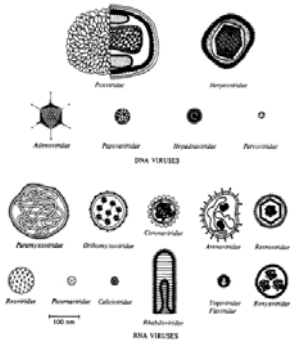


Icosahedral



Helical

Virion Morphology



From ***Principles and Practice of Infectious Diseases***

Virus Classification

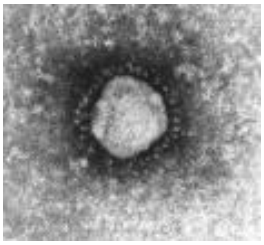
TABLE 119-1 Classification of Viruses

Family	Example	Type of Nucleic Acid	Genome Size (Kilobases or Kilobase Pairs)	Envelope	Capsid Symmetry
RNA-containing viruses					
Picornaviridae	Poliovirus	SS (+) RNA	7.2–8.4	No	I
Caliciviridae	Norwalk virus	SS (+) RNA	7.4–7.7	No	I
Astroviridae	Astrovirus	SS (+) RNA	7.2–7.9	No	I
Togaviridae	Rubella virus	SS (+) RNA	10–12	Yes	I
Flaviviridae	Yellow fever virus	SS (+) RNA	9.3–13	Yes	Unk
Coronaviridae	Coronavirus	SS (+) RNA	20–30	Yes	H
Rhabdoviridae	Rabies virus	SS (−) RNA	13–16	Yes	H
Filoviridae	Ebola virus	SS (−) RNA	19	Yes	H
Paramyxoviridae	Measles virus	SS (−) RNA	16–20	Yes	H
Orthomyxoviridae	Influenza virus	8 SS (−) RNA segments*	10–14	Yes	H
Bunyaviridae	California encephalitis virus	3 circular SS (ambisense) RNA segments	11–21	Yes	H
Arenaviridae	Lymphocytic choriomeningitis virus	2 circular SS (ambisense) RNA segments	10–14	Yes	H
Reoviridae	Rotavirus	10–12 DS RNA segments†	16–27	No	I
Retroviridae	Human immunodeficiency virus type 1	2 identical SS (+) RNA segments	7–11	Yes	I-capsid H-nucleocapsid
DNA-containing viruses					
Hepadnaviridae	Hepatitis B virus	Circular DS DNA with SS portions	3.2	Yes	I
Parvoviridae	Human parvovirus B-19	SS (+) or (−) DNA	5	No	I
Papovaviridae	Human papillomavirus	Circular DS DNA	5–8	No	I
Adenoviridae	Adenovirus	Linear DS DNA	36–38	No	I
Herpesviridae	Herpes simplex virus	Linear DS DNA	120–240	Yes	I
Poxviridae	Vaccinia virus	Linear DS DNA with covalently closed ends	130–380	Yes	Complex

*Influenza C virus: seven segments.
†Reovirus: mammalian reovirus and orbivirus: 10 segments; rotavirus: 11 segments; Colorado tick fever virus: 12 segments.
Abbreviations: DS, Double stranded; H, helical; I, icosahedral; SS, single stranded; Unk, unknown; (+), message sense; (−), complement of message sense.
Data from Murphy and Kingsbury.[1]

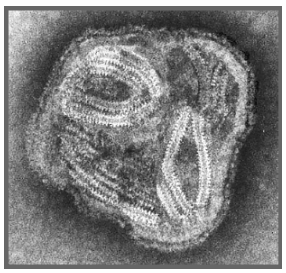
From ***Principles and Practice of Infectious Diseases***

Coronavirus



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

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

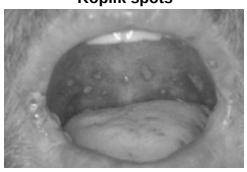
Measles

- 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 or in unvaccinated persons
- Vaccine preventable
  - Live attenuated vaccine

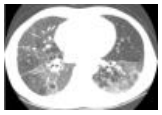
Measles

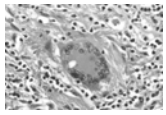
Rash

Koplik spots

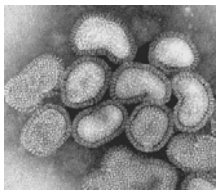


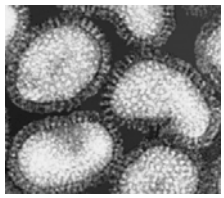
Giant cell pneumonia





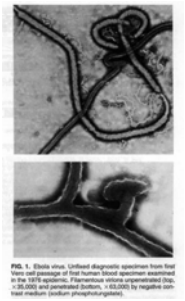
Influenza Virus





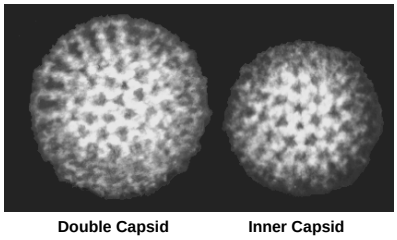
Family: Orthomyxoviridae
(-) SS RNA segmented, enveloped, helical

Ebola Virus



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

Rotavirus



Double Capsid Inner Capsid

Family: Reoviridae
DS RNA segmented, nonenveloped, icosahedral

Retroviruses

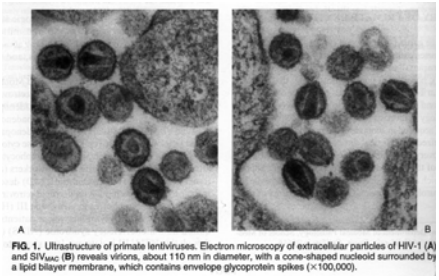
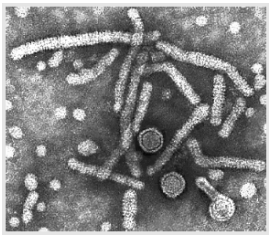


FIG. 1. Ultrastructure of primate lentiviruses. Electron microscopy of extracellular particles of HIV-1 (A) and SIV_{MAC} (B) reveals virions, about 110 nm in diameter, with a cone-shaped nucleoid surrounded by a lipid bilayer membrane, which contains envelope glycoprotein spikes (×100,000).

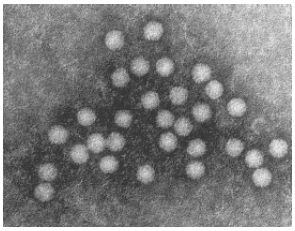
Family: Retroviridae
2 identical (+) RNA strands, enveloped, icosahedral capsid, helical nucleoprotein

Hepatitis B Virus



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

Parvovirus



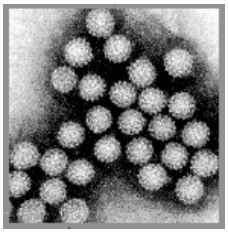
Family: Parvoviridae
SS DNA, nonenveloped, icosahedral

B19 Parvovirus: Erythema Infectiosum

Plate 8-14

From *Clinical Virology*

Papillomavirus



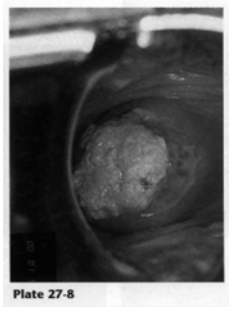
Family: Papovaviridae
Circular DS DNA, nonenveloped, icosahedral

Cutaneous Wart

Plate 27-2

From *Clinical Virology*

Cervical Wart



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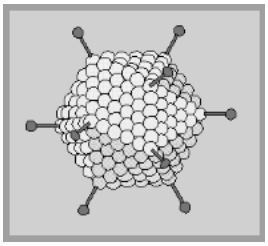
Genital Warts

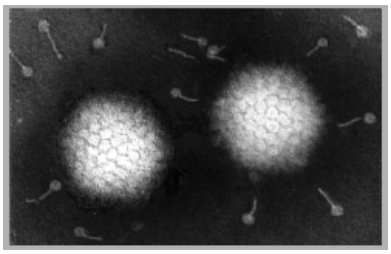
From *Clinical Virology*

Adenovirus



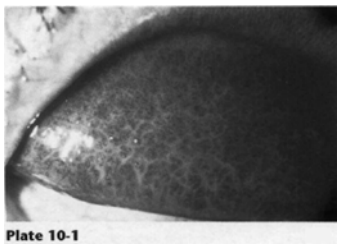
Family: Adenoviridae
Linear DS DNA, nonenveloped, icosahedral

Adenovirus



Family: Adenoviridae
Linear DS DNA, nonenveloped, icosahedral

Adenovirus Conjunctivitis



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Adenovirus Tonsillitis

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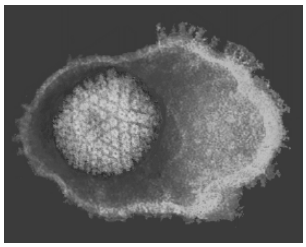
Herpesvirus



Family: Herpesviridae
Linear DS DNA, enveloped, icosahedral

Herpes Simplex Virus Keratitis

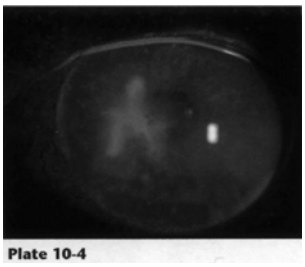


Plate 10-4

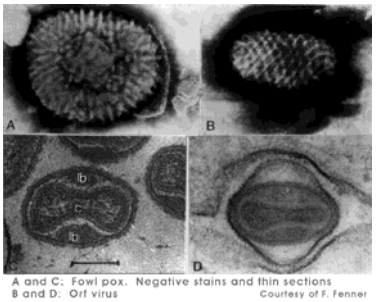
From *Clinical Virology*

Cytomegalovirus Retinitis

Plate 10-7

From *Clinical Virology*

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

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**

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

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

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

Immune Response to Viral Infections

- Innate (non-specific) immunity
  - Phagocytic cells (neutrophils and monocyte-macrophages)
  - Cytokines (e.g., interferons) and chemokines
  - Natural killer cells
  - Other 'antiviral' factors
- Adaptive (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

- 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

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

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

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

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, human papillomavirus
- 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 palivizumab, 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**