

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 45-50 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

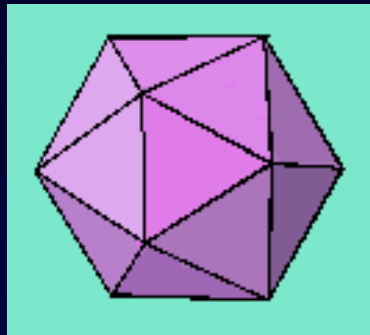
Definitions

- **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

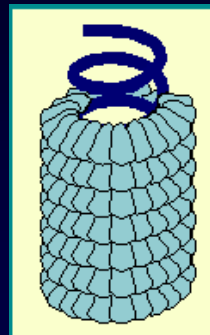
Virus Classification

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

Capsid Symmetry

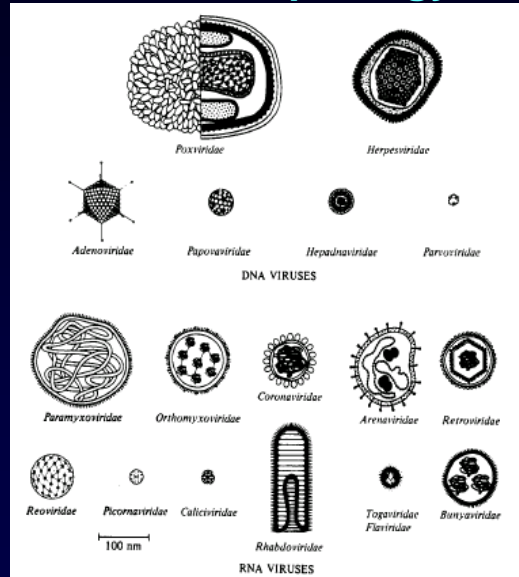


Icosahedral



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	9.5-13	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
Bunyviridae	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
Papoviridae	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.

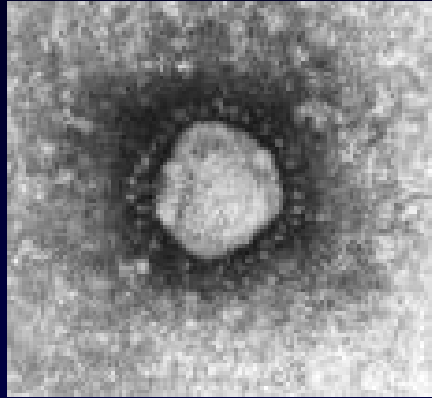
†Reovirus, mammalian reovirus and orbivirus: 10 segments; rotavirus: 11 segments; Colorado tick fever virus: 12 segments.

Abbreviations: DS, Double stranded; H, helical; I, icosahedral; SS, single stranded; Unk, unknown; (+), message sense; (-), complement of message sense.

Data from Murphy and King, 1974.

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
- Vaccine preventable
 - Live attenuated vaccine

Measles

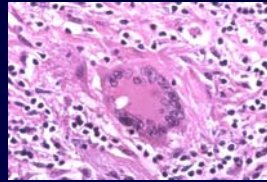
Rash



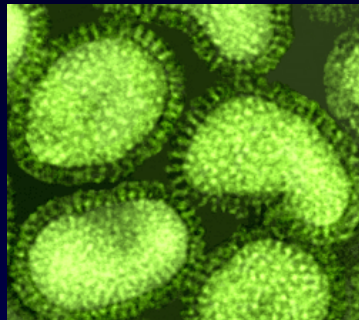
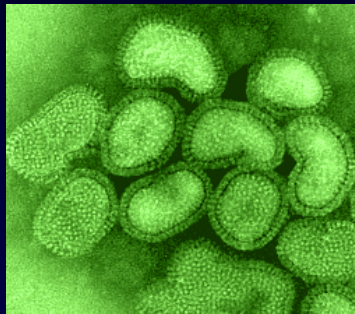
Koplik spots



Giant cell pneumonia

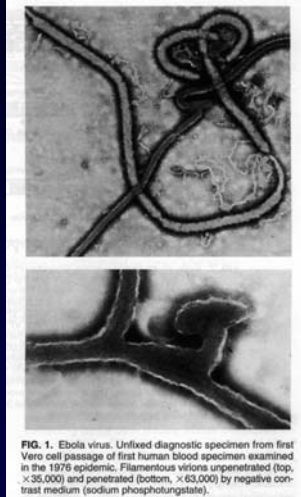


Influenza Virus



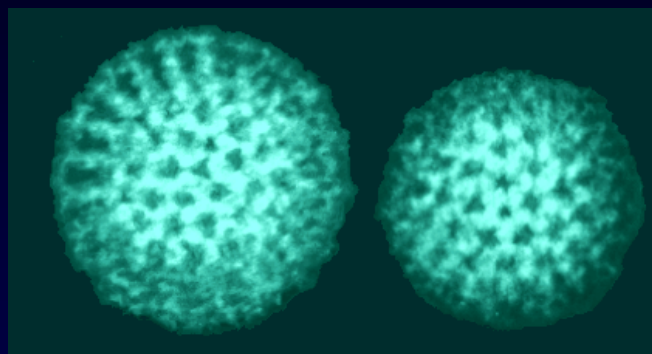
Family: Orthomyxoviridae
(-) SS RNA segmented, enveloped, helical

Ebola Virus



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

Rotavirus



Family: Reoviridae
DS RNA segmented, nonenveloped, icosahedral

Retroviruses

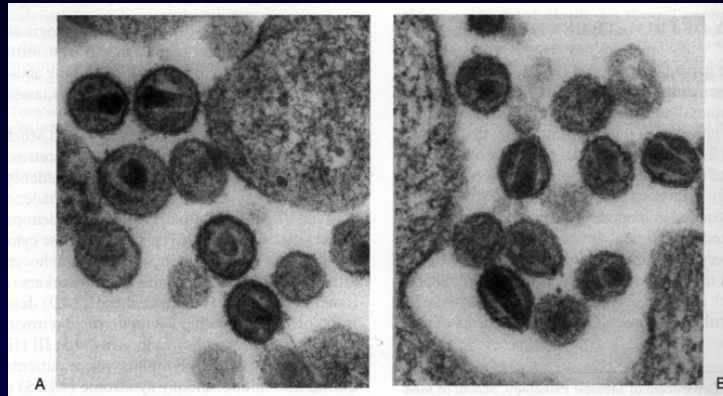
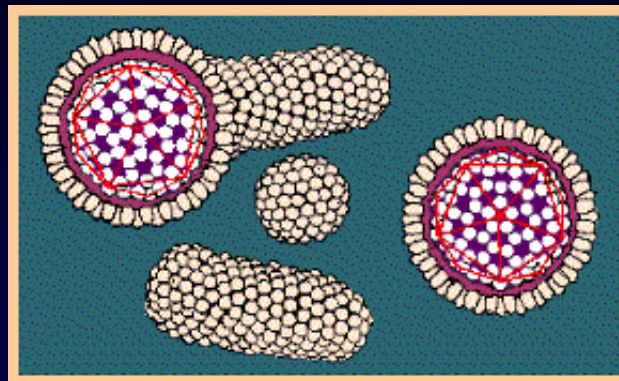


FIG. 1. Ultrastructure of primate lentiviruses. Electron microscopy of extracellular particles of HIV-1 (A) and SIV_{MAC} (B) reveals virions, about 110 nm in diameter, with a cone-shaped nucleoid surrounded by a lipid bilayer membrane, which contains envelope glycoprotein spikes ($\times 100,000$).

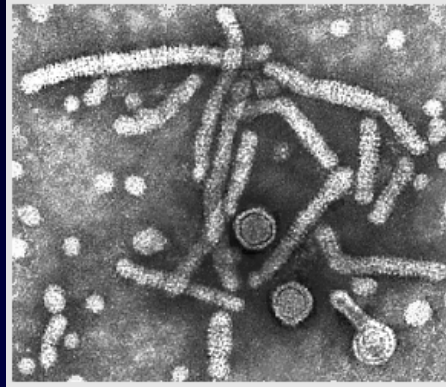
Family: Retroviridae
2 identical (+) RNA strands, enveloped,
icosahedral capsid, helical nucleoprotein

Hepatitis B Virus



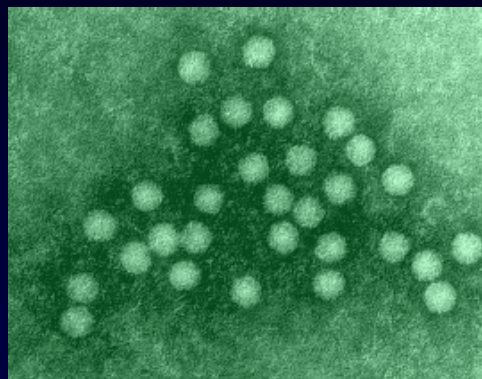
Family: Hepadnaviridae
Circular DS DNA with SS portions,
enveloped, icosahedral

Hepatitis B Virus



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

Parvovirus



Family: Parvoviridae
SS DNA, nonenveloped, icosahedral

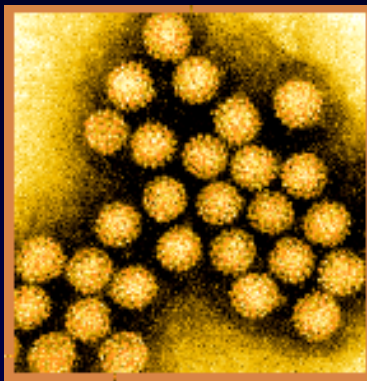
B19 Parvovirus: Erythema Infectiosum



Plate 8-14

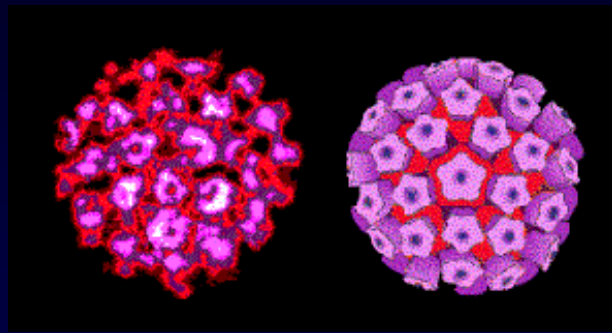
From *Clinical Virology*

Papillomavirus



Family: Papovaviridae
Circular DS DNA, nonenveloped, icosahedral

Papillomavirus



Family: Papovaviridae
Circular DS DNA, nonenveloped, icosahedral

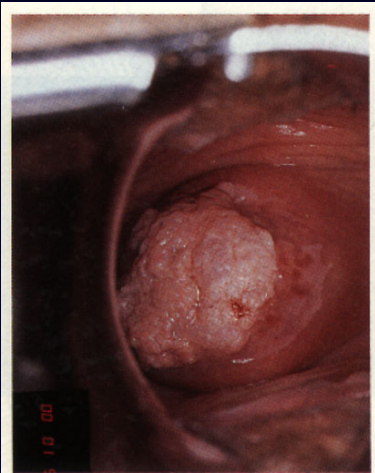
Cutaneous Wart



Plate 27-2

From *Clinical Virology*

Cervical Wart



From *Clinical Virology*

Plate 27-8

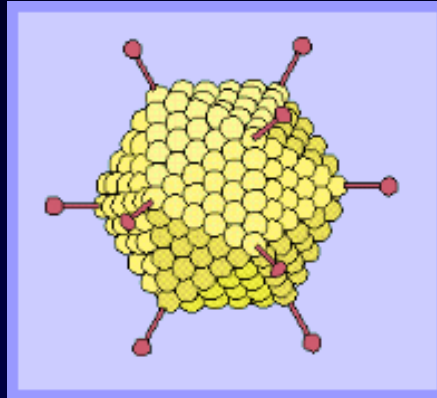
Genital Warts



Plate 8-1

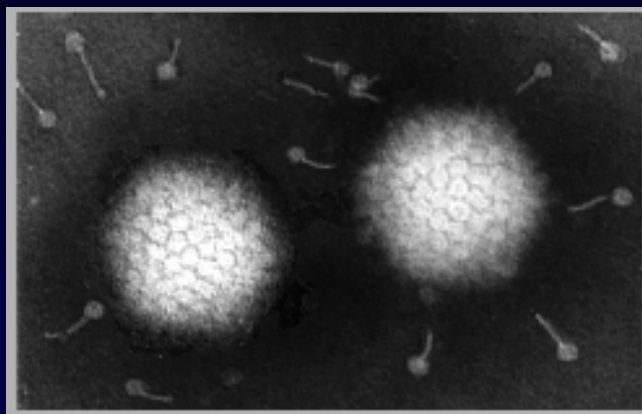
From *Clinical Virology*

Adenovirus



Family: Adenoviridae
Linear DS DNA, nonenveloped, icosahedral

Adenovirus



Family: Adenoviridae
Linear DS DNA, nonenveloped, icosahedral

Adenovirus Conjunctivitis

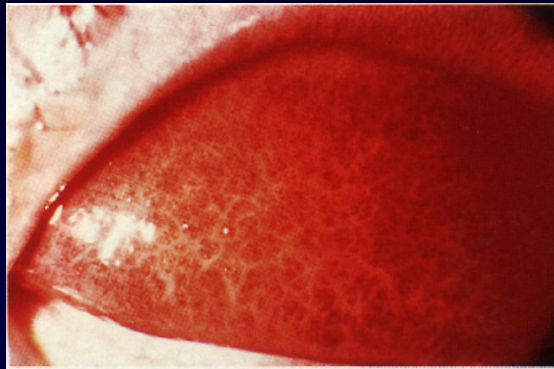


Plate 10-1

From Clinical Virology

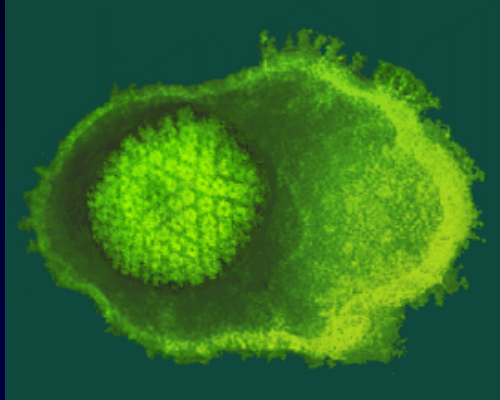
Adenovirus Tonsillitis



Plate 25-1

From Clinical Virology

Herpesvirus



Family: Herpesviridae
Linear DS DNA, enveloped, icosahedral

Herpes Simplex Virus Keratitis

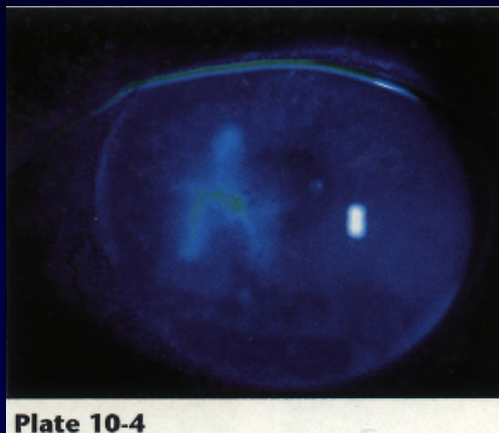


Plate 10-4

From *Clinical Virology*

Cytomegalovirus Retinitis

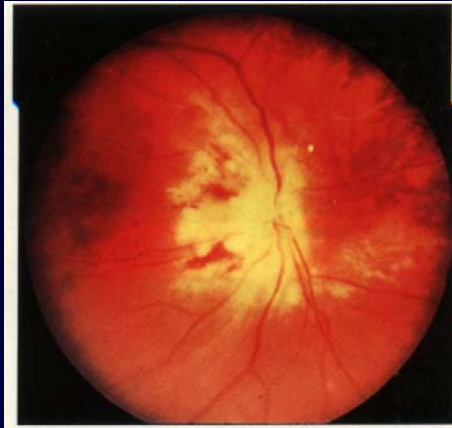
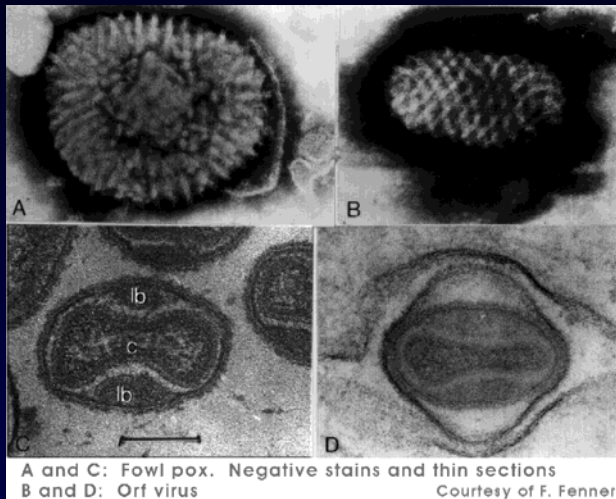


Plate 10-7

From *Clinical Virology*

Poxvirus



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

- 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

- **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
- 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