

Introduction to Virology

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'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 50+ years)

Definitions

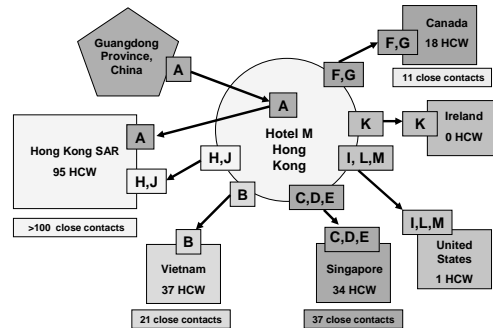
- **Satellite or defective viruses**
 - Viruses which require a second (helper) virus for replication
 - » Example: hepatitis delta virus requires hepatitis B
- **Viroids**
 - Small, autonomously replicating molecules
 - Single stranded circular RNA, 240-375 residues in length
 - Plant pathogens
- **Prions**
 - 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^{Sc} formed from normal human protein, PrP^C, through post-translational processing

Coronavirus



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

Spread from Hotel M Reported as of March 28, 2003



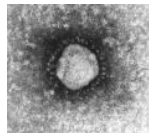
SARS

- Etiology:
 - Newly described coronavirus
 - » Fully sequenced by two groups within a few weeks after isolation
- Origin
 - Perhaps cross-species infection and viral recombination
- Power of information and laboratory technologies highlighted by this outbreak
- Globalization of infectious disease outbreaks and economic impact also highlighted

SARS - 2003

- Human cases date back to November 2002 in China
- Local chains of transmission reported in mainland China, Hong Kong, Taiwan, Hanoi, Singapore, Toronto, UK and US
- 8,096 cases in 29 countries
- 774 deaths
 - Case fatality rate 9.6%

Coronavirus



- Member of the Coronaviridae family
- Pleomorphic 100-150 nm particle with characteristic surface projections
 - Single stranded, (+) sense RNA genome (27-32 kb)
 - Cytoplasmic replication
 - Viral assembly in Golgi apparatus and endoplasmic reticulum
- Infects multiple species
 - Chickens, turkeys, mice, rats, cats, dogs, rabbits, cattle, pigs and humans
- In humans
 - Before SARS – clinical expression was mild respiratory disease in healthy persons
 - Gastrointestinal disease?
- Respiratory illness has been seasonal
 - Peaks in winter and spring
- In volunteer studies
 - Virus shed for 48 h after inoculation and continues for approx. 5 d

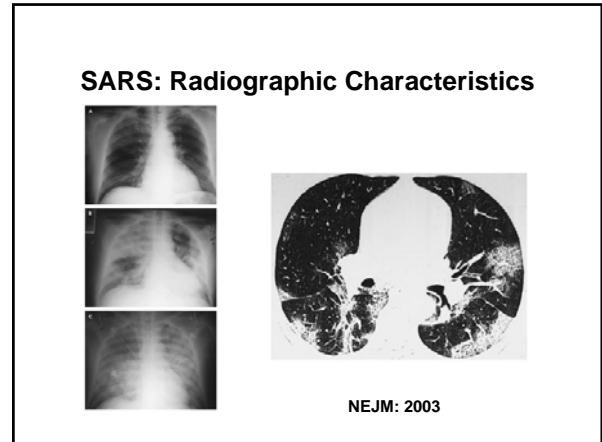
SARS: ?Origin

Guangzhou Food Market

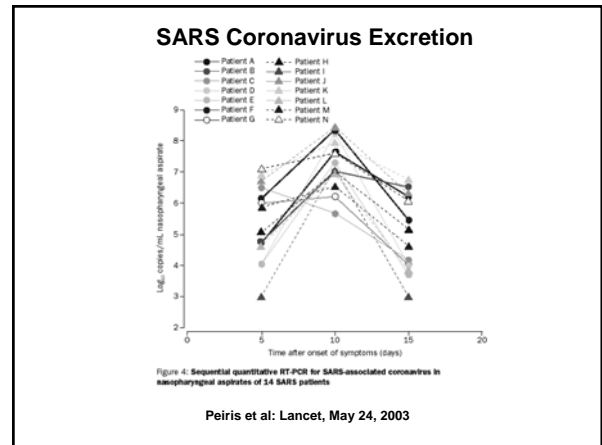


Civet

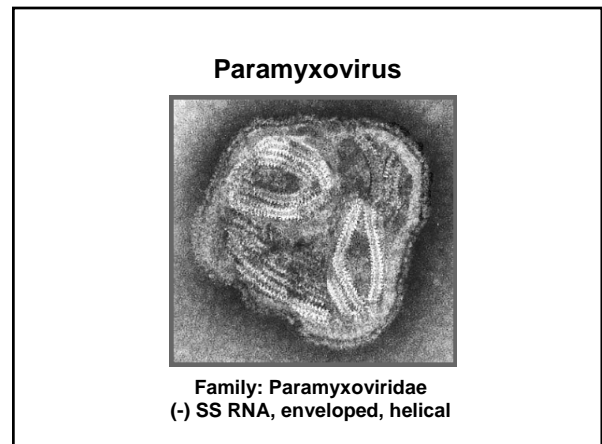




- ### SARS: Clinical Description
- Incubation period 2 – 7 days
 - Maybe as long as 10 days
 - Illness begins with prodrome of fever
 - Chills, headache, malaise, myalgia, diarrhea may also be present
 - Next phase: dry cough and/or shortness of breath
 - In 10-20% disease may be rapidly progressive and require mechanical ventilation
 - Chest films: normal → focal interstitial infiltrates → more generalized infiltrates → consolidation and ARDS
 - Lymphopenia, thrombocytopenia, elevated CPK and hepatic enzymes may be seen
 - Treatment is supportive
 - Full spectrum of disease unknown



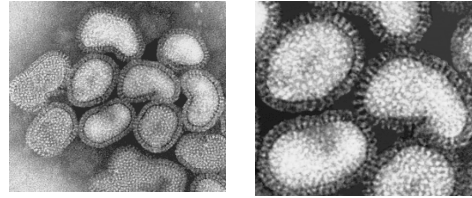
- ### SARS: Diagnosis
- Clinical suspicion
 - Particularly in a traveler from an endemic region or someone exposed to a possible/probable case
 - Laboratory
 - Still investigational
 - Sputum, blood and body fluids for viral cultures and PCR
 - Antibody
 - » May not be positive for up to 28 days



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 or in unvaccinated persons
- Vaccine preventable
 - Live attenuated vaccine

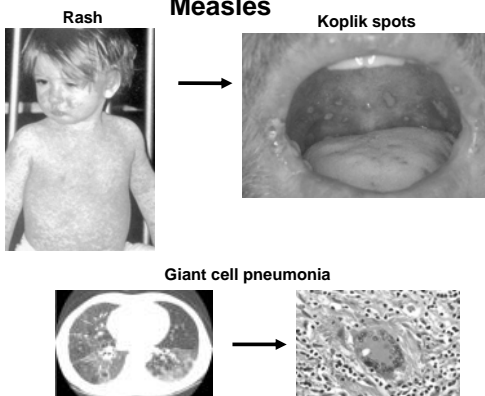
Ebola Virus



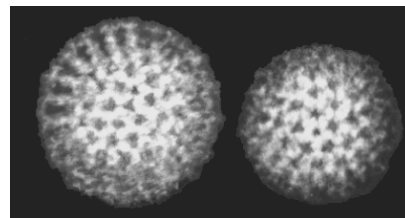
FIG. 1. Ebola virus. Unfixed diagnostic specimen from first case, and passage of first human-to-human acquisition, acquired in the 1976 epidemic. *Papio anubis* (immunoprecipitated 20k, x 25,000) and parainfluenza 2 (20k, x 60,000) by negative electron microscopy (courtesy photograph.com).

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

Measles



Rotavirus



Family: Reoviridae
DS RNA segmented, nonenveloped, icosahedral

Retroviruses

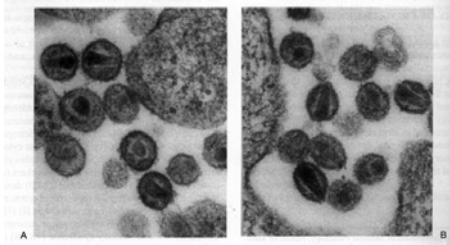


FIG. 1. Ultrastructure of primate lentiviruses. Electron microscopy of extracellular particles of HIV-1 (A) and SIVmac (B) reveals virions, about 110 nm in diameter, with a cone-shaped nucleoid surrounded by a lipid bilayer membrane, which contains envelope glycoprotein spikes ($\times 100,000$).

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

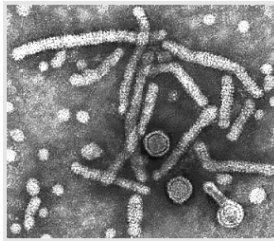
B19 Parvovirus: Erythema Infectiosum



Plate 8-14

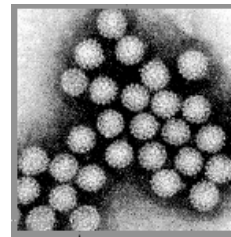
From *Clinical Virology*

Hepatitis B Virus



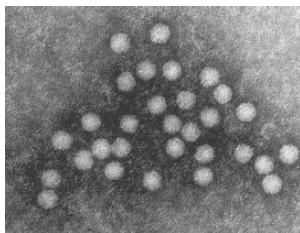
Family: Hepadnaviridae
Circular DS DNA with SS portions,
enveloped, icosahedral

Papillomavirus



Family: Papovaviridae
Circular DS DNA, nonenveloped, icosahedral

Parvovirus



Family: Parvoviridae
SS DNA, nonenveloped, icosahedral

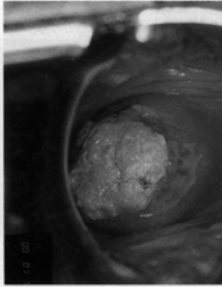
Cutaneous Wart



Plate 27-2

From *Clinical Virology*

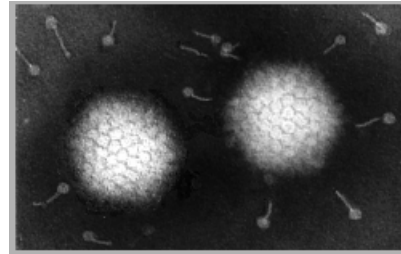
Cervical Wart



From *Clinical Virology*

Plate 27-8

Adenovirus



Family: Adenoviridae
Linear DS DNA, nonenveloped, icosahedral

Genital Warts

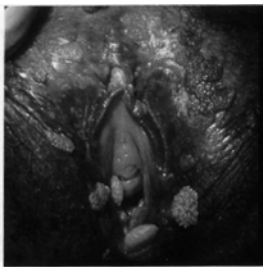


Plate 8-1

From *Clinical Virology*

Adenovirus Conjunctivitis

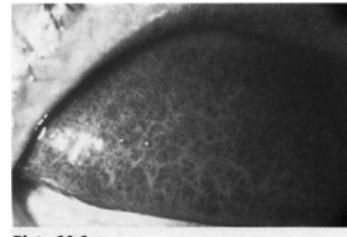
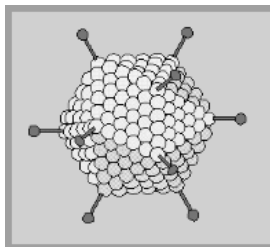


Plate 10-1

From *Clinical Virology*

Adenovirus



Family: Adenoviridae
Linear DS DNA, nonenveloped, icosahedral

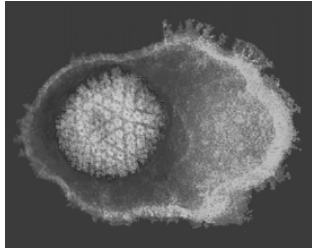
Adenovirus Tonsillitis



Plate 25-1

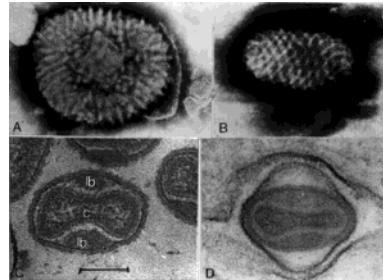
From *Clinical Virology*

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

Herpes Simplex Virus Keratitis

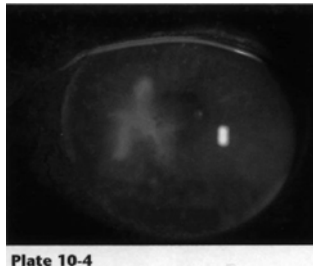


Plate 10-4

From *Clinical Virology*

Smallpox



Cytomegalovirus Retinitis

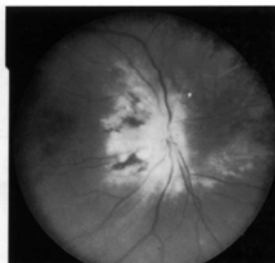


Plate 10-7

From *Clinical Virology*

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

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**

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 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

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 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

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

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

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**

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 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-1, HIV-2, HBV, HCV, HTLV-1, HTLV-2
 - In certain settings
 - » West Nile Virus
 - » CMV
- **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