Chapter 29

DNA viruses (contd)

Poxviruses

The poxvirus family includes **three** viruses of medical importance:

1. **smallpox virus**
2. **vaccinia virus**
3. **molluscum contagiosum virus (MCV)**

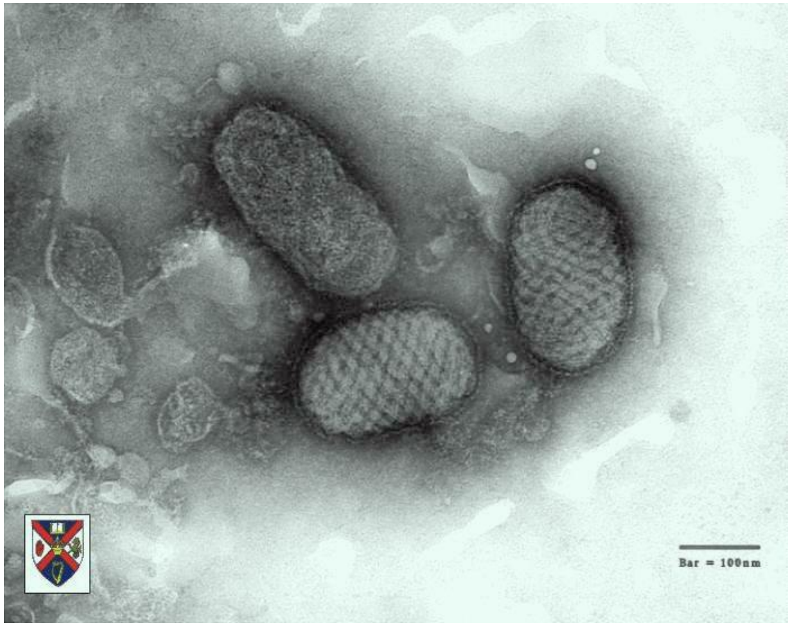
Poxviruses are the **largest** and **most complex viruses**.

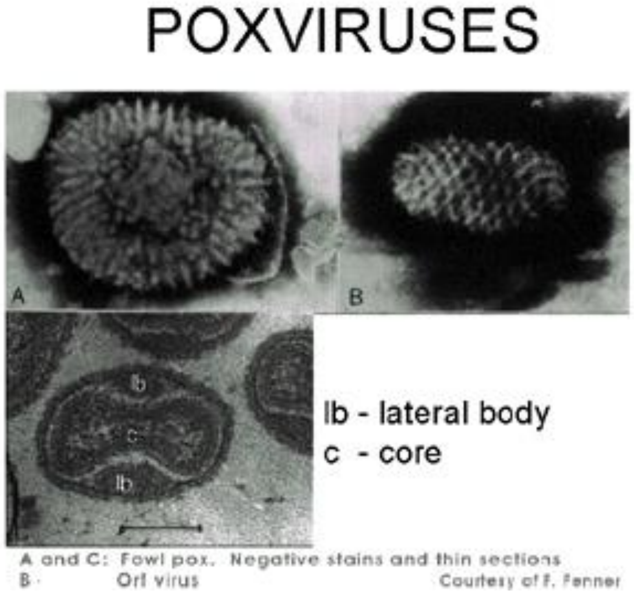
Smallpox virus

Structure

Poxviruses are **brick-shaped (240 nm by 300 nm**) and have a complex internal structure including a **double-stranded DNA genome** (130–260 kb) and associated enzymes.

Naturally released virions have an **additional outer membrane** not found on infective virions extracted artificially from infected cells.





Clinical Manifestations

Smallpox or **variola virus** **has been eradicated from the face of earth by use of vaccine.**

After an incubation period of **7-14 days**, there is a sudden onset of prodromal symptoms such as **fever** and **malaise**.

This is **followed by the rash**, which is **worse on the face and extremities** than on the trunk (**centrifugal distribution**).

The rash evolves through stages from **macules to papules, vesicles, pustules and finally crests** in 2-3 weeks.

Pathogenesis

-- Infection is usually caused by **invasion through broken skin** and in most cases remains **localized**.

-- **Smallpox** is acquired by **contact or by airborne transmission** to the **respiratory mucosa.**

-- **Initial viremia** during the incubation period **spreads infection to internal organs**.

-- A **second viremia** then spreads the **virus to the skin**.

Multiplication

-- **Poxvirus replication** takes place in **cytoplasmic inclusions**.

-- Infecting virions are **partly uncoated by cellular enzymes** and then **fully uncoated by viral enzymes** released from the virion core.

-- The viral DNA is **not infectious per se**, and other core enzymes (including a DNA-dependent RNA polymerase) play essential roles in the replication cycle.

-- The replication cycle can be divided into **functions controlled by early (prereplicative) gene products** and those **controlled by late (postreplicative) gene products.**

-- Most virions (80 to 90%) **remain within cells** and therefore **lack the outer envelope** found on naturally released virions.

-- They **acquire their envelopes by budding from the cell membrane** as they are released from the cell.

-- **All steps occur in the cytoplasm which is unusual for a DNA virus.**

Pathogenesis and Immunity

-- Smallpox begins when the **virus infects the upper respiratory tract** and **local lymph nodes** and then **enters the blood (primary viremia).**

-- **Internal organs are infected**; then the virus **reenters the blood (secondary viremia) and spreads to the skin.**

-- These events occur during incubation period when the patient is still well.

-- The **rash is the result of virus replication in skin**, followed by **damage caused by cytotoxic T cells attacking infected cells.**

-- Immunity following **disease is life long;** immunity following **vaccination lasts 10 years.**

Transmission and epidemiology

-- Smallpox virus is **transmitted via respiratory aerosol or by direct contact with virus** either in the skin lesions or on fomites such as bedding.

-- Smallpox killed **millions every year** before vaccination.

-- **Last naturally occurring case was in Somalia in 1972.**

Laboratory Diagnosis

-- In the past when disease occurred, the diagnosis was made either by **growing the virus in cell culture** or **chick embryo**.

-- Or by detecting **viral antigens in vasicular fluid by immunofluorescence**.

Prevention

-- The vaccine contains **live attenuated vaccinia virus**.

-- It was **successful** because there is **only one stable serotype**, **humans are the only host, antibody response is prompt, disease is easily recognized clinically** and there is **no carrier state**.

-- The vaccine is inoculated **intradermally.**

-- **Formation of a vesicle** is indicative of **successful vaccination**.

Hepadnaviruses

-- These are **double shelled viruses** (**42nm**) with an **icosahedral capsid covered by an envelope.**

-- **Circular, double stranded DNA is unusual because one strand is 25% incomplete.**

-- **They have an envelope.**

-- **Hepatitis B virus** belong to this group.

DNA non-enveloped viruses

Adenoviruses

Structure

-- The **icosahedral capsid** (70 to 100 nm) is made up of 252 capsomeres: 240 hexons forming the faces and 12 pentons at the vertices.

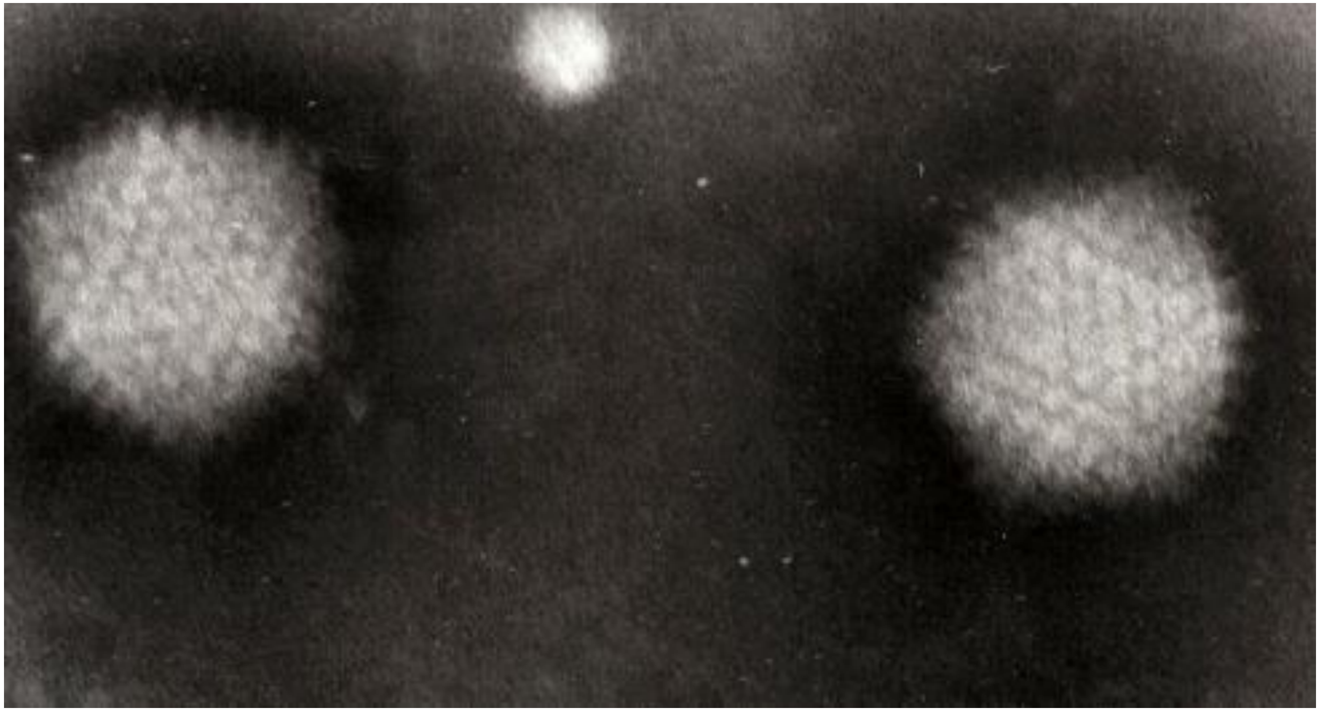
-- Each penton bears a **slender fiber**.

-- They are **the only viruses to have such fibers**.

-- These fibers are used for **attachment** and are **haemagglutinins**.

The **double-stranded linear DNA** is associated with **two major core proteins** and carries a 55-kDa protein covalently attached to its 5′ end.

On basis of fiber protein, there are **47 human adenovirus types**.



Replicative cycle

-- After attachment to cell surface via its fiber, the virus penetrates and uncoats, and **viral DNA moves to nucleus.**

-- **Host cell DNA-dependent RNA polymerase** transcribes the **early genes** and **mRNA is formed** which is translated into **non structural proteins** in the cytoplasm.

-- After viral DNA replication in nucleus, **late mRNA is transcribed** and then translated into **structural virion proteins**.

-- **Viral assembly occurs in the nucleus**, and the virus is **released by cell lysis, not by budding**.

Clinical Manifestations

-- In infants, **pharyngitis** and **pharyngeal-conjunctival fever** are common.

-- These are characterized by **fever, sore throat, coryza** (runny nose) and **conjunctivitis.**

-- In lower respiratory tract they cause **bronchitis** and **atypical pneumonia**.

-- **Hematuria** and **dysuria** are prominent in **hemorrhagic cystitis**.

-- Gastroenteritis with **non bloody diarrhea** occurs in **children below 2 years**.

-- Most infections **resolve spontaneously**.

-- Nearly half are **asymptomatic**.

Pathogenesis and Immunity

-- Infection is usually transmitted in **droplets** of respiratory or ocular secretions.

-- **Persistent (latent)** infection occurs in the **tonsils**.

-- These viruses infect **mucosal epithelium** of several organs including **respiratory tract, GITs** and **conjunctiva**.

-- **Immunity** based on neutralizing antibody is **type specific and life long**.

Transmission and Epidemiology

-- Infection is **common in children**.

-- Transmission is by **aerosol droplets, fecal-oral route,** and **direct inoculation of conjunctivas** by fingers.

-- Animal strains are **non pathogenic** for humans.

-- **Epidemics** do not occur in the general population, but outbreaks of acute respiratory disease occur in **crowded residences**, e.g., military recruits.

-- Types **3, 4, 7,** and **21** cause **respiratory disease.**

-- Types **11** and **21** cause **hemorrhagic cystitis**.

-- Types **40** and **41** cause **infantile gastroenteritis**.

Laboratory Diagnosis

-- Most frequent methods are **isolation of virus in cell culture** and detection of **4-fold or greater rise in antibody titer.**

-- **CFT** and **haemagglutination inhibition** are most important serologic tests.

Treatment

-- There is **no antiviral therapy**.

Prevention

-- Three **monovalent. live, non-attenuated** vaccines against serotypes **4, 7,** and **21** are available.

-- The virus **infects the GIT** where it causes asymptomatic infection and **induces immunity to respiratory disease.**

-- **Epidemic keratoconjunctivitis** can be prevented by **strict asepsis** and **hand washing**.

Papillomaviruses

-- **Human papilloma viruses (HPV)** cause **papillomas** which are **benign tumors of squamous cells** (e.g., warts on the skin).

-- Some **HPV** types, especially **16** and **18**, cause **carcinoma** of the genital organs and anus.

Important properties

-- **HPV** have **double stranded circular DNA** and an **icosahedral nucleocapsid**.

-- Two **early genes**, **E6** and **E7** encode proteins that **inactivate proteins encoded by tumor suppressor genes** in human cells, e.g p53 and retinoblastoma genes which leads to **transformation into cancer cell**.

-- There are at least **100 types** classified on basis of **RFLP**.

-- **Skin warts** are usually caused by **HPV-1** to **HPV-4**, and **genital warts** by **HPV-6** and **HPV-11**.

Replicative cycle

-- Virus **grows poorly**, if at all, **in cell culture**.

-- In human tissue, viral particles are found in **terminally differentiated squamous cells** rather than in the basal cells.

-- It facilitates **efficient transmission**.

-- In **malignant cells**, viral DNA is integrated into host DNA and **E6 and E7 are overexpressed under influence of E2 gene.**

-- In **latent stage**, these genes are **not overexpressed**.

Transmission and epidemiology

Transmission is by **skin to skin** or **genital contact**.

Genital warts are among the most common sexually transmitted diseases.

Skin warts are more common in children and young adults.

Neonates may be infected by mother.

Pathogenesis and Immunity

-- **HPV** infect **squamous epithelial cells** and induce a characteristic **cytoplasmic vacuole**.

-- These cells are called **koilocytes**.

-- Most warts are **benign** and do not progress to malignancy.

-- However **some** can progress to **carcinoma**.

-- Both **cell mediated immunity** and **antibody** are induced and are involved in **spontaneous regression** of warts.

-- Immunosuppressed persons are **more prone** to carcinoma.

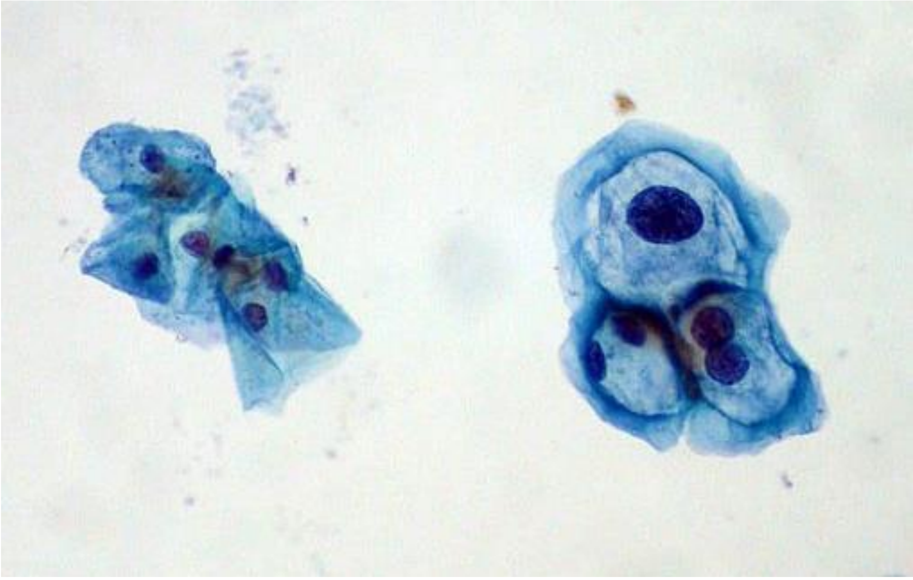
Laboratory Diagnosis

Infections are **usually diagnosed clinically**.

The **presence of koilocytes** in the lesions indicates **HPV** infection.

PCR for **14 high risk genotypes** is available.

Isolation of virus or detection of antibodies is not used.



Treatment and prevention

-- Usual treatment for **genital warts** is **podophyllin**; **alpha interferon** is also effective.

-- **Plantar warts** can be **removed surgically** or treated with **salicylic acid topically**.

-- **Cidofovir** may be useful in the treatment of severe **HPV** infections.

-- Two recombinant vaccines **Gardasil** and **Cervarix** are available.

Parvoviruses

-- **Parvovirus B 19** causes **erythema infectiosum** (**slapped cheek syndrome, fifth disease**), **aplastic anemia** and fetal infections including **hydrops fetalis**.

-- **Parvovirus B 19** is a **very small** (22 nm) virus with **single negative stranded DNA genome**.

-- Capsid has **icosahedral symmetry**.

-- There is **one serotype**.

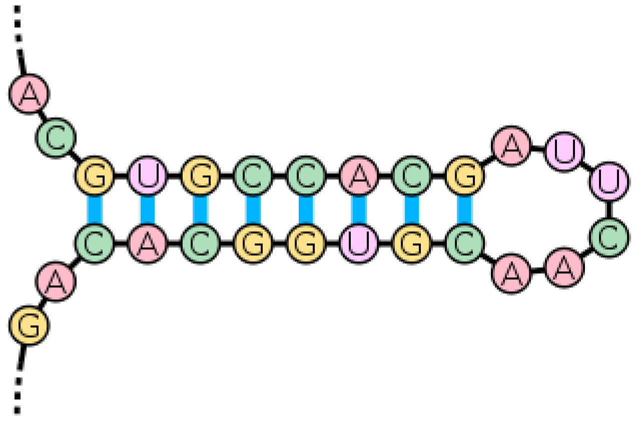
Replicative cycle

-- After absorption to host cell receptors, the virion penetrates and **moves to nucleus** where replication occurs.

-- Viral genome has **hair pin loops** at both ends which provide **double stranded areas** for cellular DNA polymerase to initiate synthesis of progeny genomes.

-- This double stranded DNA serves as **template for mRNA**.

-- The progeny virions are **assembled in the nucleus**.



Transmission and Epidemiology

-- Transmission is primarily by **respiratory route**.

-- **Transplacental transmission** may also occur.

-- **Blood transfusion** may also be a cause.

-- It has **worldwide** distribution.

-- Animals are **not a source** of human infection.

Pathogenesis and Immunity

-- **B 19 virus** primarily infects **erythroblasts in the bone marrow** to cause aplastic anemia, and **endothelial cells in blood vessels** to cause rash of **erythema infectiosum**.

-- Another reason for rashes is **immune complexes** composed of virus and IgM or IgG.

-- These complexes may also cause **arthritis** in adults.

Clinical findings

These include:

Aplastic anemia

-- Children with chronic anemia, such as **sickle cell anemia**, **thalassemia**, and **spherocytosis** can have transient but **severe aplastic anemia (aplastic crisis)** when infected with **B 19 virus**.

Erythema infectiosum (**slapped cheek syndrome**):

It is a **mild disease**, primarily of childhood characterized by **bright red rash on cheeks** accompanied by low grade fever, coryza and sore throat.

Less intense rash may appear on the body.

The symptoms resolve in one week.

Fetal infections

-- In women infected with **B 19 virus** during **first or second trimester** of pregnancy, the virus may **cross the placenta** and infect the fetus.

-- Infection in **first trimester leads to death**.

-- Infection **in second trimester leads to hydrops fetalis** which is massive edema of fetus due to congestive heart failure.

-- Third trimester infections are not important.

Arthritis

-- Infection in adults, especially women, can cause **arthritis involving small joints of hands and feet bilaterally.**

Laboratory diagnosis

-- **Erythema infectiosum** and **aplastic anemia** are usually **diagnosed by detecting IgM antibodies**.

-- In **immunocompromised persons**, antibodies are not detectable so **PCR** is used.

-- Fetal infection can be diagnosed by **PCR of amniotic fluid**.

Treatment and Prevention

-- There is **no specific treatment**.

-- **Pooled immunoglobulins** may have a beneficial effect.

-- There is **no vaccine or chemoprophylaxis**.


Thank You!!