Chapter 32

Viral Pathogenesis

The ability of viruses to cause disease has two levels:

1. Changes occurring **within infected cell**

2. Process that takes place **within infected patients**

The infected cell

There are **four** main effects of virus infection on cell:

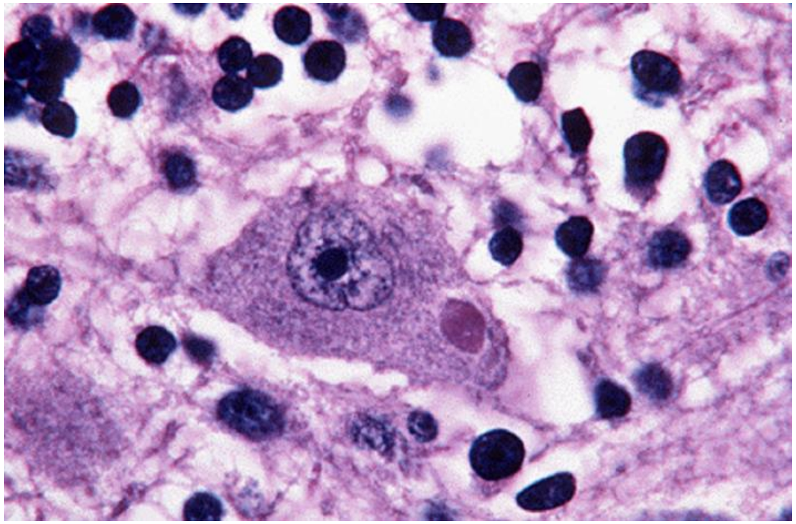
1. **Death**
2. **Fusion of cells** to form multinucleated cells
3. **Malignant transformation**
4. **No apparent** morphologic or functional change.

-- **Death** is due to **inhibition of synthesis of macromolecules**.

-- Cellular **protein synthesis stops first**, followed by nucleic acid synthesis. **But viral protein synthesis continues**.

-- Infected cells contain **inclusion bodies** which are discrete areas containing viral proteins or viral particles which gives a characteristic appearance.

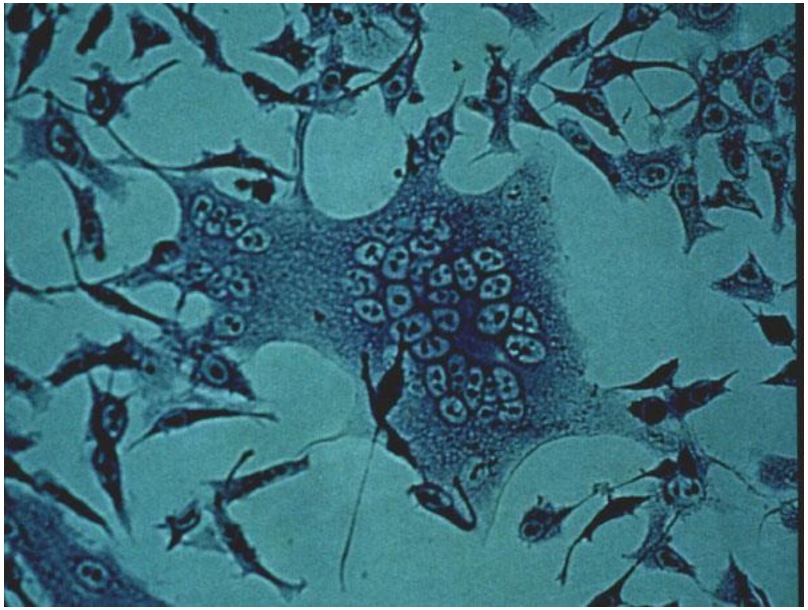
-- For example **Negri bodies** which are found in **rabies virus** infected brain neurons.



-- **Multinucleated giant cells** are characteristically formed after infection with **herpesviruses** and **paramyxoviruses**.

-- Fusion occurs probably due to insertion of viral proteins into cell membrane.

-- These giant cells are diagnostic in **herpesvirus** skin infections.



-- Many viral infections cause **CPE** (cytopathic effects).

-- The change begins with **rounding and darkening of infected cell** and culminates either in **lysis** or **giant cell formation**.

-- CPE helps in **diagnosis** and also in **quantification of virus**.

-- Certain viruses can cause **malignant transformation** characterized by unrestrained growth, prolonged survival and morphological changes such as focal areas of rounded, piled up cells.

-- In other cases, cell infection **may not result in CPE**.

The infected patient

Pathogenesis in infected patient involves:

1. **Transmission of the virus** and its entry into the host
2. **Replication of virus** and damage to cells
3. **Spread of virus** to other cells and organs
4. **Immune response**, both as host defence and autoimmune diseases
5. **Persistence of virus** in some cases

Transmission and portal of entry

-- Viruses are carried to the body by **all possible routes**.

-- Similarly, all possible sites of implantation may be used.

-- With some viruses, implantation in the fetus may occur at the **time of fertilization** through infected germ cells, as well as later in **gestation via the placenta**, or **at birth**.

-- Even at the earliest stage of pathogenesis, **certain variables may influence the final outcome** (subclinical to lethal) of the infection.

-- These include the **dose, infectivity, virulence of virus** and the **location of implantation**.

Local Replication and Local Spread

Virus that **replicates within the initially infected cell** may spread to adjacent cells **extracellularly** or **intracellularly**.

- **Extracellular spread** occurs by release of virus into the extracellular fluid and subsequent infection of the adjacent cell.

- **Intracellular spread** occurs by fusion of infected cells with adjacent, uninfected cells or by way of cytoplasmic bridges between cells.

Most viruses spread extracellularly, but **herpesviruses**, **paramyxoviruses**, and **poxviruses** may spread through both intracellular and extra cellular routes.

Intracellular spread provides virus with a partially protected environment because the antibody defense does not penetrate cell membranes.

Localized or disseminated infections

-- Spread to cells beyond adjacent cells may occur through the liquid spaces within the local site (e.g., **lymphatics**).

-- Or spread can be by diffusion through surface fluids such as the **mucous layer** of the respiratory tract.

-- Also, **infected migratory cells** such as lymphocytes and macrophages may spread the virus within local tissue.

-- Establishment of infection at the portal of entry may be followed by continued **local virus multiplication**, leading to localized virus shedding and localized disease.

-- In this way, local sites of implantation also are **target organs** and **sites of shedding** in many infections.

-- Respiratory tract infections that fall into this category include **influenza**, the **common cold**, and **parainfluenza virus** infections.

-- **Alimentary tract infections** caused by several gastroenteritis viruses (e.g., **rotaviruses** and **picornaviruses**) also may fall into this category.

- -- **Localized skin infections** of this type include **warts, cowpox**, and **molluscum contagiosum**.

- -- Localized infections may spread **over body surfaces** to infect distant surfaces, e.g., in **picornavirus** epidemic, conjunctivitis virus spreads directly from the eye to the pharynx and intestine.

- -- Other viruses **may spread internally** to distant target organs and sites of excretion (disseminated infection).

- -- A third category of viruses may cause **both local and disseminated disease**, as in herpes simplex and measles.

Dissemination from the Portal of Entry

Dissemination in the Bloodstream

-- At the **portal of entry**, multiplying virus may spread through **blood, lymphatics** and **peripheral nerves**.

-- The **most common route** of systemic spread of virus involves the **circulation**.

-- Viruses such as those causing **poliomyelitis, smallpox**, and **measles disseminate through the blood** after an initial period of replication at the portal of entry (the alimentary and respiratory tracts).

-- This infection often causes **no significant symptoms** or signs of illness because the virus kills cells that are expendable and easily replaced.

-- Virus progeny diffuse through the **afferent lymphatics** to the **lymphoid tissue** and then through the **efferent lymphatics** to infect cells in close contact with the bloodstream (e.g., endothelial cells, especially those of the lymphoreticular organs).

-- This initial spread may result in a brief **primary viremia**.

-- Subsequent release of virus directly into the bloodstream induces a **secondary viremia**, which usually lasts several days and puts the virus in contact with the capillary system of all body tissues.

-- Virus may enter the target organ from the capillaries by replicating within a **capillary endothelial cell** or **fixed macrophage** and then being released on the target organ side of the capillary.

-- Virus may also diffuse through **small gaps in the capillary endothelium** or penetrate the capillary wall through an **infected, migrating leukocyte.**

-- The virus may then replicate and spread **within the target organ** or site of excretion by the same mechanisms as for local dissemination at the portal of entry.

-- Disease occurs if the **virus replicates in a sufficient number of essential cells** and destroys them.

-- For example, in **poliomyelitis** the central nervous system is the target organ, whereas the alimentary tract is both the portal of entry and the site of shedding.

-- In some situations, the target organ and site of shedding may be the same.

Dissemination in Nerves

-- Dissemination through the nerves is **less common** than bloodstream dissemination, but is the means of spread in a number of important diseases.

-- This mechanism occurs in **rabies virus**, **herpesvirus**, and, occasionally, **poliomyelitis virus** infections.

-- For example, **rabies virus** implanted by a bite from a rabid animal replicates subcutaneously and within muscular tissue to reach nerve endings.

-- The virus spreads in the **neurites** (axons and dendrites) and **perineural cells**, where virus is shielded from antibody.

-- This nerve route leads rabies virus to the central nervous system, where disease originates.

-- **Rabies virus** then spreads **centrifugally** through the nerves to reach the salivary glands, the site of shedding.

Incubation Period

-- During most virus infections, **no signs or symptoms** of disease occur through the stage of **virus dissemination**.

-- Thus, the **incubation period** (the time between exposure to virus and onset of disease) extends from the time of implantation through the phase of dissemination, ending when virus replication in the target organs causes disease.

-- Occasionally, mild fever and malaise occur during viremia, but they often are transient and have little diagnostic value.

-- The incubation period tends to be **brief** (1 to 3 days) in infections in which **virus travels only a short distance to reach the target or**gan (i.e., in infections in which disease is due to virus replication at the portal of entry).

-- Conversely, **incubation periods in generalized infections are longer** because of the stepwise fashion by which the virus moves through the body before reaching the target organs.

- -- The mechanisms governing the long incubation period (months to years) of persistent infections are poorly understood.

- -- The persistently infected cell is often not lysed, or lysis is delayed.

- -- In addition, disease may result from a **late immune reaction** to viral antigen (e.g., **arenaviruses** in rodents).

- -- Or due to unknown mechanisms in **slow viral infections** during which no immune response has been detected, e.g., prion infections.

Pathogenesis and immunopathogenesis

-- **Death of the virus infected cell** results in a loss of function and in the **symptoms of disease**.

-- For example when **poliovirus** kills neurons, **paralysis** of relevant muscles occurs.

-- However, some **diseases are not caused by death of cells**.

-- For example **rotavirus** **diarrhea** is caused by stimulation of enteric nervous system by **cytokines produced by infected cells**.

-- It results in **excess electrolyte and fluid secretion** into bowel lumen.

-- In some other cases, **cytotoxic T cells** and **antibodies** play a role in **immunopathogenesis**.

-- In **LCM** (**lymphocytic choriomeningitis**), if the virus is inoculated in brain of **healthy adult mice, it results in death.**

-- However, when virus is inoculated in **immunosuppressed adult mice** or newborn mice, **they are not affected**.

-- If they are inoculated with immune lymphocytes, disease starts and death occurs.

-- This affect is due to **T cell attack** on cells showing new viral antigens.

- -- Same phenomenon is involved in pathogenesis of hepatitis caused by **hepatitis A, B, and C viruses**.
- -- Similarly **measles rashes** involve same phenomenon.
- -- **Immune mediated pathogenesis** also occurs when virus-antibody-complement complexes form and are deposited in various tissues.
- -- This is the phenomenon involved in arthritis related to **hepatitis B**, **parvovirus B19** and **rubella virus** infections.

Virulence

-- Strains of a virus **differ widely** in ability to cause disease, e.g. some strains of poliovirus cannot produce disease in immunocompetent individuals.

-- This variation is **based on mutations** but mechanism is poorly understood.

Evasion of host defenses

-- **Immune evasion** by some viruses (**vaccinia, fibroma**) is caused by encoding receptor proteins for various mediators such as IL-1 and TNF.

-- They **bind to mediators** and stop them from activating immune cells.

-- They are called **cytokine decoys**.

-- Some others (**HIV, herpesviruses**) can reduce expression of class 1 MHC proteins **reducing the ability of T killer cells to kill** infected cells, or they can inhibit complement.

-- Several viruses (**HIV, adenoviruses**) synthesize RNAs which **reduce the ability of interferon** to block viral replication.

-- Similarly **CMV virus** produce a microRNA that act **on natural killer cells.**

-- Collectively these viral virulence factors are called **virokines**.

-- Production of **multiple serotypes** is another way by which viruses evade immune system.

-- **Rhinovirus** has 100 serotypes. This is the reason why “common cold’ is so common.

-- Same is true for **influenza, hepatitis C** and **HIV** viruses.

-- Majority of viruses have a single or a few serotypes.

Persistent viral infections

In some viral infections, virus **may persist for long periods after recovery** by:

1. **Integration** of a DNA provirus into host cell DNA as occurs with **retroviruses**
2. **Immune tolerance** because antibodies are not formed
3. **Formation of virus-antibody complexes** which remain infectious.
4. **Location within an immunologically sheltered "sanctuary"** such as brain
5. **Rapid antigenic variation**
6. **Spread from cell to cell** without an extracellular phase
7. **Immunosuppression** as in AIDS

There are **three types** of persistent viral infections of clinical importance

Chronic carrier infection

-- The carrier state can follow an **asymptomatic infection** as well as the **actual disease**.

-- It can be asymptomatic or result in chronic disease.

-- Examples are chronic hepatitis in hepatitis B and C carriers.

Latent infections

-- In these, e.g., in **herpesviruses**, patient recovers from initial infection and virus production stops.

-- Symptoms may recur due to virus activation.

-- **HSV 1** is latent in trigeminal ganglion whereas **HSV 2** resides in lumbar and sacral ganglia.

Slow virus infections

-- The term also refers to **prolonged period between the initial infection and the onset of disease** which is usually measured in years.

-- It is **not because of slow viral growth** but due to prolonged incubation period or slow progression of disease.

-- Example is **PML** (progressive multifocal leukoencephalopathy) caused by **JC virus**, a **papovavirus**.


Thank You!!