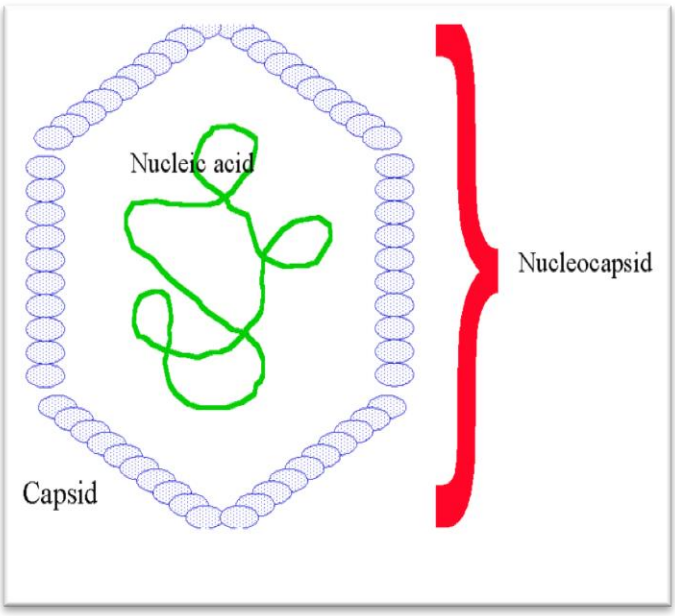
1. Viruses, general properties; disease and host response

INTRODUCTION:

A **virus** is a small infectious agent that replicates only inside the living cells of other organisms. Viruses can infect all types of life forms, from animals and plants to microorganisms, including bacteria. There are millions of types of viruses, out of which about 5000 virus species have been described in detail.

Viruses are found in almost every ecosystem on Earth and are the most abundant type of biological entity. **Virology** is the study of virus and the relationship between viruses and hosts. Viruses can infect all living things including the Animal kingdom, Plant kingdom and the microbial kingdom. Viruses often cause serious diseases, relate to some cancers and congenital deformities. **Viruses are Obligate Intra-cellular Parasites**. **Virion is a complete infective Virus particle. Viruses cannot be seen with the help of a light microscope. Viruses can only be seen with the help of an electron Microscope. The size of a virus is measured in nanometers (nm). The size varies from 20 nanometers up to 450 nanometers (diameter). Viruses are inactive macromolecules outside of the host cells and active only inside host cells.**



. **Fig 1: Basic shape of a virus**

All virions have nucleocapsid. **Nucleocapsid is composed of a nucleic acid, (DNA or RNA), held within a protein coat called the capsid. Capsid protects viral genetic material and helps in its transfer between host cells.**

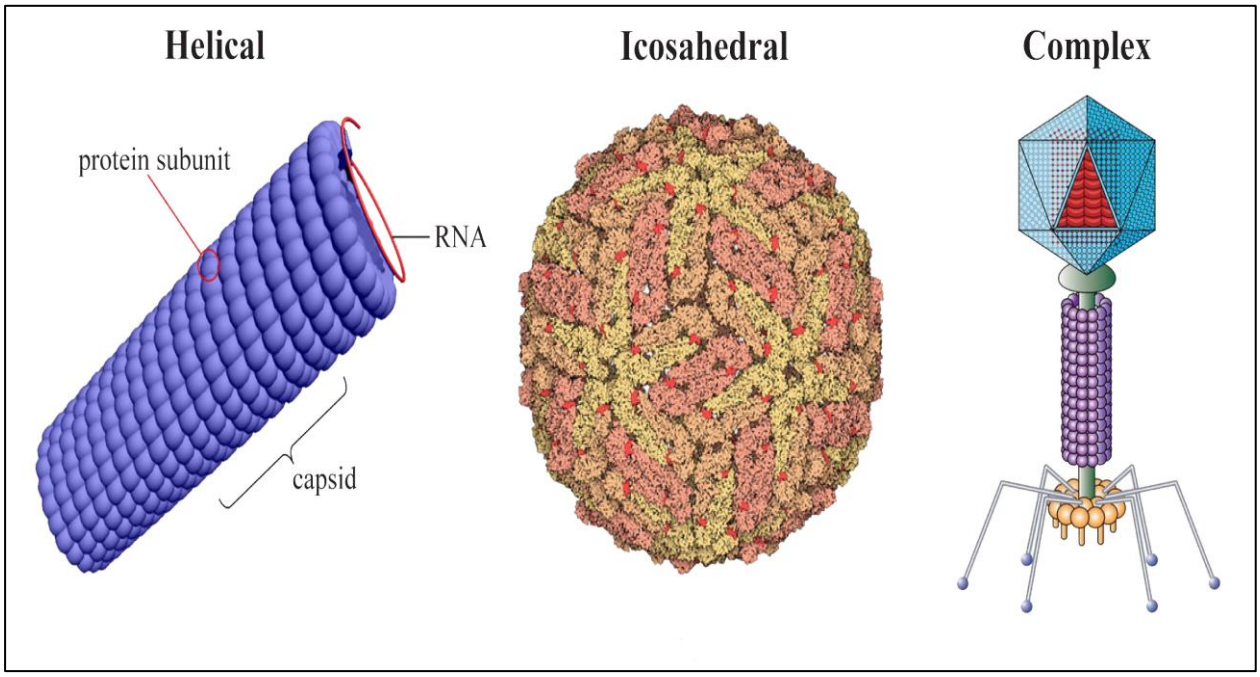
While not inside an infected cell or in the process of infecting a cell, viruses exist in the form of independent particles. These viral particles, consist of two or three parts:

(i) The genetic material made from either DNA or RNA, long molecules that carry genetic information;

(ii) A protein coat, called the capsid, which surrounds and protects the genetic material; and in some cases

(iii) An envelope of lipids that surrounds the protein coat.

The shapes of these virus particles range from helical, icosahedral and complex structures. In some viruses an envelope can also be found. .



Depending upon the presence of an envelope, viruses can show 5 basic types of viral structures: (fig 3 to 7)

1. **Naked Icosahedral virus (eg: Adenovirus, Foot and mouth disease virus etc.)**
2. **Enveloped Icosahedral virus (eg: Herpes simplex virus, etc.)**
3. **Naked Helical Virus (eg: Tobacco mosaic virus, etc.)**
4. **Enveloped Helical Virus (eg: Influenza virus, Rabies virus, etc.)**
5. **Complex structure (eg: Bacteriophages, etc.)**

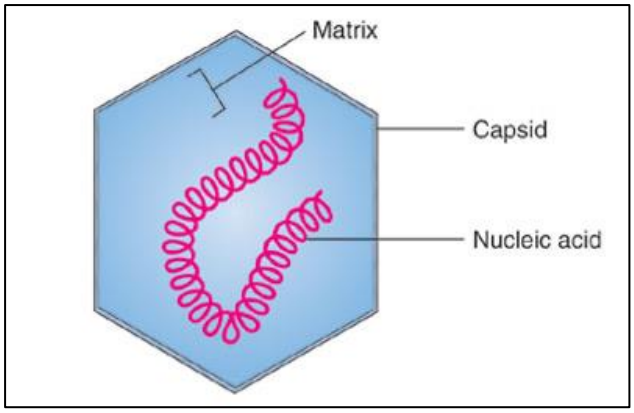


Fig:3 Naked Icosahedral Virus

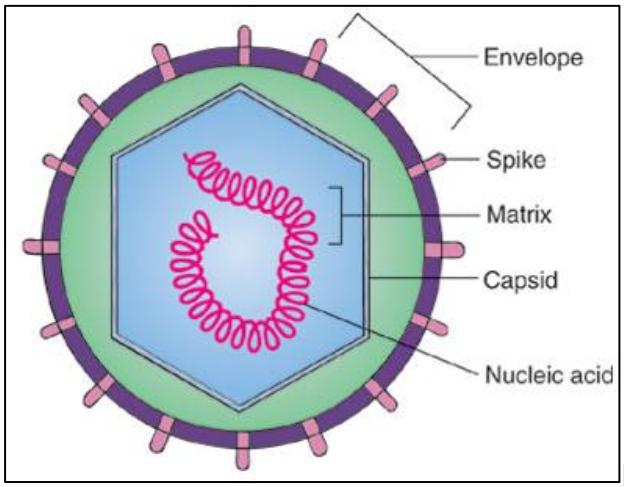


Fig 4: Enveloped Icosahedral virus

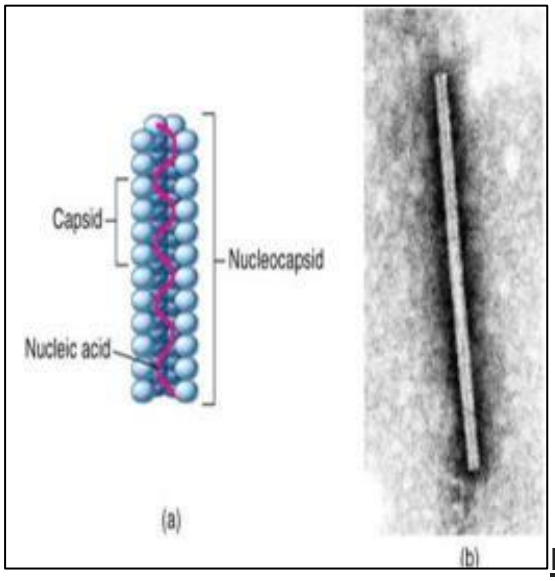


Fig 5: Naked Helical virus

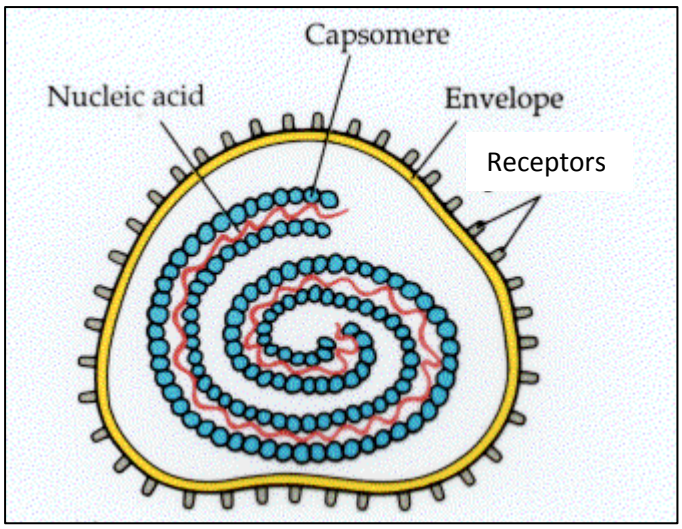


Fig 6: Enveloped Helical virus

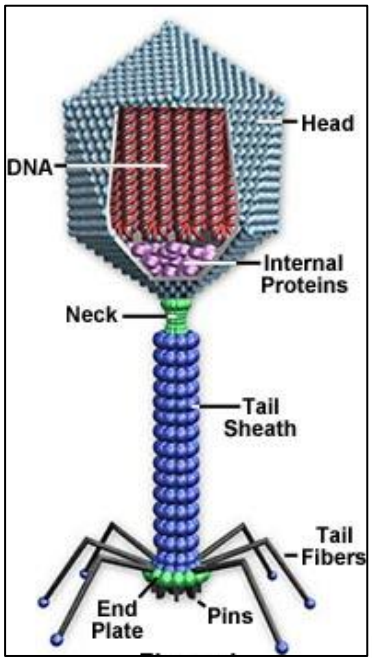


Fig 7: Complex virus structure (Bacteriophage)

Bacteriophages are virus infecting bacteria.

OTHER NONCELLULAR INFECTIOUS AGENTS:

1. **PRIONS are misfolded proteins. They contain no nucleic acid. Prions cause spongiform encephalopathies – holes in the brain. Prions cause Scrapie in sheep and goats, Bovine spongiform encephalopathies (BSE) or Mad Cow disease in Cows and Creutzfeldt – Jakob Disease (CJD) in humans.**
2. **VIROIDS are short pieces of RNA. They have no protein coat. They have only been identified in plants, so far. They have a circular genome with 250 to 400 nucleotides.**

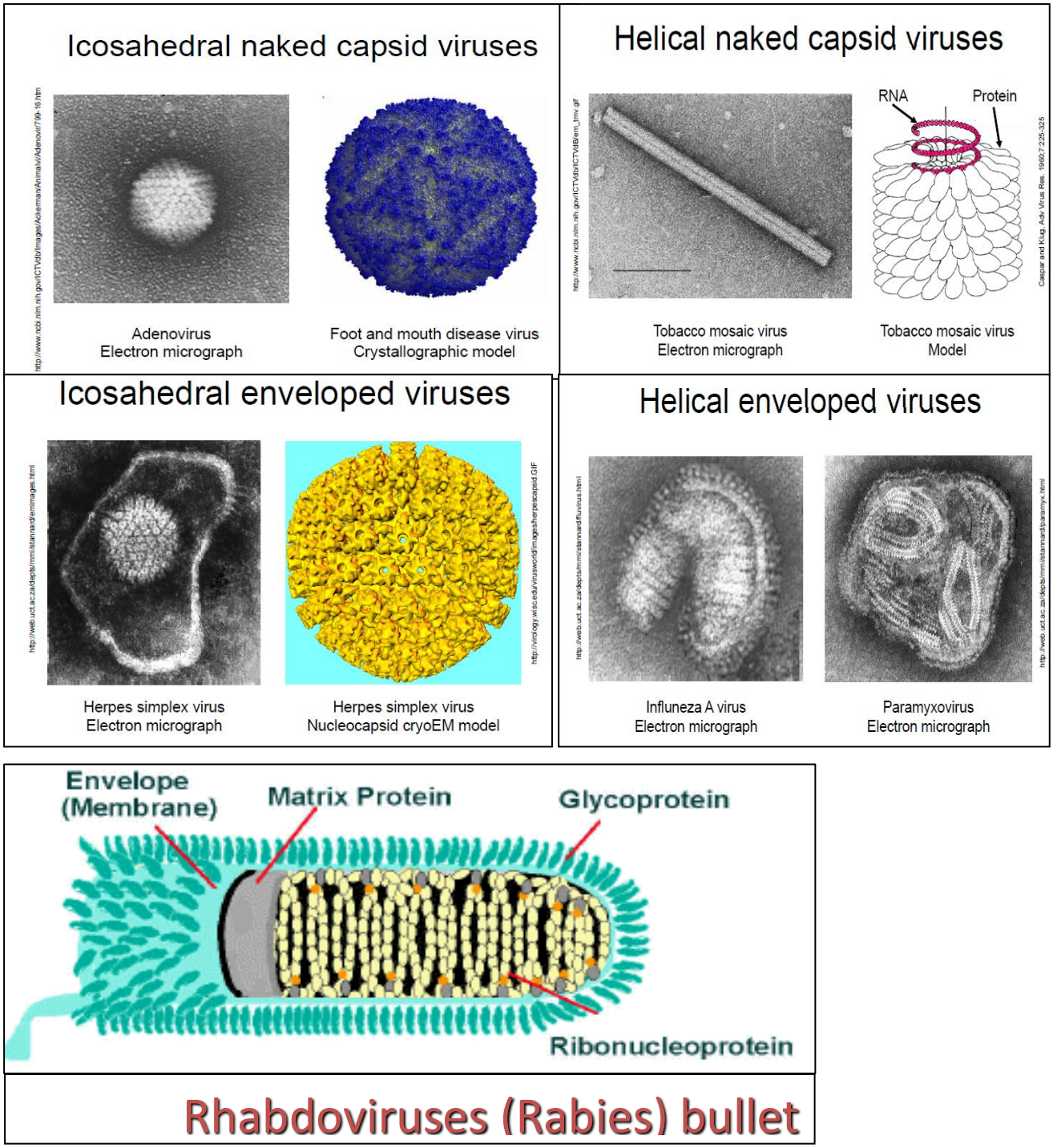


Fig 8: Different virus structures

The origins of viruses in the evolutionary history of life are unclear. Viruses are considered by some to be a life form, because they carry genetic material, reproduce, and evolve through natural selection, but lack key characteristics (such as cell structure) that are generally considered necessary to count as life. Because they possess some but not all such qualities, viruses have been described as "organisms at the edge of life", and as replicators.

Viruses spread in many ways; viruses in plants are often transmitted from plant to plant by insects that feed on plant sap, such as aphids; viruses in animals can be carried by blood-sucking insects. These disease-bearing organisms are known as vectors. Influenza viruses are spread by coughing and sneezing. Norovirus and rotavirus, common causes of viral gastroenteritis, are transmitted by the faecal–oral route and are passed from person to person by contact, entering the body in food or water. HIV is one of several viruses transmitted through sexual contact and by exposure to infected blood.

Viral infections in animals provoke an immune response that usually eliminates the infecting virus. Immune responses can also be produced by vaccines, which confer an artificially acquired immunity to the specific viral infection. Some viruses including those that cause AIDS and viral hepatitis evade these immune responses and result in chronic infections. Antibiotics have no effect on viruses, but several antiviral drugs have been developed.

Cultivation of Virus:

Viruses need specific host cells to infect and grow in. Animal viruses can be cultivated / grown in.

Animal viruses can be cultivated in:

a) **living animals (eg: mice, rabbits, monkeys etc.)**
b) **Bird embryos in eggs (eg: chicken or duck eggs)**
c) **Tissue culture (eg: organ culture, Primary tissue culture, cell lines, etc.)**

Fig 9: Researcher examines eggs that will be inoculated with Influenza.

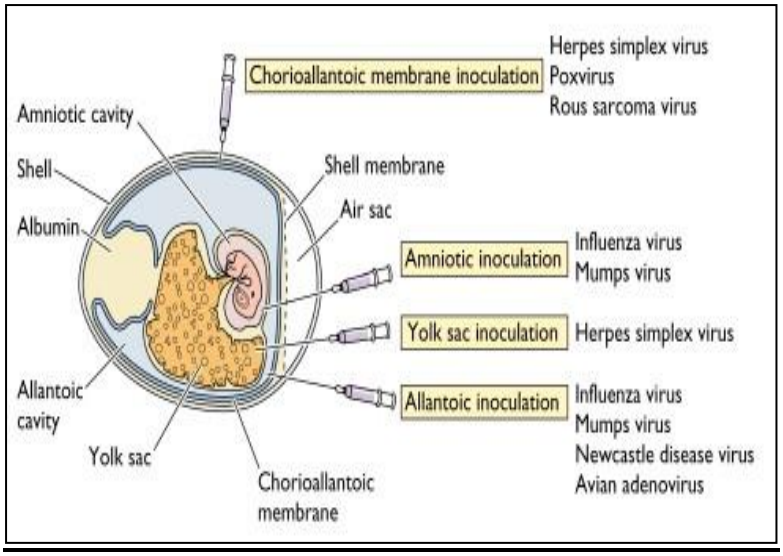


Fig 10: Comparison of a normal 18-day old chicken embryo (right) and two infected embryos of the same age, showing dwarfing.

The Primary purposes of viral cultivation are:

1. **To isolate and identify viruses in clinical specimen**
2. **To prepare viruses for vaccines**
3. **To do detailed research on viruses**

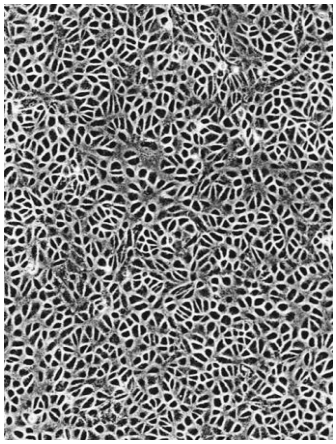
Viral Cytopathological Effects (CPE):

Development of characteristic cytopathological effects help in identification of viral isolates in tissue culture.

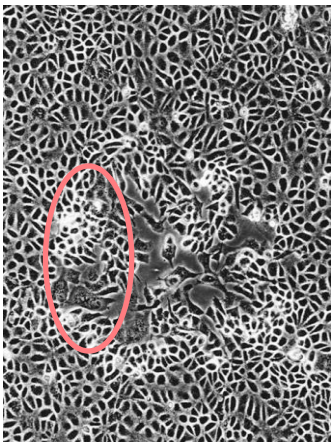
CPE include:

1. **Cell death**: Cell rounding/Degeneration/Aggregation
   Loss of attachments to substrate
2. **Inclusion bodies** in the nucleus or cytoplasm, margination of chromatin
3. **Syncytia:** multinucleated giant cells caused by virus-induced cell-cell fusion

4. **Cell surface changes:** Viral antigen expression, Hemadsorption (hemagglutinin expression)



A: normal cells in tissue culture



B: CPE in tissue culture

<u>Effects of virus growth on cells:</u> There are five main effects on viral growth on host cells –

1. DEATH: The infection is lethal. It causes Cytopathic effect (CPE) which kills the cell
2. TRANSFORMATION: The cell is not killed but changed from a normal cell to malignant or cancerous cell
3. LATENT INFECTION: the virus remains within the cell in a potentially active state but produces no obvious effect on cell function.
4. HAEMADSORPTION: some viruses have Haemagglutinin on their outer coats which adheres to RBC's causing them to agglutinate.

CLASSIFICATION OF VIRUSES

Viruses can be classified on the basis of:

1. **Virion morphology**
2. **Virus genome properties**
3. **Virus protein properties**
4. **Genome organization and replication**
5. **Antigenic properties**

Baltimore classification (first defined in 1971) is a classification system that places viruses into one of seven groups depending on a combination of their nucleic acids (DNA or RNA)

- **I: double stranded DNA viruses (eg. Adenoviruses, Poxviruses, etc.)**

- **II: single stranded DNA viruses (+strand or sense) (eg. Parvoviruses)**
- **III: Double stranded RNA viruses (eg. Reoviruses)**
- **IV: (+) Single stranded RNA viruses (+ strand or sense) (eg. Picornaviruses)**
- **V: (-) single stranded RNA viruses (- strand or antisense) (eg. Orthomyxoviruses)**
- **VI: Single stranded RNA – RT viruses (+ strand or sense) with DNA intermediate in life cycle (eg. Retroviruses)**
- **VII: Double stranded DNA – RT viruses (DNA with RNa intermediate in life cycle (eg. Hepadnaviruses)**

Viral disease:

Viruses are important and common cause of human disease (especially in children).**Most viral infections are mild & patients makes full recovery. Many viral diseases are silent (virus multiplies in body without symptoms). Some viruses may cause severe diseases in susceptible patients.** A few viral diseases are severe and can cause death.

Entry of virus in body:

Viruses can enter the body via-

- **Inhalation: via respiratory tract**
- **Ingestion: via the gastrointestinal tract**
- **Inoculation: through skin abrasions, mucous membrane and via the bite of arthropods**
- **Blood and blood products**
- **Sexual**

Invasiveness:

Main pathogenic mechanism of viruses is invasion. Disease is produced by direct spread of virus to tissue & organs. Virus replication in cells usually kills the infected cells. CPE in vivo causes lesions & so dysfunction in the tissue or organ concerned (signs and symptoms)

Host Response to Virus infection

The body defense mechanism to virus infection are of 2 types: NON-SPECIFIC & SPECIFIC:

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NON – SPECIFIC: Body defense mechanism not specifically directed to a particular infectious agent but which serves as a non-immunological barrier to infection.

- **Skin:** effective & impermeable barrier
- **Respiratory tract**: upwards flow of mucous and ciliated epithelial cells
- **Gastrointestinal tract:** stomach acid, bile, movement of intestinal contents, etc.
- **Urinary tract**: flow of urine flushes viruses
- **Conjunctiva:** tears flush viruses
- **Phagocytosis:** viruses are ingested by Phagocytic cells

<u>SPECIFIC:</u> Specific immunological defense mechanisms are of two types:

- **HUMORAL - leads to neutralization of viruses**
- **CELLULAR – localizes lesions : kills virus infected cells**

<u>HUMORAL IMMUNITY</u>:

Viruses cause production of antibodies in blood. Antibodies are Immunoglobulins (proteins that react specifically with Antigens which are present on virus particles). They are produces by Plasma cells (B lymphocytes are activated by encounter with Antigen). Y shaped structure: Fab region combines with Antigen and Fc region activates complement system.

There are 3 main types responsible to humoral immunity in virus infection:

IgM: earliest Antibody produced (***PRIMARY Ab***), formed about a week after infection, lasts for about 4 – 6 weeks (sometimes longer), pentameric (5 IgG)

IgG: formed later than IgM **(*SECONDARY Ab*),** persists for long time (may be 10 years) Responsible for immunity to reinfection

IgA: ***Secretory Ab***, dimeric molecule, found in body secretions like saliva, respiratory secretions, tears, intestinal contents. Main Ab involved in immunity to respiratory viruses & enteric viral infections.

Antiviral effects:

- **Neutralization: antiviral antibodies neutralize virus infectivity and are principal mechanism for immunity** – often life long, it also prevents reinfection
- **Antibody dependent Cell mediated Cytotoxicity**

SPECIFIC CELLULAR IMMUNITY

Cell Mediated Immunity: cellular immunity is the mechanism to eliminate virus infected cell. It is mediated by 3 types of T cells: helper T cells, Suppressor T cells and Cytotoxic T cells. CMI is extremely complex and involves other cells and cytokines. Virus is recognized as Ag with the help of Helper T cells when presented by Macrophages/Dendritic cells acting as APC's. Recognition is dependent of HLA class II present on Macrophages.
Helper T cells **stimulate cytotoxic cellular response & cause activation of B cells: these effects are produced by secretions of cytokines – Interleukin IL-2. They have CD4 surface receptors.**
Suppressor T cells **control & regulate cytotoxic cellular response by suppression of T Helper cells. They have CD8 surface receptors**
Cytotoxic T cells **are the main effector cells which kill virus infected target cells. Class I HLA Ag compatibility is required.**

Lysis of virus infected cells is mediated by several mechanisms:

1. **Antibody independent or direct killing by**
   - **Cytotoxic T cells**
   - **Natural Killer (NK) cells present in non-immune hosts**
2. **Antibody dependent –** (cellular cytolysis) ADCC: mediated by Fc binding between Fc portion of Antiviral IgG bound to virus on cell surfaces and Fc receptors on
   - **-Killer (K) cells – lymphocytes present in immune as well as non immune hosts**
   - **-Polymorphonuclear leucocytes**
   - **-Activated Macrophages**
3. **Interferons: are cytokines,** 3 types- Alpha (leucocytes), Beta (Fibroblasts) and Gamma (T – lymphocytes)
   - **They have anti-proliferative activity on cells & immune system and on virus replication**
   - **Interferons are host specific, wide antiviral spectrum, induced by viruses and nucleic acids & acts on both viral replication & protein synthesis**

Difference between a Bacteria and a Virus:

	Bacteria	Virus
Growth on artificial media	Yes	Never
Division by binary fission	Yes	No
Nucleic acid	Contain DNA and RNA	Contain DNA or RNA
Protein synthesis machinery	Yes	No
Sensitivity to antibiotics	Yes	No
Sensitivity to Interferon	No	Yes

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