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College of Science
Department of Biology

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الصباحي والمسائي

المرحلة الرابعة – الدراستين الصباحية والمسائية

الفصل الدراسي الثاني

أ.د. حلا يونس فاضل

أ.م.د. ليلى فؤاد علي

Lec 1 **Virology** **2017-2018**

History of virology:-

1796:

Edward Jenner (1749-1823) used cowpox to vaccinate against smallpox. In 1774, a farmer named Benjamin Jesty had vaccinated his wife and two sons with cowpox taken from the udder of an infected cow and had written about his experience. Jenner was the first person to deliberately vaccinate against any infectious disease, i.e. to use a preparation containing an antigenic molecule or mixture of such molecules designed to elicit an immune response. Although Jenner is commonly given the credit for vaccination, variolation, the practice of deliberately infecting people with smallpox to protect them from the worst type of the disease, had been practised in China at least two thousand years previously.

1885:

Louis Pasteur (1822-1895) experimented with rabies vaccination, using the term "virus" (Latin, poison) to describe the agent. Although Pasteur did not discriminate between viruses and other infectious agents, he originated the terms "virus" and "vaccination" (in honour of Jenner) and developed the scientific basis for Jenner's experimental approach to vaccination.

1886:

John Buist (a Scottish pathologist) stained lymph from skin lesions of a smallpox patient and saw "elementary bodies" which he thought were the spores of micrococci. These were in fact smallpox virus particles - just large enough to see with the light microscope.

1892:

Dmiti Iwanowski (1864-1920) described the first "filterable" infectious agent - tobacco mosaic virus (TMV) - smaller than any known bacteria. Iwanowski was the first person to discriminate between viruses and other infectious agents, although he was not fully aware of the significance of this finding.

1898:

Martinus Beijerinick (1851-1931) extended Iwanowski's work with TMV and formed the first clear concept of the virus "contagium vivum fluidum" - soluble living germ. Beijerinick confirmed and extended Iwanowski's work and was the person who developed the concept of the virus as a distinct entity.

1915:

Frederick Twort (1877-1950) discovered viruses infecting bacteria.

1917:

Felix d'Herelle (1873-1949) independently discovered viruses of bacteria and coins the term bacteriophage. The discovery of bacteriophages provided an invaluable opportunity to study virus replication at a time prior to the development of tissue culture when the only way to study viruses was by infecting whole organisms.

1935:

Wendell Stanley (1887-1955) crystallized TMV and showed that it remained infectious (Nobel Prize, 1946). Stanley's work was the first step towards describing the molecular structure of any virus and helped to further illuminate the nature of viruses.

1938:

Max Theiler (1899-1972) developed a live attenuated vaccine against yellow fever (Nobel Prize, 1951). Theiler's vaccine was so safe and effective that it is still in use today! This work saved millions of lives and set the model for the production of many subsequent vaccines.

1940:

Helmuth Ruska (1908-1973) used an electron microscope to take the first pictures of virus particles. Along with other physical studies of viruses, direct visualization of virions was an important advance in understanding virus structure.

1945:

Salvador Luria (1912-1991) and Alfred Hershey (1908-1997) demonstrated that bacteriophages mutate (Nobel Prize, 1969). This work proved that similar genetic mechanisms operate in viruses as in cellular organisms and laid the basis for the understanding of antigenic variation in viruses.

During the last few decade much information have been gathered on isolation and culture of viruses, replication processes, preparation of maps, immunization processes, genetic engineering, molecular biology, vaccine development, etc.

What is a virus?

Virus is a parasite in all types of organisms. They infect animals, plants, bacteria, algae, insects, etc. So far the exact nature of viruses is unclear whether they are living or non living organisms. If we look into life, it is a complex set of processes taking place through the action of proteins controlled by nucleic acid. The nucleic acid of the living organism is functional in all time. Outside the living cell, viruses remain inactive. Therefore, they cannot be said as living organism. In addition, if we consider the diseases caused by them they act as pathogen against bacteria, fungi, protozoa, etc. So from this angle viruses may be regarded as exceptionally simple living organism or as exceptionally complex aggregation or non- living chemicals, then how may viruses be defined.

Viruses (The word is from the Latin virus referring to poison and other noxious substances) are small, filterable and obligate intracellular parasite requiring a living host for its multiplication; however both of these properties are shared by certain small bacteria and rickettasias. Viruses consist of two or three parts:

a) All viruses have genes made from either DNA or RNA, long molecules that carry genetic information.

b) All have a protein coat that protects these genes.

c) Some have an envelope of fat that surrounds them when they are outside a cell.

Viruses have few or no enzymes of their own metabolism; they take over the metabolic machinery of the host cells.

Origins of viruses:

Viruses are found wherever there is life and have probably existed since living cells first evolved. The origin of viruses is unclear because they do not form fossils, so molecular techniques have been the most useful means of investigating how they arose. These techniques rely on the availability of ancient viral DNA or RNA, but, unfortunately, most of the viruses that have been preserved and stored in laboratories are less than 90 years old. There are three main hypotheses that try to explain the origins of viruses:

1) Regressive hypothesis

Viruses may have once been small cells that parasitized larger cells. Over time, genes not required by their parasitism were lost. The bacteria rickettsia and chlamydia are living cells that, like viruses, can reproduce only inside host cells. They lend support to this hypothesis, as their dependence on parasitism is likely to have caused the loss of genes that enabled them to survive outside a cell. This is also called the degeneracy hypothesis.

2) Cellular origin hypothesis

Some viruses may have evolved from bits of DNA or RNA that "escaped" from the genes of a larger organism. The escaped DNA could have come from plasmids (pieces of naked DNA that can move between cells) or transposons (molecules of DNA that replicate and move around to different positions within the genes of the cell). Once called "jumping genes", transposons are examples of mobile genetic elements and could be the origin of some viruses. They were discovered in maize by Barbara McClintock in 1950. This is sometimes called the vagrancy hypothesis.

3) Co-evolution hypothesis

Viruses may have evolved from complex molecules of protein and nucleic acid at the same time as cells first appeared on earth and would have been dependent on cellular life for many millions of years. Viroids are molecules of RNA that are not classified as viruses because they lack a protein coat. However, they have characteristics that are common to several viruses and are often called subviral agents. Viroids are important pathogens of plants. They do not code for proteins but interact with the host cell and use the host machinery for their replication. The hepatitis delta virus of humans has an RNA genome similar to viroids but has protein coat derived from hepatitis B virus and cannot produce one of its own. It is therefore a defective virus and cannot replicate without the help of hepatitis B virus. Similarly, the virophage 'sputnik' is dependent on mimivirus, which infects the protozoan Acanthamoeba castellanii. These viruses that are dependent on the presence of other virus species in the host cell are called satellites and may represent evolutionary intermediates of viroids and viruses.

Morphology of Viruses:

1) Shape

Viruses are of different shapes such as spheroid or cuboid (adenoviruses), elongated (potato viruses), flexuous or coiled (beet yellow), bullet shaped (rabies virus), filamentous (bacteriophage M13), pleomorphic (alfalfa mosaic), etc.

2) Size

Viruses are of variable size. Sizes vary from 20 nm to 300 nm in diameter. They are smaller than bacteria; some are slightly larger than protein and nucleic acid molecules and some are about of the same size (small pox virus) as the smallest bacterium and some virus (virus of lymphogranuloma, 300-400 um) are slightly larger than the smallest bacterium.

3) Viral structure

Virion: complete infectious virus particle, consists of nucleic acid core surrounded by a protective coat of protein called a capsid. These are (capsid) formed from identical protein subunits called capsomers. The complete set of virion is known nucleocapsid. In turn the nucleocapsid may be naked or enveloped by a loose covering (figure 1).

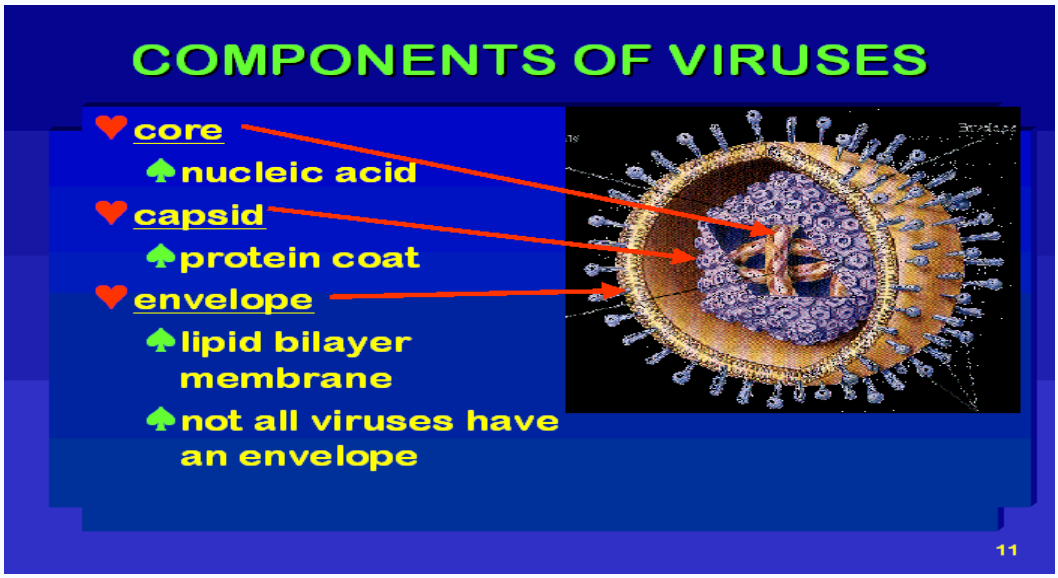
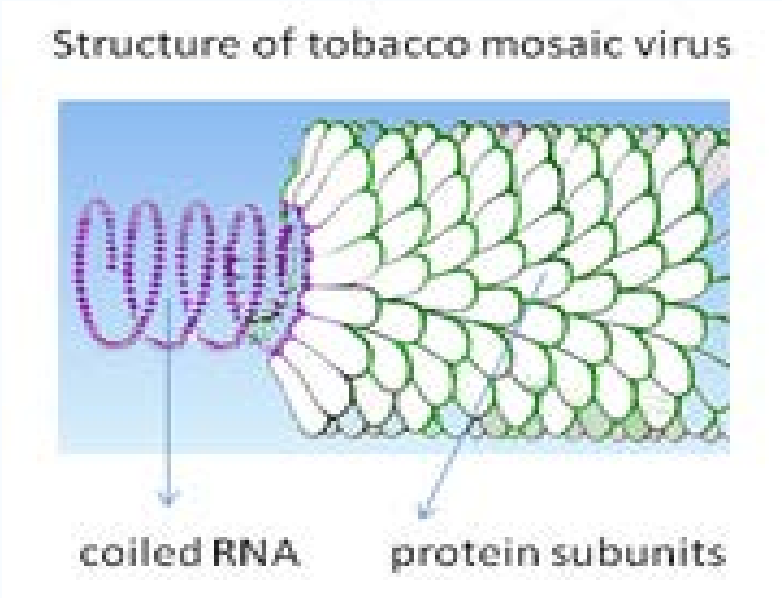


Figure 1: Component of viruses.

Chemically the envelope is made up of proteins and glycoproteins. Due to the presence of lipid the envelope seems flexible and loose. Envelope is composed of both the host and viral components i.e. protein (virus specific) and carbohydrates (host specific). There are certain projections on the envelope known as spikes which are arranged into distinct units. In general, there are four main morphological virus types:

1 - Helical (cylindrical) viruses:

These viruses are composed of a single type of capsomer stacked around a central axis to form a helical structure, which may have a central cavity, or hollow tube. This arrangement results in rod-shaped or filamentous virions: these can be short and highly rigid, or long and very flexible. The genetic material, generally single-stranded RNA, but ssDNA in some cases, is bound into the protein helix by interactions between the negatively charged nucleic acid and positive charges on the protein. Overall, the length of a helical capsid is related to the length of the nucleic acid contained within it and the diameter is dependent on the size and arrangement of capsomers. The well-studied Tobacco mosaic virus is an example of a helical virus, figure 2.



RNA coiled in a helix of repeating protein sub-units

Figure 2: Tobacco mosaic virus.

2-Icosahedral (polyhedral) viruses:

Most animal viruses are icosahedral or near-spherical with icosahedral symmetry. A regular icosahedron is the optimum way of forming a closed shell from identical sub-units. The minimum number of identical capsomers required is twelve, each composed of five identical sub-units. Many viruses, such as rotavirus, have more than twelve capsomers and appear spherical but they retain this symmetry. Capsomers at the apices are surrounded by five other capsomers and are called pentons. Capsomers on the triangular faces are surrounding by six others and are call hexons figure 3.

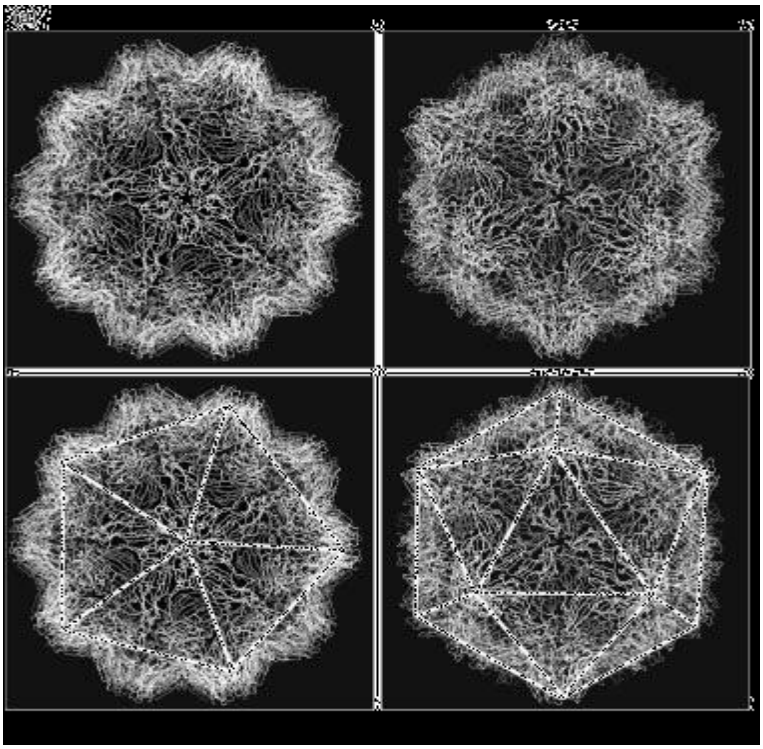
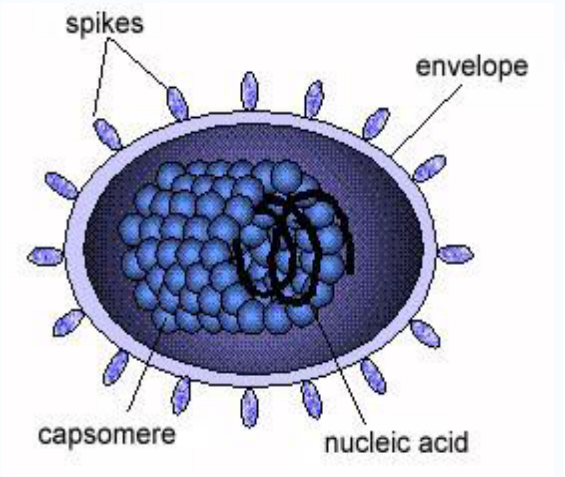


Figure 3 :Electron micrograph of icosahedral adenovirus.

3-Envelope viruses:

Some species of virus envelope themselves in a modified form of one of the cell membranes, either the outer membrane surrounding an infected host cell, or internal membranes such as nuclear membrane or endoplasmic reticulum, thus gaining an outer lipid bilayer known as a viral envelope. This membrane is studded with proteins coded for by the viral genome and host genome; the lipid membrane itself and any carbohydrates present originate entirely from the host. The influenza

virus and HIV use this strategy. Most enveloped viruses are dependent on the envelope for their infectivity figure 4.



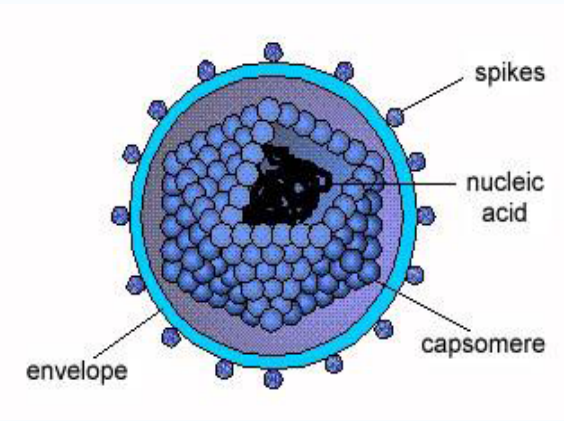


Figure 4: Enveloped helical virus **Enveloped icosahedral virus**

4- Complex viruses:

These viruses possess a capsid that is neither purely helical, nor purely icosahedral, and that may possess extra structures such as protein tails or a complex outer wall. Some bacteriophages, such as Enterobacteria phage T4 have a complex structure consisting of an icosahedral head bound to a helical tail, which may have a hexagonal base plate with protruding protein tail fibers. This tail structure acts like a molecular syringe, attaching to the bacterial host and then injecting the viral genome into the cell figure 5.

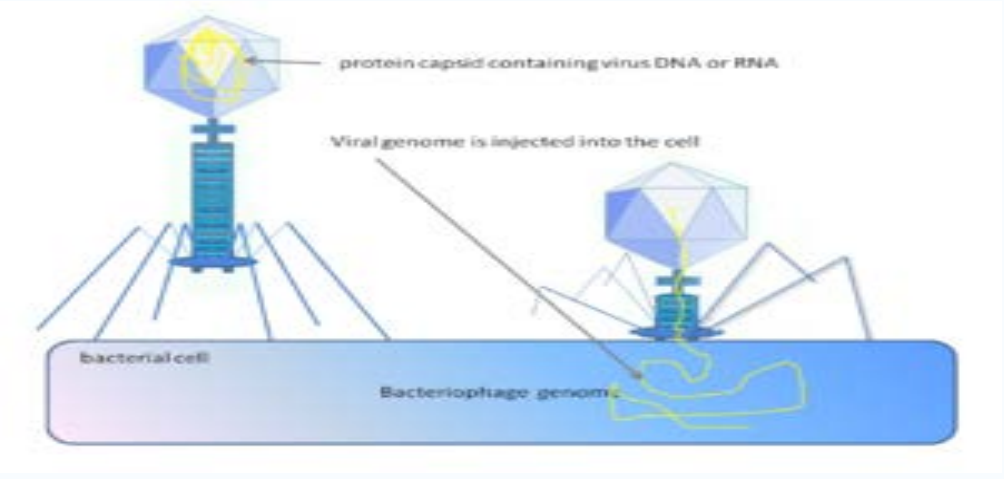


Figure 5: Some bacteriophages inject their genomes into bacterial cells.

Chemical composition of Viruses:

1) Viral protein

Proteins found in viruses may be grouped into the four categories:

a- Envelope protein: Envelope of viruses consists of proteins specified by both virus and host cell. Membranes of all class of enveloped viruses contain glycoprotein which differ from virus to virus, for example, one glycoprotein in rhabdoviruses, two glycoprotein in paramyxoviruses and four in orthomyxoviruses.
b- Nucleocapside protein: the viral capsids are made up totally of protein of identical subunits (promoters). The helical capsids contain single type of protein (TMV) and icosahedral capsid contains several types of protein (adenovirus contain 14 protein type).
c- Core protein: Protein found in the nucleic acid is known as core protein.
d- Viral enzyme: In animal viruses especially in the enveloped viruses, many virion specific enzymes have been characterized, for example RNase, reverse transcriptase in retrovirus.

The structural proteins have several impotent functions. The major purpose is to facilitate transfer of viral nucleic acid from one host cell to another. The serve to protect the viral genome against inactivation by nucleases, participate in the attachment of the virus particle to a susceptible cell, provide structural symmetry of the virus particle, and determine the antigenic characteristics of the virus.

2) Viral nucleic acid

Viruses contain either single or double strand DNA or RNA molecules that encode the genetic information necessary for viral replication. The nucleic acid may be in linear or circular form, and segmented or nonsegmented.

3) Viral envelope

There are containing plant and animal viruses and bacteriophages, both icosahedral and helical, which are surrounded by a thin membranous envelope. This envelope is about 10-15 µm thick. It is made up of protein, lipids and carbohydrate which are combined to form glycoprotein and lipoprotein. Lipid provide flexibility to the

shape, therefore, viruses look of variable sizes and shapes. The spikes attached to the outer surface of the envelope are made up of glycoproteins figure 6.

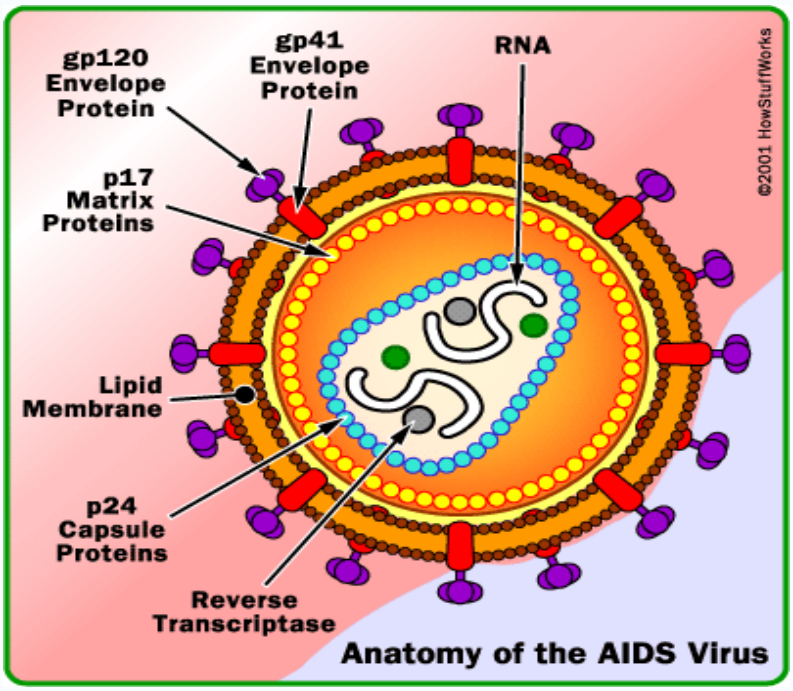


Figure 6: HIV virus

4) Viral carbohydrates

A substantial amount of carbohydrate specified by rather host cell (arbovirus) or viral genome (vaccinia virus) is found in viral envelope. For example galactose, mannose, glucose, glucosamine, galactosamine are found in influenza virus, parainfluenza virus (figure 7).

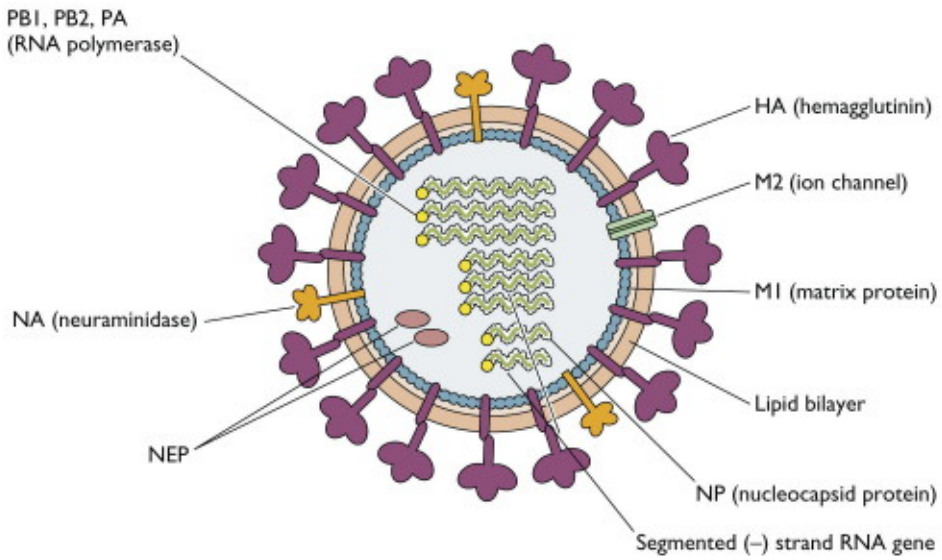


Figure 7: Influenza virus.

Taxonomy and classification of viruses:-

Virus classification involves naming and placing viruses into a taxonomic system. Like the relatively consistent classification systems seen for cellular organisms, virus classification is the subject of ongoing discuss and suggestions. This is largely due to the pseudo-living nature of viruses, which are not yet definitively living or non-living. As such, they do not fit neatly into the established biological classification system in place for cellular organisms, such as eukaryotes and prokaryotes.

Basis of Classification

The following properties have been used as a basis for the classification of viruses. The amount of information available in each category is not the same for all viruses. The way in which viruses are characterized is changing rapidly. Genome sequencing is now often performed early in virus identification, and genomic sequence data are advancing taxonomic criteria (eg, gene order) and may provide the basis for the identification of new virus families.

(1) Virion morphology, including size, shape, type of symmetry, presence or absence of peplomers, and presence or absence of membranes.

(2) Virus genome properties, including type of nucleic acid (DNA or RNA), size of genome in kilobases (kb) or kilobase pairs (kbp), strandedness (single or

double), whether linear or circular, sense (positive, negative, ambisense), segments (number, size), nucleotide sequence, G + C content, and presence of other special features.

(3) Physicochemical properties of the virion, including molecular mass, buoyant density, pH stability, thermal stability, and susceptibility to physical and chemical agents, especially ether and detergents.

(4) Virus protein properties, including number, size, and functional activities of structural and nonstructural proteins, amino acid sequence, modifications (glycosylation, phosphorylation, myristylation), and special functional activities (transcriptase, reverse transcriptase, neuraminidase, fusion activities).

(5) Genome organization and replication, including gene order, number and position of open reading frames, strategy of replication (patterns of transcription, translation), and cellular sites (accumulation of proteins, virion assembly, virion release).

(6) Antigenic properties.

(7) Biologic properties, including natural host range, mode of transmission, vector relationships, pathogenicity, tissue tropisms, and pathology.

1- ICTV classification

The International Committee on Taxonomy of Viruses began to devise and implement rules for the naming and classification of viruses early in the 1990s, an effort that continues to the present day. The ICTV is the only body charged by the International Union of Microbiological Societies (IUMS) with the task of developing, refining, and maintaining a universal virus taxonomy. The system shares many features with the classification system of cellular organisms, such as taxon structure. Viral classification starts at the level of order and follows as thus, with the taxon suffixes given in italics:

Order (*-virales*)

Family (*-viridae*)

Subfamily (*-virinae*)

Genus (*-virus*)

Species

So far, six orders have been established by the ICTV:

1- *Caudovirales* are tailed dsDNA (group I) bacteriophages.
2- *Herpesvirales* contains large eukaryotic dsDNA viruses.
3- *Mononegavirales* includes non-segmented (-) strand ssRNA (Group V) plant and animal viruses.
4- *Nidovirales* is composed of (+) strand ssRNA (Group IV) viruses with vertebrate hosts.
5- *Picornavirales*, contains small (+) strand ssRNA viruses that infect a variety of plant, insect, and animal hosts .
6- *Tymovirales* contains monopartite ssRNA viruses that infect plants.

Currently (2012) 7 orders, 96 families, 22 subfamilies, 420 genera, and 2,618 species of virus have been defined.

2- Baltimore classification

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 acid (DNA or RNA), strandedness (single-stranded or double-stranded), Sense, and method of replication. Other classifications are determined by the disease caused by the virus or its morphology, neither of which are satisfactory due to different viruses either causing the same disease or looking very similar. In addition, viral structures are often difficult to determine under the microscope. Classifying viruses according to their genome means that those in a given category will all behave in a similar fashion, offering some indication of how to proceed with further research. Viruses can be placed in one of the seven following groups:

- I: **dsDNA viruses** (e.g. Adenoviruses, Herpesviruses, Poxviruses)
- II: **ssDNA viruses** (+)sense DNA (e.g. Parvoviruses)
- III: **dsRNA viruses** (e.g. Reoviruses)
- IV: **(+)ssRNA viruses** (+)sense RNA (e.g. Picornaviruses, Togaviruses)
- V: **(−)ssRNA viruses** (−)sense RNA (e.g. Orthomyxoviruses, Rhabdoviruses)
- VI: **ssRNA-RT viruses** (+)sense RNA with DNA intermediate in life-cycle (e.g. Retroviruses)
- VII: **dsDNA-RT viruses** (e.g. Hepadnaviruses)

3- Holmes classification

Holmes (1948) used binomial nomenclature to classify viruses into 3 groups under one order, Virales. They are placed as follows:

- **Group I:** *Phaginae* (attacks bacteria)
- **Group II:** *Phytophaginae* (attacks plants)
- **Group III:** *Zoophaginae* (attacks animals)

4-LHT System of Virus Classification

The LHT System of Virus Classification is based on chemical and physical characters like nucleic acid (DNA or RNA), Symmetry (Helical or Icosahedral or Complex), presence of envelope, diameter of capsid, number of capsomers. This classification was approved by the Provisional Committee on Nomenclature of Virus (PNVC) of the International Association of Microbiological Societies (1962). It is as follows:

- **Phylum Vira** (divided into 2 subphyla)
- **Subphylum Deoxyvira** (DNA viruses) **Subphylum Ribovira** (RNA viruses)
- **Class Deoxybinala** (dual symmetry) **Class Ribocubica**
- **Order Urovirales** **Order Togovirales**
- **Family Phagoviridae** **Family Arboviridae**

Modes of Transmission of Viruses

Ecology is the study of interactions between living organisms and their environment. Different viruses have evolved ingenious and often complicated mechanisms for survival in nature and transmission from one host to the next. The mode of transmission utilized by a given virus depends on the nature of the interaction between the virus and the host.

Viruses may be transmitted in the following ways:

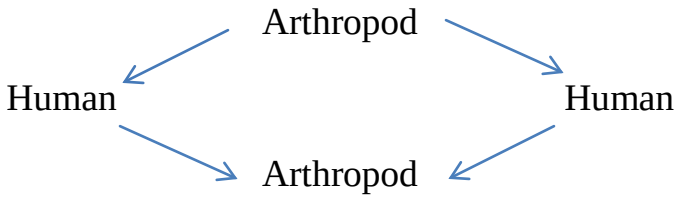
(1) Direct transmission from person to person by contact. The major means of transmission may be by droplet or aerosol infection (eg, influenza, measles, smallpox); by the fecal-oral route (eg, enteroviruses, rotaviruses, infectious hepatitis A); by sexual contact (eg, hepatitis B, herpes simplex type 2, human immunodeficiency virus); by hand-mouth, hand-eye, or mouth-mouth contact (eg, herpes simplex, rhinovirus, Epstein-Barr virus); or by exchange of contaminated blood (eg, hepatitis B, human immunodeficiency virus).

(2) Transmission from animal to animal, with humans an accidental host. Spread may be by bite (rabies) or by droplet or aerosol infection from rodent-contaminated quarters (eg, arenaviruses, hantaviruses).

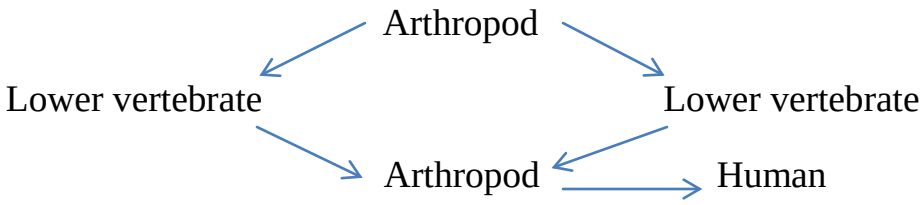
(3) Transmission by means of an arthropod vector (eg, arboviruses, now classified primarily as togaviruses, flaviviruses, and bunyaviruses).

At least three different transmission patterns have been recognized among the arthropod-borne viruses:

(1) **Human-arthropod cycle:** ***Examples:*** Urban yellow fever, dengue.

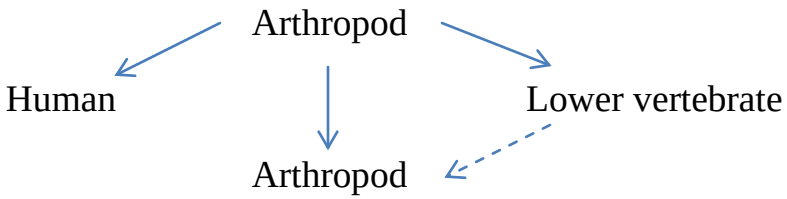


(2) **Lower vertebrate-arthropod cycle with tangential infection of humans:** ***Examples:*** Jungle yellow fever, St. Louis encephalitis. The infected human is a "dead end" host. This is a more common transmission mechanism.



(3) **Arthropod-arthropod cycle with occasional infection of humans and lower vertebrates:** ***Examples:*** Colorado tick fever, LaCrosse encephalitis.

In this cycle, the virus may be transmitted from the adult arthropod to its offspring through the egg (transovarian passage); thus, the cycle may continue with or without intervention of a viremic vertebrate host.



In vertebrates, the invasion of most viruses evokes a violent reaction, usually of short duration. The result is decisive. Either the host succumbs or it lives through the production of antibodies that neutralize the virus. Regardless of the outcome, the sojourn of the active virus is usually short, although persistent or latent infections that last for months to years may occur (hepatitis B, herpes simplex, cytomegalovirus, retroviruses). In arthropod vectors of the virus, the relationship is usually quite different. The viruses produce little or no ill effect and remain active in the arthropod throughout the latter's natural life. Thus arthropods, in contrast to vertebrates, act as permanent hosts and reservoirs.

Virus replication

Viruses are obligate intracellular pathogens and require cellular enzymes to help them replicate. Unlike bacteria, which replicate by binary fission, viruses have to 'disassemble' their structure before they can replicate. The steps of viral replication can be broadly divided into: attachment, cell entry, virus disassembly or uncoating, transcription and translation of viral genome, and viral assembly and release.

1-Attachment

The first step in the replication cycle is the attachment of the virus particle to the cell surface. To do this specific viruses use specific cellular receptors on the cell surface and therefore are very specific in the cell type that they can infect cell, this gives them the 'cell tropism' and is important in disease pathogenesis (i.e. why some viruses affect certain organs only). Influenza viruses use the haemagglutinin (HA) protein to attach to the sialic acid-containing oligosaccharides on the cell surface. Viruses may use more than one cell receptor, for example HIV uses the CD4 receptor to attach to the CD4 T-helper cells, but it also uses a chemokine receptor CCR5 as a co-receptor. It is now believed that most viruses use more than one receptor on the cell surface in a sequential binding process.

2-Cell entry

Viruses may enter the cell directly by endocytosis or, for enveloped viruses, by fusion of their lipid envelope with the cell membrane.

3-Virus disassembly or uncoating

Before the virus can replicate, the viral genome has to be exposed by removal of the associated viral proteins. This is usually mediated by the endocytosed viral particle merging with cellular lysosomes; the resulting drop in pH dissociates the viral genome from its binding protein.

4-Transcription and translation of viral genome

How a virus replicates is dictated by the structure of its viral genome.

- **Viruses containing SS+ RNA** use their+ RNA as mRNA and utilize the cell's ribosomes and enzymes to translate the information contained in this RNA to produce viral proteins. One of the first proteins to be produced is a RNA-dependent RNA polymerase, which then transcribes viral RNA into further RNA genomes. These viruses, because they can subvert the cellular system for their own replication, do not need to carry the information for the initial replication enzymes within their genome (e.g. Picornaviruses, Togaviruses).

- **Viruses containing SS -RNA** need to convert it first to a +RNA strand, which is then used as an mRNA template for translation or direct transcription to the genomic -RNA. They therefore need to carry a viral-specific RNA-dependent RNA polymerase (e.g. Orthomyxoviruses, Rhabdoviruses).

- **DS RNA viruses** have to first convert the -RNA strand of the DS RNA into a complementary +RNA to be used as mRNA. The +RNA strand of the DS RNA acts as a template for viral genome replication. These viruses also need to carry the RNA-dependent RNA polymerase to initiate the first steps of viral replication (e.g. Reoviruses).

- **SSRNA-RT viruses (+ strand or sense) RNA with DNA intermediate in life-cycle** (e.g. Retroviruses). Instead of using the SS +RNA as an mRNA template, the RNA is first transcribed into complementary DNA by an RNA-dependent DNA polymerase in a process called reverse transcription (hence the name, retro = reverse). The normal transcription is always from DNA to RNA. Further transcription then occurs as for other SS DNA viruses, see below.

- **DNA virus** mRNA is transcribed from the DS DNA viruses in a similar fashion to cellular DNA replication. These viruses can therefore completely depend upon the cellular process to replicate. The genome of these viruses (e.g. cytomegalovirus (CMV), Epstein–Barr virus (EBV)) needs to carry information to code for the virus specific proteins only. Regulatory proteins and those required for viral

DNA synthesis are coded early on and the later proteins are generally structural proteins (e.g. Adenoviruses, Herpesviruses, Poxviruses).

- **Single stranded DNA** viruses are first converted into double stranded, and then mRNA is transcribed as for the DS DNA viruses (e.g. Parvoviruses).

5-Viral assembly and release

Before the virus particle can be released its proteins and genome have to be assembled within the cell as a 'viral package'. This process may require the cell to alter viral proteins by glycosylation etc. Viral release may occur either through cell death or through viral budding from the cell membrane. Enveloped viruses use the latter mechanism and acquire their lipid envelope at this stage. Viral enzymes such as the neuraminidase (NA) of influenza viruses (which acts on the sialic-acid bond on the cell surface to release the infectious virus particle) may be required for the viruses released via budding.

VIRAL PATHOGENESIS

1- Entry and Primary Replication

In order for host infection to occur, a virus must first attach to and enter cells of one of the body surfaces-skin, respiratory tract, gastrointestinal tract, urogenital tract, or conjunctiva. Most viruses enter their hosts through the mucosa of the respiratory or gastrointestinal tract (Table 1). Major exceptions are those viruses that are introduced directly into the bloodstream by needles (hepatitis B, HIV), by blood transfusions, or by insect vectors (arboviruses).

Table 1. Common Routes of Viral Infection in Humans.

Route of Entry	Virus Group	Produce Local Symptoms at Portal of Entry	Produce Generalized Infection Plus Specific Organ Disease
Respiratory tract	Parvovirus	-	B19
	Adenovirus	Most types	
	Herpesvirus	Epstein-Barr virus, herpes simplex virus	Varicella virus
	Poxvirus	-	Smallpox virus
	Picornavirus	Rhinoviruses	Some enteroviruses
	Togavirus		Rubella virus
	Coronavirus	Most types	
	Orthomyxovirus	Influenza virus	
	Paramyxovirus	Parainfluenza viruses, respiratory syncytial virus	Mumps virus, measles virus
Mouth, intestinal tract	Adenovirus	Some types	
	Herpesvirus	Epstein-Barr virus, herpes simplex virus	Cytomegalovirus
	Picornavirus		Some enteroviruses, including poliovirus and hepatitis A virus
	Reovirus	Rotaviruses	
Skin Mild trauma	Papillomavirus	Most types	
	Herpesvirus	Herpes simplex virus	
	Poxvirus	Molluscum contagiosum virus, orf virus	

Injection	Hepadnavirus		Hepatitis B
	Herpesvirus		Epstein-Barr virus, cytomegalovirus
	Retrovirus		Human immunodeficiency virus
Bites	Togavirus		Many species, including eastern equine encephalitis virus
	Flavivirus		Many species, including yellow fever virus
	Rhabdovirus		Rabies virus

Viruses usually replicate at the primary site of entry. Some, such as influenza viruses (respiratory infections) and rotaviruses (gastrointestinal infections), produce disease at the portal of entry and have no necessity for further systemic spread. They spread locally over the epithelial surfaces, but there is no invasion of underlying tissues or spread to distant sites.

2- Viral Spread and Cell Tropism

Many viruses produce disease at sites distant from their point of entry (eg, enteroviruses, which enter through the gastrointestinal tract but may produce central nervous system disease). After primary replication at the site of entry, these viruses then spread within the host. Mechanisms of viral spread vary, but the most common route is via the bloodstream or lymphatics. The presence of virus in the blood is called **viremia.** Virions may be free in the plasma (eg, enteroviruses, togaviruses) or associated with particular cell types (eg, measles virus) (Table 2). Some viruses even multiply within those cells. The viremic phase is short in many viral infections. In some instances, neuronal spread is involved; this is apparently how rabies virus reaches the brain to cause disease and how herpes simplex virus moves to the ganglia to initiate latent infections.

Table 2. Viruses Spread Via the Bloodstream		
Cell Type Associated	**DNA Viruses**	**RNA Viruses**
Lymphocytes	Epstein-Barr virus, cytomegalovirus, hepatitis B virus, JC virus, BK virus	Mumps, measles, rubella, human immunodeficiency virus
Monocytes-macrophages	Cytomegalovirus	Poliovirus, human immunodeficiency virus, measles virus
Neutrophils		Influenza virus
Red blood cells	Parvovirus B19	Colorado tick fever virus
None (free in plasma)		Togavirus, picornavirus

Viruses tend to exhibit organ and cell specificities. Thus, tropism determines the pattern of systemic illness produced during a viral infection. As an example, hepatitis B virus has a tropism for liver hepatocytes, and hepatitis is the primary disease caused by the virus.

Tissue and cell tropism by a given virus usually reflect the presence of specific cell surface receptors for that virus. Receptors are components of the cell surface with which a region of the viral surface (capsid or envelope) can specifically interact and initiate infection. Receptors are cell constituents that function in normal cellular metabolism but also happen to have an affinity for a particular virus. The identity of the specific cellular receptor is known for some viruses but is unknown in many cases.

Factors affecting viral gene expression are important determinants of cell tropism. Enhancer regions that show some cell-type specificity may regulate transcription of viral genes. For example, the JC polyomavirus enhancer is much more active in glial cells than in other cell types.

Another mechanism dictating tissue tropism involves proteolytic enzymes. Certain paramyxoviruses are not infectious until an envelope glycoprotein undergoes proteolytic cleavage. Multiple rounds of viral replication will not occur in tissues that do not express the appropriate activating enzymes.

Viral spread may be determined in part by specific viral genes. Studies with reovirus have demonstrated that the extent of spread from the gastrointestinal tract is determined by one of the outer capsid proteins.

3- Cell Injury and Clinical Illness

Destruction of virus-infected cells in the target tissues and physiologic alterations produced in the host by the tissue injury are partly responsible for the development of disease. Some tissues, such as intestinal epithelium, can rapidly regenerate and withstand extensive damage better than others, such as the brain. Some physiologic effects may result from nonlethal impairment of specialized functions of cells, such as loss of hormone production. Clinical illness from viral infection is the result of a complex series of events, and many of the factors that determine degree of illness are unknown. General symptoms associated with many viral infections, such as malaise and anorexia, may result from host response functions such as cytokine production. Clinical illness is an insensitive indicator of viral infection; inapparent infections by viruses are very common.

4- Recovery from Infection

The host either succumbs or recovers from viral infection. Recovery mechanisms include both innate and adaptive immune responses. Interferon and other cytokines, humoral and cell-mediated immunity, and possibly other host defense factors are involved. The relative importance of each component differs with the virus and the disease.

The importance of host factors in influencing the outcome of viral infections is illustrated by an incident in the 1940s in which 45,000 military personnel were inoculated with hepatitis B virus-contaminated yellow fever virus vaccine. Although the personnel were presumably subjected to comparable exposures, clinical hepatitis occurred in only 2% (914 cases), and of those only 4% developed serious disease.

In acute infections, recovery is associated with viral clearance. However, there are times when the host remains persistently infected with the virus. Such long-term infections are described below.

5- Virus Shedding

The last stage in pathogenesis is the shedding of infectious virus into the environment. This is a necessary step to maintain a viral infection in populations of hosts. Shedding usually occurs from the body surfaces involved in viral entry. Shedding occurs at different stages of disease depending on the particular agent involved. It represents the time at which an infected individual is infectious to contacts. In some viral infections, such as rabies, humans represent dead-end infections, and shedding does not occur.

Lec. 5 **Virology**

Immunity to viruses

The immune response to viral infections could be divided in to:

(a) Innate immune response .

(b) Specific immune response .

A- Innate immune response:- (non–specific immure responses): include :

(1)- Cells of the innate immune system include: - Monocytes and Macrophages, natural killer cells (NK), dendritic cells and poly – morphonuclear leucocytes (PMNs). These populations are dependent on bone marrow for development and maturation.

Monocytes and Macrophages and dendrite cells are generally found at high concentrations in lymph nodes as well as blood and spleen while NK cells are not generally found in lymph nodes during systemic viral infection, but they have been shown to be called into draining lymph nodes after local challenge with antigen or parasites.

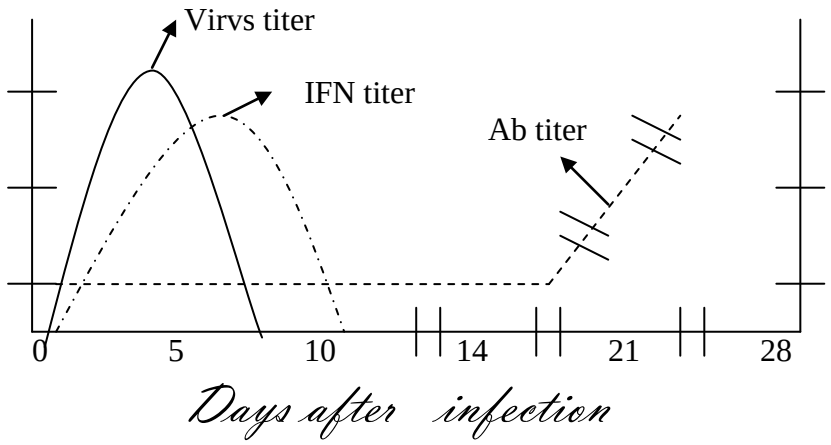
Active NK cells are detected within 2- days of a virus infection. They have been identified as major effectors cell against herpes viruses and in particular cytomegalovirus (CMV). NK cells are also one of the main mediators of Antibody – dependent cell – mediated cytotoxicity (ADCC).

(2)- Interferons :

- These cytokines are the most important to virologists.
- They discovered by Isaacs and Lindenmann in 1957.
- They are host – coded proteins that inhibit viral replication and are produced by intact animals or cultured cells in response to viral infection or other inducers.
- They are produced by all vertebrate species.
- They are believed to be the body's first line of defense against viral infection.
- They are modulating humoral and cellular immunity and have broad cell-growth regulatory activities.
- There are 3-general groups of interferon (IFN)
  (a) I FN -α: synthesized mainly by leucocytes
  (b) IFN -β: synthesized mainly by fibroblasts
  (c) IFN -γ (immune IFN): synthesized mainly by lymphocytes.

- ❖ The different IFNs are similar in size, but the three classes are antigenically distinct.
- ❖ RNA viruses are stronger inducers of interferon than DNA viruses.
- ❖ IFNs also can be induced by double – stranded RNA, bacterial endotoxin, and small molecules.
- ❖ IFN-γ: is not produced in response to most viruses but is induced by mitogern stimulation.
- ❖ The different types of IFN are roughly equivalent in antiviral activity.

- IFN- γ (type I) is produced soon (within a day) after infection.
- The cell regulatory activity of IFN –γ is much greater than that of IFN – α or β.
- IFNs- are almost always a host species- specific in function, by contrast, IFN activity is not specific for a given virus: the replication of a wide variety of viruses can be inhibited.



Mechanism of action :- After a cell has come in contact with a virus or some other IFN induced , IFN released from virus infected cells binds to receptors on neighboring cells and induces an antiviral state , the mechanism may involve inhibition of viral protein or nucleic acid synthesis or may be virus assembly , it also may inhibit cell growth .

The mechanism in which IFN –inhibit protein synthesis , is by induce the synthesis of two enzymes , protein kinase and oligoadinylate synthetase and these two enzymes subsequently block viral reproduction .

IFN also may increase recognition of viral antigens by the immune system and it may activate the NK cell, macrophages, B-cell and cytotoxic cells.

(3) Complement: The complement system is an important component of the innate immune response to infection and present in all vertebrates

(4) Acute – phase proteins: These comprise several plasma proteins which are more important in immuring to bacterial than viral infection. They are mostly produced in the liver and include C- reactive protein.

(5) Collectins : These proteins bind to carbohydrate molecules or microbial surface and activate the alternative complement pathway .

B- Specific immune resporse:-

Host defense involving B and T cells: -

1- Humoral immunity:-

Abs and complement can limit viral spread or reinfection and Abs can neutralize the activity of viruses. Additional effects of Abs are:-

- Antibodies provide a major barrier to virus spread between cells and tissues and are particularly important in restricting virus spread in the blood stream.
- Opsonization: facilitation of phagocytosis by the attachment of Ab to virion.
- Lyses of infected cells by activation of the complement system.
- Antibody- dependent cellular cytotoxicity (ADCC): killer cell bears receptors for FC end these cells are attached to the FC of Ab molecule which in turn are attached to viral Ag on the cell surface.

2- Cellular mediated immunity (CMI):

T-cell mediate viral immunity exhibit a variety of functions in antiviral immunity. Most of Ab response in thymus- dependent requiring the presence of CD4+ T cell. CD4+ T cells also help in the induction of CD8+ cytotoxic T-cells and activation of macrophages at sites of virus infection. MHC (major histocompatibilty cells) class I restricted cytotoxic T CD8+ cells focus at the site of virus replication and destroy virus infected cells.

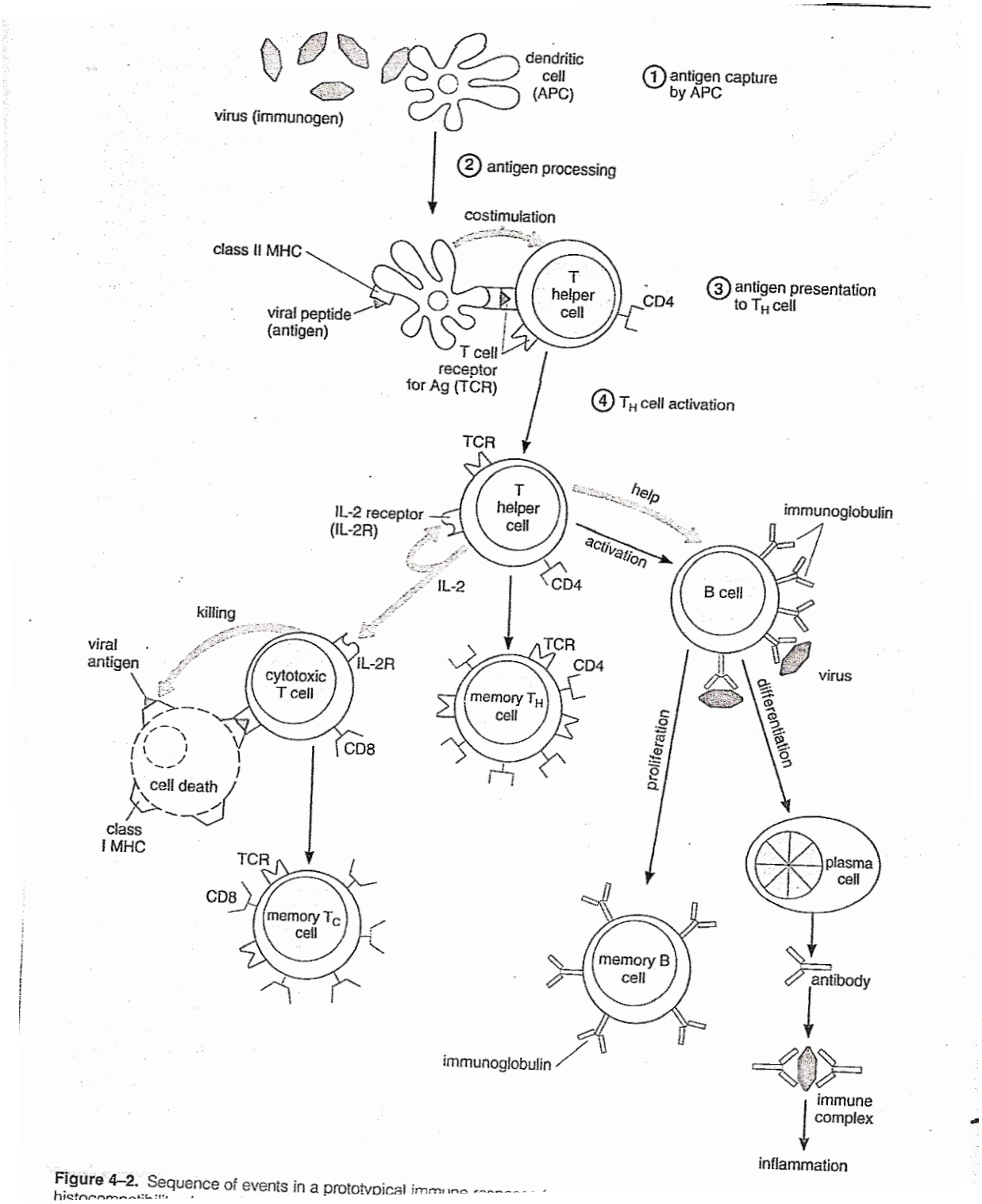
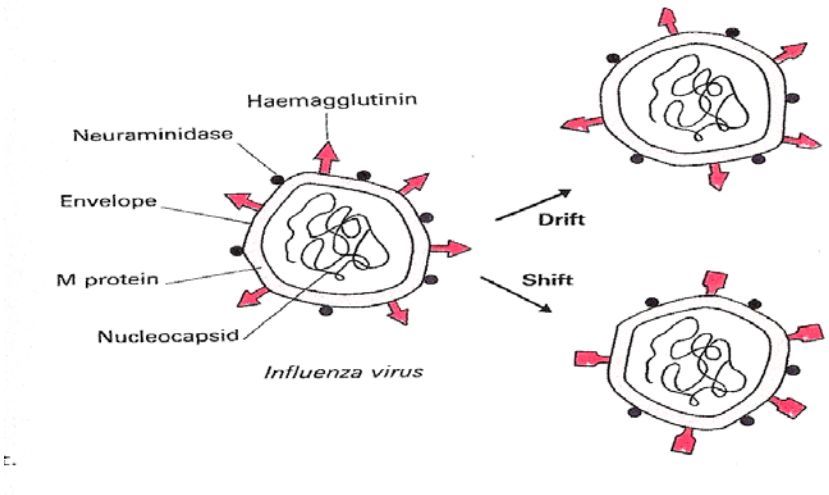


Figure 4–2. Sequence of events in a prototypical immune response (histocompatibility

Antigenic shift and drift:

Viruses have evolved various strategies to evade recognition by Ab, this occurs by antigenic variation. E.g. HIV and foot and mouth disease virus and influenza virus that is responsible for the antigenic shift and drift.

In influenza virus the major surface antigens are haemagglutinine and neuraminidase. This virus can change its surface slightly (antigenic drift) or radically (antigenic shift).



Viral vaccines:

General principle: Immunity to viral infection is based on the development of an immune response to specific antigen located on the surface of viral particles or virus- infected cell. For enveloped virus, the important antigens are the surface glycoprotein.

Vaccination is major factor to control disease and the main effect is to protect individual against infection. Vaccines can be divided in to:

A. **Killed- virus vaccines (inactivated vaccine):** They are made by purifying viral preparation to a certain extent and then inactivating viral infectivity in a way that does minimal damage to the viral structural proteins: mild formalin treatment is frequently used. They generally stimulate the development of circulating Ab against the coat proteins of the virus.

♦The immunity is often brief and must be boosted.

♦ Extreme care should be made that no residual live virulent virus is present in the vaccines.

♦ The cell-mediated response to inactivated vaccines is generally poor.

♦ Some killed- virus vaccines have induced hypersensitivity to subsequent infection.

♦ It could be either whole virus vaccine or subunit vaccine.
Ex. Hepatitis A, Poliomyelitis (subcutaneous), Influenza, Rabies

B. Attenuated live- virus vaccines: It is utilizing viral mutants that antigenically overlap with wild-type virus.
They selected naturally attenuated strains or by cultivating the virus serially in various hosts and cultures.

- They acting like natural infection.
- They multiply in the host and tend to stimulate longer- lasting Ab production to induce a good cell- mediated response, and to induce Ab production. But there is a risk of reversion to greater virulence during multiplication within the vaccine.
  Ex. Varicella, measles, mumps, Rubella, poliomyelitis (oral).

"Advantages and Disadvantages live and inactivated virus vaccine"

Properties	Live vaccine	Inactive vaccine
Rout of administration	By any route e.g. orally,IM,or injection	Injection
Number of doses	Single	Multiple
Need for adjuvant	No	Yes
Duration of immunity	Many years	Generally less
Antibody response	IgG, IgA	IgG
Cell mediated immunity	Good	Poor
Heat liability	Heat liable	Heat stable
Interference	Occasionally	No
Side- effect	Mild symptoms	Severe
Dose coast	Low	High
Reversion to virulence	yes	No

Treatment (Antiviral chemotherapy):

Because viruses are obligate intracellular parasites, antiviral agents must be capable of inhibiting viral function without damaging the host. There is a need for antiviral drugs active against viruses for which vaccines are not available or not highly effective, because of a multiplying of serotypes (e.g. rhinoviruses, influenza, HIV).

In general antiviral agents are very limited because of their toxicity. Antiviral chemotherapy should be chosen in such a way that they affect on the steps of replication of the virus either they inhibit entry of the virus in to the host cells or they prevent replication of the virus by inhibiting certain peptides which are responsible for viral replication.

"Major antiviral compounds used for treatment of viral infection"

Drug	Mechanism of action	Viral spectrum
Acyclovir	Viral polymerase inhibitor	Herpes virus
Vidarabine	= = =	Herpes simplex, Varicella-Zoster
Ganciclovire	= = =	Cytomegalovirus (CMV)
Foscarnet	= = =	CMV, Hepes simplex, Varicella-Zoster, HIV-1
Amantadine	Blocks viral uncoating	Influenza A
Didanosine	Reverse transcriptase inhibitor	HIV-1, HIV-2
Zalcitabine	= = =	= =
Zidovudine	= = =	= =
Idoxuridine	Viral thymidine kinase inhibitor	Viral herpes keratitis
Ribavirine	Perhaps blocks capping of viral m-RNA	Respiratory syncytial virus, influenza A, &B, Lassa fever

Viral Diseases

Introduction of Viruses with medical important

Viruses are particles of parasitic DNA or RNA. Most DNA viruses are double- stranded, except for the single- stranded Parvoviruses. RNA viruses are single- stranded, except for the double- stranded reoviruses.

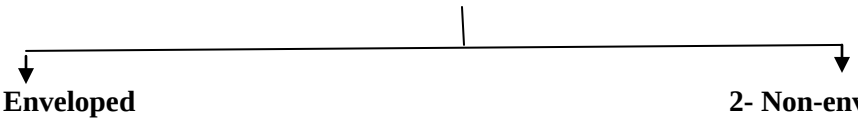
Viral disease varies in severity, depending on virulence of the virus and age, health, and habitat of the human host. Lifelong immunity develops to some but not all viral agents. Virus infection can be diagnosed by overt symptoms, cultures, antigen detection, and nucleic acid probes.

Most DNA and some RNA viruses can cause chronic infection and combine with the host genome. They also have the potential to activate host oncogenes.

Survey of DNA virus groups:

There are six major groups of DNA viruses; enveloped DNA viruses include the poxvirus, herpes viruses, and hepadnaviruses. The non- enveloped group include adenoviruses papoviruses and parvoviruses.

DNA virus Family



1- Enveloped

***Poxviridae:** Small pox, molluscum Contagiosum

Complex structure,lack capsid

*** herpesviridae:** Cold sore, Mononucleosis

Bud off nucleus, tend to be latent

***Hepadnaviridae:** Hepatitis B

Unusual genome containing both Double and single- stranded DNA

2- Non-enveloped

***Adenoviridae:** Common cold Keratoconjunctivitis

***Papovoviridae:** Common and genital warts

***Parvoviridae:** Erythema contagiosum

Unusual single- stranded DNA

I- Enveloped Viruses

1-Pox viruses:

These are the largest viruses of all. They measure about 230* 270 nm and when suitably stained can just be seen with an ordinary light microscope. Their structure is referred to as complex.

Unlike most DNA viruses, the pox viruses replicate only in cytoplasm. The virion enters the cells either by endocytosis or by a fusion event, and release from the cells by budding.

Poxviruses produce eruptive skin pustules called pocks or pox, which have depressed scars (pock markers) upon healing.

Among the best known poxviruses are Variola, the agent of small pox and Vaccinia a closely related virus used in vaccination. The incubation period of variola was 12 days.

Exposure to small pox usually occurred through inhalation of droplets or skin crust. Infection was associated with fever, malaise, prostration and later a rash that began in the pharynx, spread to the face and progressed to the extremities.

Lab. Diagnosis:

Small pox was usually diagnosed by clinical sign and symptoms. It must be differentiated from chickenpox, disseminated herpes, vaccinia, monkey pox and certain non viral lesions. Scanning stained smears of vesicular fluid for cytoplasmic inclusion bodies. The virus can be isolated by inoculation the chorioallantoic membrane of chicken eggs with species and looking for pocks, or by direct examination of clinical material in the electron microscope.

Serology: Antibody assay can be used to confirm a diagnosis and can be detected by neutralization assay, ELISA or immunofluorescence test.

Treatment and Prevention:

Vaccinia immunoglobulin can be used or ***Methisazone,** a thiosemicarbazone, would prevent or modify an attack if given during the incubation period.

*New antiviral drug **"Marboran",** a thiosemicarbazone, was used to treat some of the last smallpox infections three decade ago.

* A more modern drug **"Cidofovir",** show antiviral effects in animal models.

Prevention: There was an effective vaccine.

2-Herpes viruses:

There are seven herpes viruses that commonly infect humans, herpes simplex virus type 1 and 2, Varicella- Zoster virus, Cytomegaloviruses, Epstein- Barr virus and human herpes viruses 6 and 7.

Important properties of herpes viruses:

1- **Virion:** Herpes viruses are large viruses, with dss DNA with icosohedral symmetry and have 162 capsomers. The nucleocapsid is surrounded by an envelope that is derived from the nuclear membrane of the infected cells and contains viral glycoprotein spikes "some virion is naked". The herpes virus genome is large enough to code for at least 100 different proteins.

2- **Replication:** Herpes viruses enter the cell by fusion with the cell membrane after binding to specific cellular receptors by an envelope glycoprotein. The nucleocapsid transported through the cytoplasm to a nuclear pore, uncoating occurs and the DNA become associated with the nucleus and then viral DNA replication begins. Maturation occurs by budding. The length of the replication cycle varies from about 18 hrs for herpes simplex to 70 hrs for cytomegalovirus.

- Herpes viruses establish latent infection, persist indefinitely in infected host and are frequently reactivated in immunosupressed hosts.

***Herpes virus disease:**

A wide variety of diseases are associated with infection of herpes viruses. Primary infection and reactivation by herpes virus may involve different cell types and present different clinical pictures.

A- Herpes Simplex virus: Type 1 and 2 infect epithelial cells and established latent infections in neurons. **Type 1** is classically associated with oropharyngial lesions and cause recurrent attacks of "fever blister". **Type 2** primarily infect the genital mucosa and is mainly responsible for genital herpes. Both viruses are also cause neurologic disease, and both of them can cause neonatal infections which are often severe.

Laboratory diagnosis:

1- Inoculations of tissue cultures with appearance of CPE in cell culture in 2-3 days suggest the presence of HSV.

2- Serology: Abs appear in 4-7 days after infection. They can be measured by NT, CF, ELISA, and RIA. The diagnoses value of serologic assay is limited by the multiple antigens shared by HSV-1 and HSV- 2.

3- EM.

Treatment and Prevention: A cyclovir is effective for herpes virus and experimental vaccines of various types are developed.

B- Varicella- Zoster virus: Varicella (chicken pox), Zoster (Herpes zoster or Shingles zona).

Varicella: is a mild highly infectious disease of children characterised clinically by a vesicular eruption of the skin and mucous membrane and in immunocompromised children, the disease may be severe.

Zoster: is a sporadic in capacitative disease of adult (is recurrent manifestation of chicken pox after 10-50 years), that is characterised by an inflammatory reaction of the posterior nerve roots and ganglia accompanied by crops of vesicles over the skin.

Both diseases are caused by the same virus.

The incubation period in varicella is usually 14-21 days and there is malaise and fever followed by the rash all over the body.

The incubation period in zoster is unknown and the disease start with malaise and fever followed by severe pain in the area of skin or mucosa and appearance of vesicles over the skin supplied by the affected nerve.

Lab. Diagnosis:

1- Microscopic examination of scrapings or swab of the vesicular lesion, multinucleated giant cells is seen using haematoxylin- eosin staining.
2- Immunofluorescence staining.
3- Serology: by ELISA, CFT, and IFT.

Treatment: 1- By Gamma globulin of high specific Ab titer.

2-In cancer patients the early treatment of zoster with IFN.
3-A cyclovir and Vidarabine.

C- Cytomegalovirus (CMV): Cause opportunistic infections of tow forms:

1- <u>Congenital infection:</u> or cytomegalic inclusion disease. The virus transmitted through placenta especially in first few weeks.
The affected child with jaundice, hepatospleenomegally, thrombocytopenia, haemolytic anaemia, and mental retardation (due to CNS damage).
The cells are large (cytomegalo cells) with large intranuclear inclusion found in the salivary gland, lung, liver, kidney, and pancreas.

2- <u>Post- natal infection:</u> In children acquired infection may result in hepatitis, intestinal pneumonitis, or acquired anaemia in adults.
CMV can cause an infectious mononucleosis like disease.
The incubation period is about 30-40-days, and is transmitted by blood transfusion, organ transplantation, and prolonged shedding of virus in urine and saliva suggests a urine- hand- oral route of infection.

Lab. Diagnosis: 1- By isolation of virus in tissue culture and clinically by specimen of urine sample, throat swab and blood.

2-serological way by: ELISA, CFT, and RIA, for CMV class to confirm the recent infection especially in pregnant and immunocompromised patients.

Treatment: No specific treatment, neither immunogamma globulin nor DNA virus inhibitory drugs have any effect.

D- Epstein- Barr virus (EBV): Is the causative agent of **acute infectious mononucleosis** and has been associated with **Burkitts' lymphoma** and a factor in the development of **nasopharyngeal carcinoma**, and other lymphproliferative disorders in immunodeficient individual.

3- Hepatitis virus: viral hepatitis is a systemic disease, primarily involving the liver. Most cases of acute viral hepatitis in children and adults are caused by one of the following agents: hepatitis A virus (HAV) (RNA), HBV (DNA), HCV (RNA), and HEV (also called non A non B virus). Other viruses can cause hepatitis such as CMV, HAV, Rubella virus, EBV, and yellow fever virus.

Hepatitis virus produces acute inflammation of the liver, resulting in a clinical illness characterized by similar symptoms that are fever, gastrointestinal symptoms such as nausea and vomiting and jaundice, dark urine, yellowish in skin and eyes, and diarrhoea.

5% of infected person fail to dominate the virus and become persistently infected, the high risk groups include babies, children and immunocompromised patients. Patients who had persistent infection are at high risk to develop hepatocellular carcinoma (HCC).

Mode of transmission of virus is blood transfusion or blood products, contaminated syringes, or by sexual intercourse because viruses secreted in genital secretions also virus secrete in saliva, also pregnant women can infects fetus and the baby will be carried the virus and fecal contamination of food.

Lab. Diagnosis: virus surface antigen can be detected by ELISA or detecting viral particle by using electron microscope or detection of antibodies by using ELISA test.

Treatment and Control: For HB virus there is antiviral drug (vidarabin) and a vaccine that has been available.

II-Non-enveloped DNA Viruses:

1- Adenoviruses: These are 80 strains discovered and classified as Adenoviruses, but about 30 types are associated with human infection and the rest are animal pathogen.

Epidemiology: They are spread from person to person by means of respiratory and ocular secretions.

Pathogenicity: The patient infected with an adenovirus is typically feverish, with acute rhinitis, cough, and inflammation of pharynx, enlarged cervical lymphnodes and a macular rash. Also cause keratoconjuctivitis.

Treatment and Prevention:

Severe cases of adenovirus infection can be treated with interferon in the early stage.

An inactivated polyvalent vaccine prepared from viral antigens is an effective preventive measure.

2- Papovaviruses: (Papilloma virus)

A papilloma is a benign, squamous epithelial growth commonly referred to as a wart, or verruca, and caused by one of 40 different strains of human papilloma virus (HPV).

1- Painless, elevated, rough growths on the fingers and occusionaly on other body parts are called common, or seed, warts. These are commonly occurring in children and young adults.

2- Plantar warts are deep, painful papillomas on the sole of the feet; flat warts are smooth, skin- colored lesions that develop on the face, trunk, elbows and knees.

3- A special form of papilloma known as genital warts is a prevalent STD and is linked to some types of cancer.

Epidemiology: Warts are transmissible through direct contact with a wart or contaminated fomites, and they can also spread on the same person by autoinoculation. The incubation period varies from 2 weeks to more than a year.

Lab. Diagnosis: The warts caused by papilloma viruses are usually distinctive enough to permit reliable clinical diagnosis without much difficulty. A biopsy and histological examination can help by sensitive DNA probes.

Treatment and Prevention:

For all warts types, direct chemical application of podophyllin and physical removal of affected skin or laser surgery.

Interferon is effective in many cases. Because treatment may not completely destroy the virus. Warts can be recurred.

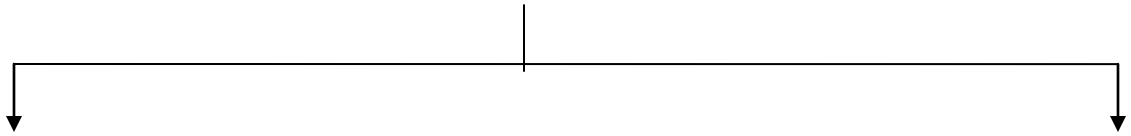
3-Parvoviruses (PV):

They are unique among the viruses in having single- stranded DNA molecules. They are also notable for their extremely small diameter (18-26 nm) and genome size.

The most important human PV is (B 19), the cause of erythema contagiosum, a common infection in children. Often the infection goes unnoticed, though the child may have a low- grade fever and a bright red rash on the cheeks. The same virus can be more dangerous in children with immunodeficiency or sickle- cell anemia, because it destroy red blood stem cells.

RNA- viruses of Medical Important

RNA-Virus Family



1- Enveloped

I-Segmented, single-stranded, negative-sense Genome (ssRNA,_ve sense)

***Orthomyxoviridae:** Influenza

***Bunyaviridae:** California encephalitis virus
Hantavirus hemorrhagic fever

***Arenaviridae:** Hemorrhagic fevers, Lassa fever virus

II-Non-segmented,ssRNA,_ve sense

***Paramyxoviridae:** Mumps virus,
Measles v., Respiratory syncytial v.

***Rhabdoviridae:** Rabies

***Filoviridae:** Ebola fever v.

III-Non- segmented, ssRNA,+ve sense

***Togaviridae:** Rubella v.

***Flaviviridae:** Yellow fever, Dengue fever v.

Coronaviridae: Common cold v., SARS

IV- SSRNA,+ve sense, Reverse transcriptase

***Retroviridae:**AIDS (HIV),T-cell leukemia v.

2- Non- enveloped

I- Nonsegmanted,ssRNA,+ve Sense Genome

***Picrnaviridae:** Poliov.,Hepatitis A,
Rhinoviruses

***Claciviridae:** Norwalk agent

II- Segmented,DsRNA,+ve sense, Double capsid

***Reoviridae:** Tick fever v.,
Rotavirus gastroenteritis

Note: If the RNA of the virus is in a form ready to be translated by the hosts' machinery, it is considering + ve sense genome, and if it is not directly translatable by the host, it is _ ve sense genome.

- **Orthomyxoviridae:**

Orthomyxovirus virions consist of pleomorphic lipid-containing envelope with large peplomers within which is a helical neucleocapsid with a diameter of 9-15 nm. Virions are 90-120 nm in diameter but may be filamentous with length up to several micrometers.

The genome consists of seven (infl. C) or eight (Infl. A&B) segments of linear, _ ve sense ssRNA.

Most orthmyxovirus particles have spikes as a part of their outer wall. During replication the helical nucleocapsid is first detected in nucleus, whereas the hemagglutinin (HA) and neuraminidase (NA) are formed in the cytoplasm.The virus matures by budding at the cell surface membrane.

Influnza A,B and C viruses are infect human.

Influenza A viruses are infect swine, horses, fowl, and many other species of bird. Influnza C virus is infecting swine.

Human strains can infect different animals. They grow well in chick embryo.

The viruses enter the respiratory tract in air borne droplets. Virus is present in the nasopharyngeal from 1-2 days before to 1-2 days after onset of symptoms. The local symptoms due to cell mediated immune response and interferon production.

Even when neutralizing antibodies are in the blood they may not protect against infection, antibodies must be present in sufficient concentration at the superficial cells of the respiratory tract, and this can be achieved only if the AB level in the blood is higher or if Ab is secreted locally.

Clinical findings: The incubation period is 1 or 2 days. Chills, malaise, fever, muscular aches, and cough.

Epidemic recorded: (Influenza A)

1890 H2N8

1900 H1N1

*1918 H3N8 (this kills 20-40 million in 12 months).

1957 H2N2

*1997 H5N1 (bird flu) – avian influenza

*2005, all eyes are focused on H5N1 — bird flu

*2008 H1N1 (swine flu)

The death usually of secondary bacterial infection that may infect damaged respiratory epithelium.

Global pandemic may occur if:

1- New subtype of influenza A virus is introduced into the human population.
2- The virus cause serious illness in human.
3- The virus can be spread from person to person.

Lab. Diagnosis: 1- Virus isolation: nasal washing and throat swabs are the best specimens for viral isolation. The cell culture is done in embryonated egg by amniotic rout and monkey kidney.

2- **Serology:** by CFT, HI, NT, virus detected in nasal swab and tested for IF Abs.

Prevention and Treatment: Amantadine hydrochloride and Remantadine may induce protection from influenza A illness, but drug resistant mutants of virus developed and spread. Vaccine is the prevention of influenza but control of disease by immunization is difficult.

Paramyxoviruses and Rubella virus:

The paramyxoviruses include the most important agents of respiratory infection of infant and young children (respiratory syncytial virus and para influenza viruses) as well as the causative agents of tow of the most common contagious disease of childhood (mumps and measles).

All members of the paramyxoviridae family initiate infection by the respiratory tract; replication of the respiratory pathogens is limited to the respiratory epithelia, whereas measles and mumps become disseminated throughout the body and produce generalized disease.

Paramyxoviruse **virion** is spherical 150-300 nm in diameter (helical nucleocapsid), ssRNA, viral genome is linear, nonsegmented –ve sense, the nucleocapsid is surrounded by a lipid envelope; it contains viral hemagglutinin and neuraminidase activities and is responsible for host cell attachment. **Viruses replicate** in the cytoplasm of the host cells and bud from plasma membrane.

Viruses are transmitted by direct person to person contact or by large-droplet. The infection may spread deeper to the lower trachea and bronchi.

**Lab. Diagnosis: ***Throat and nasal swabs are good specimens for isolation.

* Tissue culture in human and monkey kidney.

* Hemagglutination inhibition.

* Serology by NT, HI, ELISA, or CF test.

Mumps: It is acute contagious disease, characterised by enlargement of paratoid glands and salivary glands. Infected man unable to eat, drink without discomfort. Other glands may be involved; ovary, thyroid, testes, and breast.

Diagnosis: 1- Virus isolation: from saliva or urine inoculated to monkey kidney culture, detected by RBC adsorption.

2- Rise in Ab titre by CFT, HI.

Treatment and Control: There are no available anti-viral drugs effective against mumps virus. Immunization with attenuated live mumps virus vaccine is the best approach to reduce mumps association infection.

Measles: It is acute highly infectious disease characterised by macuolopapular rash, fever and respiratory symptoms. When virus reaches the brain, it is become fetal disease that results in brain disorders causing mental deterioration; it is of persistent infection those develope years after measles infection.

Diagnosis: 1- Virus isolation: From blood in human amnion or cell kidney.

2- Serology: By NT, HI, and CFT.

Treatment and Control: There are no available antiviral drugs effective against measles. For control a highly effective, attenuated live measles vaccine is available.

Rubella: virus classified as a togavirus because of its chemical and physical properties but it can be considered with the paramyxoviruses on an epidemiologic basis.

Most of this family (Togavirus) infects human, they are mosquito born viruses except Rubella which has no insect vector, it spread directly from person to person.

Rubella (German measles): Virion: Are spherical, single stranded RNA, + sense. **Replication** in the cytoplasm and bud through host cell membrane.

Its mild disease however shows high risk to pregnant women, causing congenital rubella syndrome, and fetus.

MMR vaccine: Life attenuated vaccine for mumps, measles, and rubella viruses.

Coronaviridae:

The members of this family infect human, cattle, pigs, rodents, dogs and birds. The virus is regular shaped, enveloped; they have spikes act as receptors binding, some types have HA and esterase, they are + ve sense RNA.

- There replication cycle is slow (24hr), compared to influenza (6-8hr).
- The virus enters by endocytosis and membrane fusion, and replicates in the cytoplasm.
- In human: the virus cause: Severe Acute Respiratory Syndrome (SARS), enteric infections mostly in infants < 12 months.

SARS: It is form of viral pneumonia, when the infection in the lower respiratory tract. It appears in China and HongKong in 2002-2003, about 800 individuals were dead.

Symptoms: Influensa like symptoms, fever, dry cough, hypoxemia (low blood oxygen concentration); the infected person has elevated amino transferase, due to damaged liver. Death may result due to alveolar damage.

The worsen symptoms may be due to patients immune response rather than viral replication, but patients may relapse.

Diagnosis: 1- Serology: detected Abs by IF, ELISA, Abs appears >21 days after onset.

2- PCR can detected viral genome within 10 days after onset.

Vaccines: SARS virus is mutating into 2 forms, this complicate the work to develop vaccine.

Retroviridae: They infect wild range of animal species, causing many diseases as tumor, haemolytic anemia, acquired immune deficiency syndrome (AIDS), they include:

- HTLV-1 causes T cell leukemia, lymphoma.
- HIV-1 and HIV-2: AIDS.

HIV: The virus is +ve ssRNA, diploid, enveloped, undergoes variation, it has the **reverse transcriptase enzyme,** which make a copy of DNA from RNA, this DNA is integrated in to host DNA.

*The virus infect Th cell which carry the CD4 receptor, and macrophage. About 14 million individuals are infected up to 2004-2005, mostly in Africa.

Pathogenesis: The duration between primary infection and progression to clinical disease may take 10 years. The immune response occurs 1 week to 3 months after infection, but this immune response is unable to clear the infection and the virus persist in lymph nodes, this is called LATENCY.

The patients suffer from **opportunistic infections,** and the virus may reach the brain through monocytes, which release cytokines that are toxic to the neurons and the brain, patients may develop **Kaposi Sarcoma** (tumor of epithelial cells).

Symptoms: Rash, diarrhoea, fever, weight loss, white patches on tongue. The opportunistic infections by:

Protozoa: Toxoplasma; **Fungi:** *Candida albicans*; **Bacteria:** *M. tuberculosis, Salmonilla, Streprococcus*; **Viruses:** (CMV, HSV, HBV,VZV); **cancer:** lymphoma, Kaposi Sarcoma.

Diagnosis: 1- Virus isolation: From lymphocytes of blood, v. Growth in T.C. and then it's tested for reverse transcriptase activity or specific viral antigens.

2- PCR **3- Serology:** IgG detection (4-6 weeks after infection) viral antigens (envelop glycoprotein).

Treatment and Cotrol: There are 4- antiviral drugs used in treatment: Zidavodine, Didanosine, Zalcitabine, and Stavudine. These drugs are slow the progression of disease. Whole virus vaccine or subunit vaccines are typically preventive. **But the problems..... 1- the virus can mutate 2- lack of an appropriate animal model for HIV.**

Picornsviridae: They include the oldest known viruses 400BC. They are + ve sense RNA, with icosahedra capsid, they replicate in the cytoplasm and the viruses released when cell lyses.

Polioviruses: They belong to Enteroviruses. Virus is transmitted by facial and oral routs. Primary site for replication is lymphoid tissue associated with the gut, the production of the virus at this site leads to viremia then the virus infects CNS. Tow cell types are infected (lymphoid epithelial cells and neurons) this means there are 2 receptors.

Diagnosis: 1- CSF: increase leucocytes & increase protein content.

2- Virus isolation: from throat in monkey kidney culture.

3-Serology: by CFT, NT.

Treatment and Control: There is no antiviral drug available. Control by using either live- virus or killed virus vaccine.

EFFECTS OF VIRAL INFECTION ON CELLS

Viral pathogenesis is the process by which a viral infection leads to disease. The consequences of viral infections depend on the interplay between a numbers of viral and host factors.

These effects on infected cells may demonstrate:

1- Morphological alterations.

2- Lytic infection.

3- Persistence infection.

4- Transformation.

Lytic infection (Cytocidal)

Lysis of the cell is more common response to viral infection and these are the infection that most commonly studied in the laboratory because cell killing is the easiest effect to observe and production of infection progeny can usually be monitored without difficulty.

The mechanisms of host cell damage may due to the following:

1-Many viruses can inhibit host DNA, RNA and protein synthesis.

2-Cell lysosome may be damaged resulting in the release of hydrolytic enzymes and cell destruction.

3-Virus infection can alter plasma membrane through the insertion of virus specific proteins, so that the infected cells are attacked by the immune system.

4-High concentration of protein from the virus such as mumps virus, influenza virus can have a toxic effect on cells.

5-Inclusion bodies, which are the result of clustering of virion or subunits within the host cell nucleus or cytoplasm.

6-Chromosomal disruption result from infection by some viruses such as *herpesviruses*.

7-The host cell may not be directly destroyed but transformed into malignant cell.

Note: In general the cell lysis is a characteristic of infection by naked viruses but only some enveloped viruses may cause cell lysis.

Persistent Viral Infection

This infection results from a delicate balance between the virus and the host organism, last for long period, in which ongoing virus replication occurs, but the virus adjusts its replication and pathogenicity to avoid killing the host (Continuous production of virus particles). Retroviruses do not generally cause cell death, being released from the cell by budding rather than by cell lysis, and cause persistent infections. Conversely, Picornaviruses cause lysis and death of the cells in which they replicate, leading to fever and increased mucus secretion in the case of Rhinoviruses, paralysis for Poliovirus or death (usually due to respiratory failure).

The mechanisms that may play a role in the persistence of viruses include:

(1) Integration of a DNA virus into host cell DNA, as occurs with retroviruses, EBV and HPV.

(2) Immune tolerance, because neutralizing antibodies are not formed e.g. rubella virus present during a time of immunological immaturity in development.

(3) Formation of virus-antibody complexes, which remain infectious.

(4) Location within an immunologically sheltered "sanctuary, e.g., the virus present in brain.

(5) Rapid antigenic variation like HSV-1.

(6) Spread from cell to cell without an extracellular phase, so that virus is not exposed to antibody e.g. HPV.

(7) Immunosuppression, as in AIDS.

THERE ARE THREE TYPES OF PERSISTENT VIRAL INFECTIONS OF CLINICAL IMPORTANCE:

A. Chronic infections:

A chronic infection is a type of persistent infection that is last more than six months, replicate widely throughout the body with disease symptoms and may eventually cleared by the host, while latent or slow infections last the life of the host, (e.g. CMV, EBV, Hepatitis virus, HPV).

B. Latent infections:

The patient recovers from the initial infection, virus production stop and remains silent for long period with no symptoms or antibodies are detected. Subsequently, reactivation to cause acute disease e.g. herpes (genus Varicella virus) causing shingles (zoster), HSV-1 that activation at any time permitting virus to replicate and migrate to the facial over and produce disease. The rubella virus that may be acquired during pregnancy can persist silent in newborn for 12-18 months after birth. In some cases, virus remain a long silent period before disease e.g. HIV.

In a latent infection, the virus is able to down regulate its gene expression and establish an inactive state. Its genome may be integrated into the cellular genome or exists as episome to cause cancers e.g. EBV, HPV, HBV, HCV, HHV-8.

C. Slow vius infection:

A poor term for viruses causing slowly progressive disease. It include the viruses may cause diseases after a long incubation period in which symptoms may take months-years to emerge , particularly measeles virus, JC polyomavirus, PML, rabies (depending on the infection route), and prion.

Two of these diseases are caused by conventional viruses:

Subacute sclerosing panencephalitis (**SSPE**) is progressive encephalitis caused by a persistent infection measles virus (which can be a result of a mutation of the virus

itself) which follows several years after measles. The presence of the virus within the brain cells prevents them working properly and passing messages to each other. No cure for SSPE exists, but the condition can be managed by medication if treatment is started at an early stage.

Progressive multifocal leukoencephalopathy (PML) is a rare and usually fatal viral disease. It is caused by a type of polyomavirus called the JC virus. Immunosuppressive drugs prevent the immune system from controlling the virus. It occurs almost exclusively in people with severe immune deficiency, such as transplant patients on immunosuppressive medications, receiving certain kinds of chemotherapy, or has AIDS.

TRANSFORMATION (CANCER FORMATION)

Transformation is alteration in a cell's properties that leads to immortalization and different growth patterns that result from alteration in cell cycle.

Among the many altered properties of the transformed cell are [1]Loss of growth control (loss of contact inhibition in cultured cells), [2]Tumor formation, [3]mobility, [4]reduced adhesion, transformed cells frequently exhibit [5]chromosomal aberrations. *Cell transformation is accompanied by the persistence* of all or part of the viral genome and continual expression of a limited number of viral genes.

Oncogene: A gene that codes for a protein that potentially can transform a normal cell into a malignant cell. Cellular oncogenes (**Proto-oncogenes**) have growth control and differentiation functions, cells also have anti-oncogenes **(Tumor suppressor genes)** that suppress transformation. **Proto-oncogenes** (c-onc e.g. *myc*, *bcl*, *tcl*) are the form of cellular genes that inactive normally but can incorporate with the viral genome to produce a highly oncogenic virus. An oncogene may be transmitted by a virus in which case it is known as **viral oncogenes** (v-onc). V-onc is altered form of c-onc which characterized by rapid onset, high efficiency tumorigenesis (acute transforming). Viral-onc not essential viral gene & unrelated to strategy of viral replication.

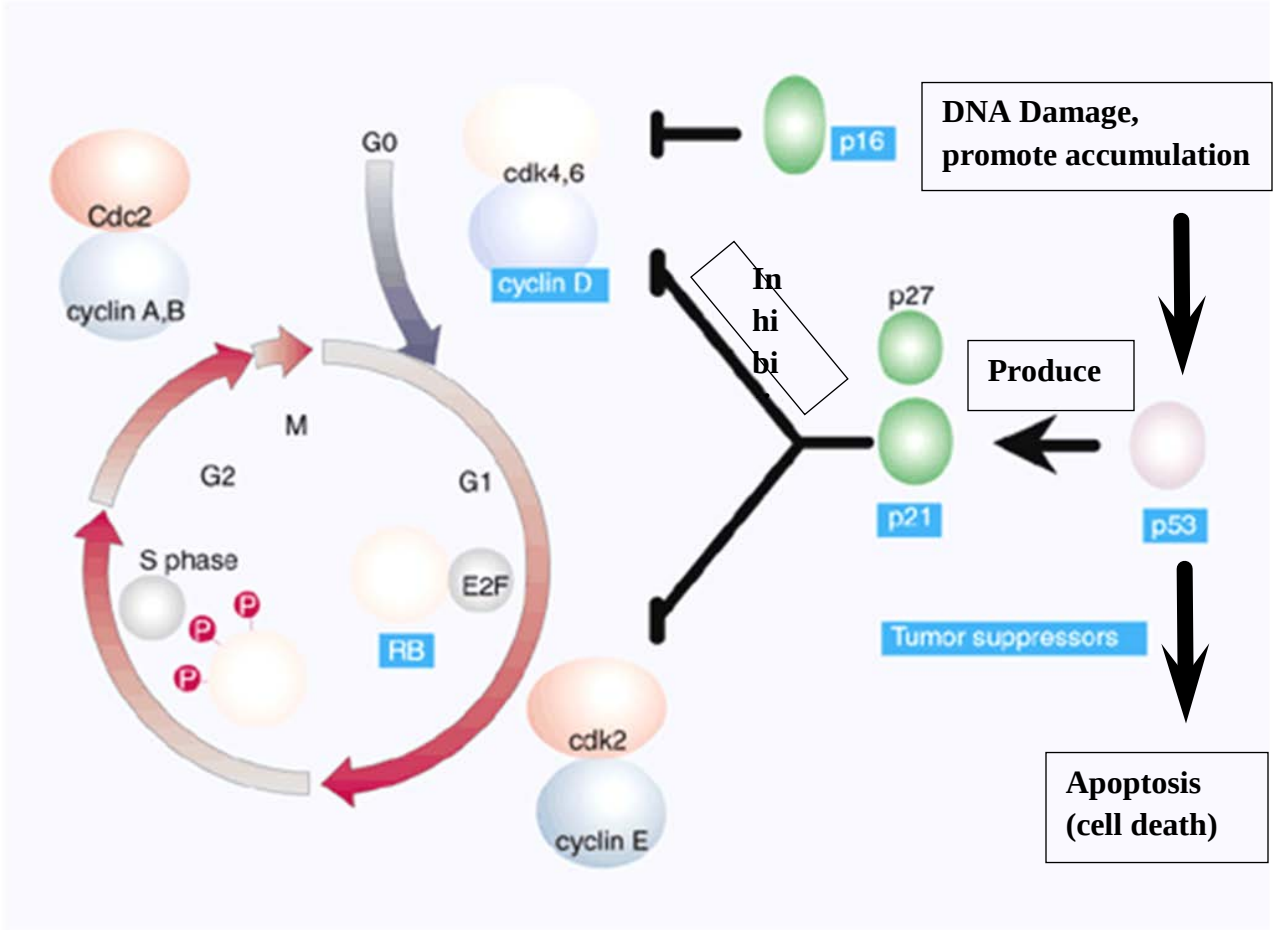
Activated Oncogenes: Stimulate Proliferation, Inhibit Differentiation, and Inhibit apoptosis.

Tumor Suppressor Genes: Inhibit proliferation, Promote differentiation, and Stimulate apoptosis.

Two different types of changes contribute to cancer formation: **inactivating, mutations** in tumor suppressor genes.

Tumor suppressor genes are **p53** and **Rb**, these are inactivated by oncogenes. p53 protects against cancer by inducing cell cycle arrest and/or apoptosis. Meanwhile, Rb binds to transcription factor E2F and prevents gene expression of proteins needed to go to S phase.

When p53 and Rb inactive form, DNA-damaged cells are not arrested in G1, DNA repair does not take place and enter to S phase.



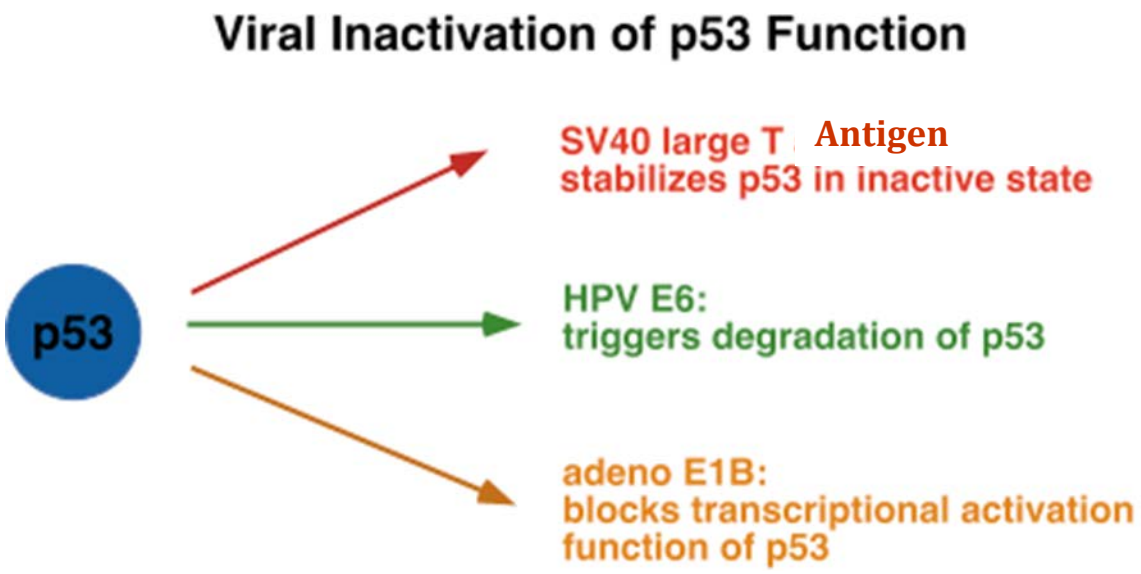
Taxonomy of Tumor Viruses

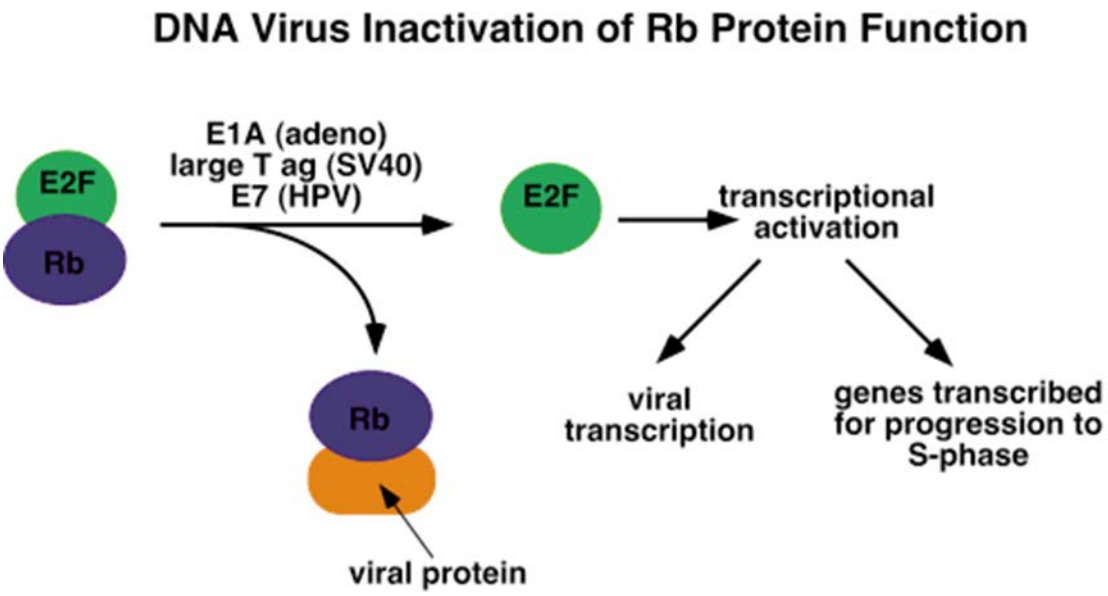
Oncogenic viruses may be RNA or DNA, 20% of human cancers believed to be of viral origin, whereas the Major cause of liver & cervical cancer was viral origin.

- DNA viruses are negating tumor suppressors and encode cellular mimics to activate signal transduction pathways that enhance cell proliferation.

Table 1. Human oncogenic viruses.

Taxonomic Grouping	Examples	Oncogenes	Tumor Types
1. DNA viruses			
Adenoviridae	Adenovirus types 12, 18, 31	E1A, E1B	Various solid tumors only in rodents
Hepadnaviridae	HBV	HBx	Hepatocellular carcinoma
Herpesviridae	EBV	LMP-1, BARF-1	Burkitt's lymphoma, B-cell lymphoma, NPC
	KSHV	vGPCR	Kaposi sarcoma, primary effusion lymphoma
Papovaviridae	Merkel cell polyomavirus	T antigens	Merkel cell carcinoma
	BK virus, JC virus		Solid tumors in rodents and primates
Papillomaviridae	HPV 16, 18, 31, 45	E6, E7	Cervical and anal cancer, Oral cancer
2. RNA Viruses			
Flaviviridae			
Hepacivirus	Hepatitis C virus	?	Hepatocellular carcinoma
Retroviridae			
HTLV	Human T-cell leukemia virus type I	Tax	Adult T-cell leukemia/lymphoma





➢ One of several EBV genes implicated in immortalization of B cells. EBV encodes a viral oncogene, LMP1 (latent membrane protein-1). LMP1 is expressed in EBV-associated lymphoma and is essential for B-cell transformation and for disruption of cellular signal transduction. BARF1 (BamHI-A reading frame-1) is also an early gene but is expressed as a latent gene in most nasopharyngeal carcinoma (NPC). Recent studies have suggested that BARF1 may have an important role in NPC oncogenesis.

➢ Kaposi sarcoma-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV8) infection is associated with all forms of Kaposi sarcoma, primary effusion lymphoma or body cavity–based B-cell lymphoma, and multicentric Castleman disease. KSHV encodes a viral G protein–coupled receptor (vGPCR) that presumably functions as a viral oncogene in immortalization of human endothelial cells and induction of angioproliferative tumors.

➢ Two human polyomaviruses (BK virus and JC virus) have been described as oncogenic in rodents and nonhuman primates. Recently, a new human polyomavirus, Merkel cell polyomavirus (MCV), was established MCC cell line contains monoclonal MCV DNA integration. The integrated MCV DNA encodes a mutant T antigen that prevents autoactivation of integrated virus replication.

- ➢ some serotypes, such as adenovirus types 2, 5, 12, 18, and 31, are capable of transforming rodent cells in culture and inducing tumors in hamsters or rats.

Two viral oncogenes, E1A and E1B, have been identified as responsible for the adenovirus tumorigenicity.

- Although the precise role of HBV in causing liver cancer is not yet understood, some compelling evidence suggests that the HBx gene could be a viral oncogene, as its protein product can disrupt signal transduction and deregulates cell growth. Recent studies indicate that HBx functions through the inhibition of proteasome activities to enhance HBV replication in vivo. HBx also binds to and enhances the enzymatic activity of phosphatidylinositol 3-kinase class III, an enzyme critical for the initiation of autophagy.

RNA tumor viruses "create OR activate" oncogenes by acquiring, modifying, deregulating cellular genes (***proto-oncogenes***) through:

1-Retroviral transduction of oncogene (Viral acquisition of cellular proto-oncogene with capacity to transform if deregulated, usually ***replacing*** viral coding sequences).

2-Oncogene (c-onc) activation by retroviral ***insertion*** (random retroviral integration into cell DNA, ***Cis activation*** by enhancer insertion next to proto-oncogene encoded by exons 1-3).

3-Oncogenesis mediated by essential retrovirus proteins (long-latency retrovirus).

4- HTLV-I transformed lymphocytes demonstrate wide range of chromosomal abnormalities, rearrangements, duplications and euploidy.

5-HepC (no DNA phase) - chronic inflammation and damage. Subsequently, viral proteins interact with p53 and lead to cell proliferation and prevent apoptosis (oncogene activate).

VIRAL GENETIC CHANGES AND NEW PROGENY

Regarding genetic variation in viruses, there are two principal mechanisms are involved mutations and interactions.

Antigenic variation is a direct result of mutation and interaction among viruses that play a prominent role in the epidemiology of influenza virus, coronavirus (SARS) and HIV in the human population, and mutation to drug resistance offers a significant challenge to the clinical management of virus infections with antiviral drugs.

A- Mutations

1-Temperature- Sensitive Mutation is a type of conditional lethality in which mutant can grow at low temperature (altered protein), but not a high temperature, in contrast to wild type virus which grows at both temperatures. This mutation produced by mixing the virus with chemical mutagen in order to live vaccine preparation, which used only for respiratory virus that give it intranasal and multiply in the upper respiratory tract when the temperature is lower than 37c this permissive to produce local immunity.

2-Plaque- morphology Mutations (show altered pathogenicity) in which the appearance of mutant plaques is readily distinguishable from wild type plaques. Most commonly, the morphologic distinction is plaque size; that is mutant plaques may be larger or smaller than wild type plaques. Examples from animal virus research include *large plaque mutants* of adenovirus and syncytial mutants of herpes simplex virus. The large plaque phenotype in adenovirus results from faster than normal release of virus from infected cells. Syncytial mutants of herpes virus express altered virus surface glycoproteins and result in fusion of infected cells, whereas wild type virus causes cells to round and clump without significant fusion. Thus, syn mutants form large plaques readily distinguishable from the smaller dense foci caused by wild type virus.

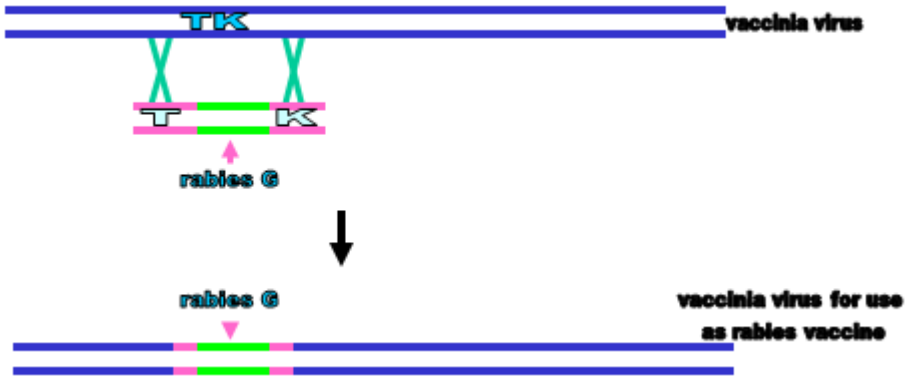
3-Host-Range Mutation is broadly defined as a mutant that grows on one cell type and not on another, in contrast to wild-type virus, which grows on both cell types. Two general subcategories of host-rang mutants exist: natural and engineered. Natural host-range virus mutants are relatively rare. Engineered host-range mutants are constructed by *deleting an essential gene of interest in the virus while creating a cell line that expresses the gene*. The engineered cell line provides a permissive host for growth of the mutant virus because it complements the missing virus function, whereas the normal host lacking the gene of interest provides a non-permissive host for study of the phenotype of the virus. This technology has been useful for attenuated vaccine preparation and for study of a variety of viruses, notably ***adenovirus*** and ***herpes simplex virus***, where it has facilitated the study of several essential virus genes.

B- Interactions

I- Genetic Interactions

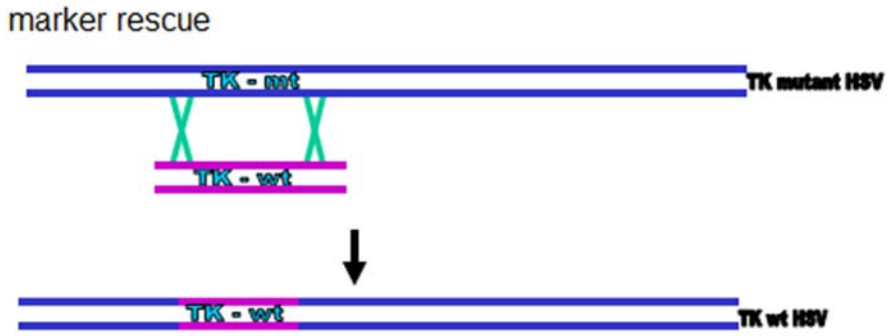
1- **Recombination (novel virus genotypes):** recombination describes a process by which nucleic acid sequences from two genotypically different parental viruses are exchanged so that the progeny contain sequences derived from both parents (emergence virus like SARS). In viral systems there exist three distinct mechanisms of recombination, which are dictated by the structures of the viral genomes. For DNA viruses, recombination occurs by the ***physical breakage and rejoining of parental DNA molecules*** (Fig.1) through regions of sequence homology, in a fashion similar to the same process in bacteria or higher organisms. Of the RNA viruses containing nonsegmented genomes, only picornaviruses, coronaviruses, togaviruses, and retroviruses display efficient recombination, which is thought to occur during replication via ***copy choice,*** namely switching templates (Fig.2) during replication such that the newly synthesized genome contains sequence from different parental molecules. For RNA viruses containing segmented genomes (e.g. Influenza virus), recombination occurs through ***reassortment*** of individual parental genome segmented into progeny viruses.

**Development of recombinant viruses for vaccines and therapeutic reasons.



2- **Genetic Reactivation**

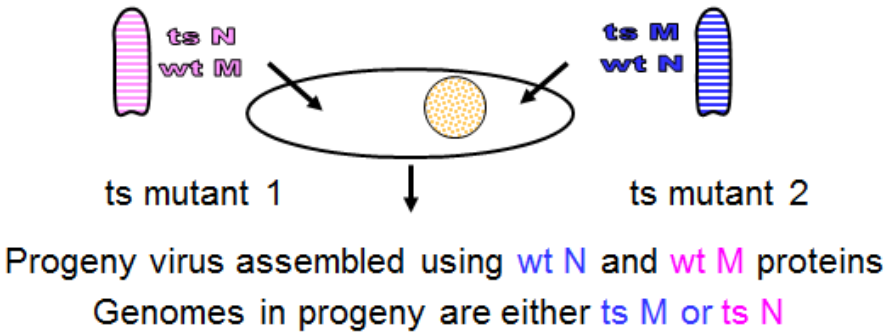
A- Marker rescue occurs between the genome of viral particle that has been inactivated in some way a portion of the genome of the inactivated virus recombines with that of the active parent so that certain markers of the inactivated parent are rescued and appear in the viable progeny none of the progeny are identical to the inactivated parent and the progeny carrying the rescue marker of the inactivated parent are genetically.



B- Multiplicity reactivation: This may occur when a heavily damaged nucleic acid of the parent producing a viable genome (active virus) that can replicate. The grantor the damage to the parental genomes the larger the number of inactivate particles required per cell to insure formation of a viable genome.

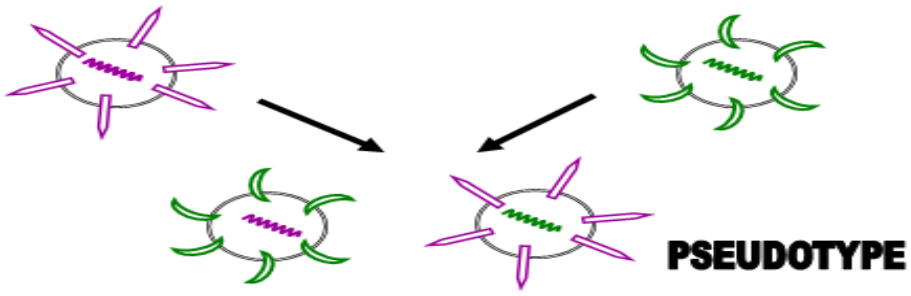
II- Non-Genetic Interactions

1- Complementation: Interaction at functional level, not nucleic acid in the cell infected between two viruses. In complementation one virus provides a ***gene product*** in which the second is defective that allowing the second virus to grow. If both mutants are defective in the same gene products, they will not be able to complement each other's growth.

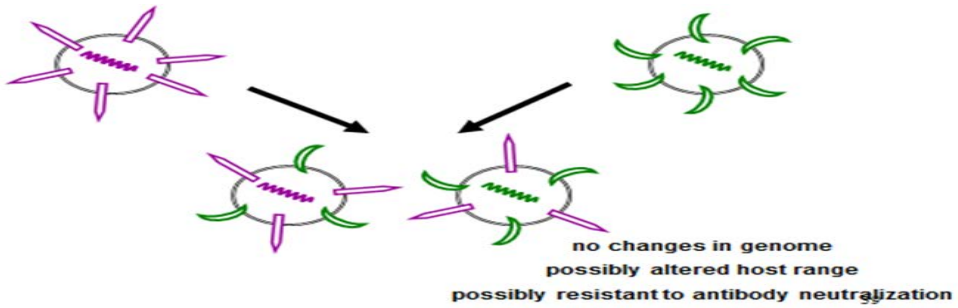


2-Phenotypic Mixing: This means the association of a *genotype with heterologous phenotype*. It usually occurs between different members of the same viral family like picornaviruses as distantly related as echovirus 7 and coxsackievirus A9. In the case of **enveloped viruses**, phenotypic mixing consists of packing the nucleocapsid (*Transcapsidation*) of one virus within an envelope of a heterologous virus, and the resulting viruses are called ***pseudotypes***. For example, pseudotypes have been formed that contain retrovirus envelope antigens combined with nucleocapsid from paramyxoviruses, orthomyxoviruses, or herpesviruses. In naked viruses, the genome of one virus becomes randomly incorporated within capsid consisting of both virus components.

- Transcapsidation and pseudotype formation.



- Capsid derived from both viruses.



3-Interference: This phenomenon whereby infection by one virus results in inhibition of replication of another virus.

Auto-interference: interfere with their own replication.

Homologous interference: occur between related viruses.

Heterologous interference: occur between unrelated viruses.

Mechanisms of interference:

1- Blocking of receptor (inhibition of adsorption) ex: retroviruses; enteroviruses, or destroying its receptors like orthomyxoviruses.

2- Competition for components of the replicative apparatus (sites and/ or polymerase).

3- Inhibitors of replication (interferon).

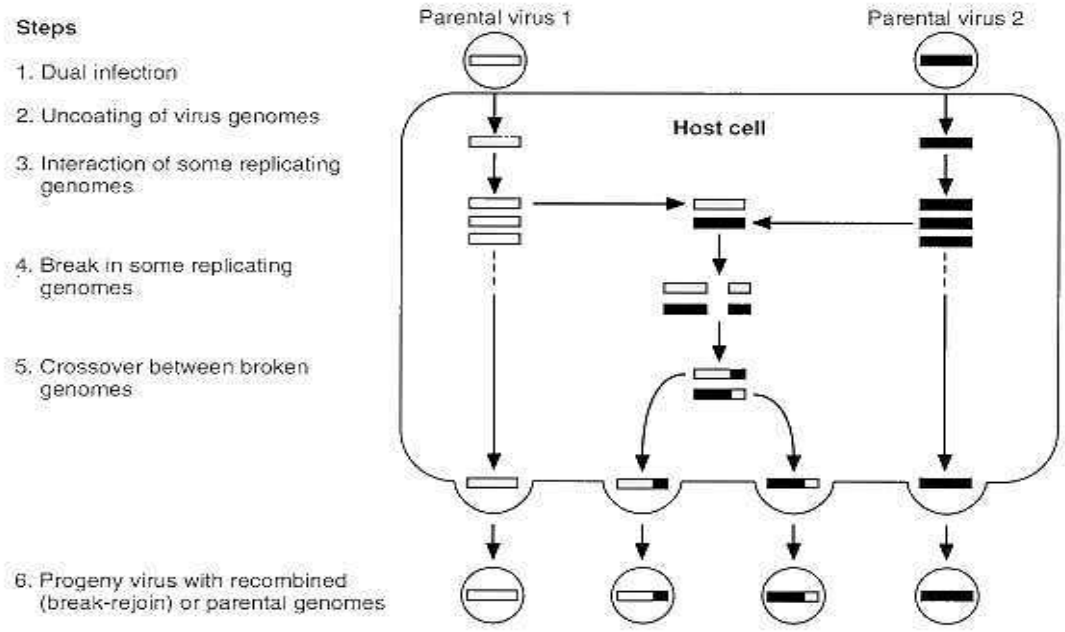


Fig.1 Recombination by break-rejoin of incompletely linked genes

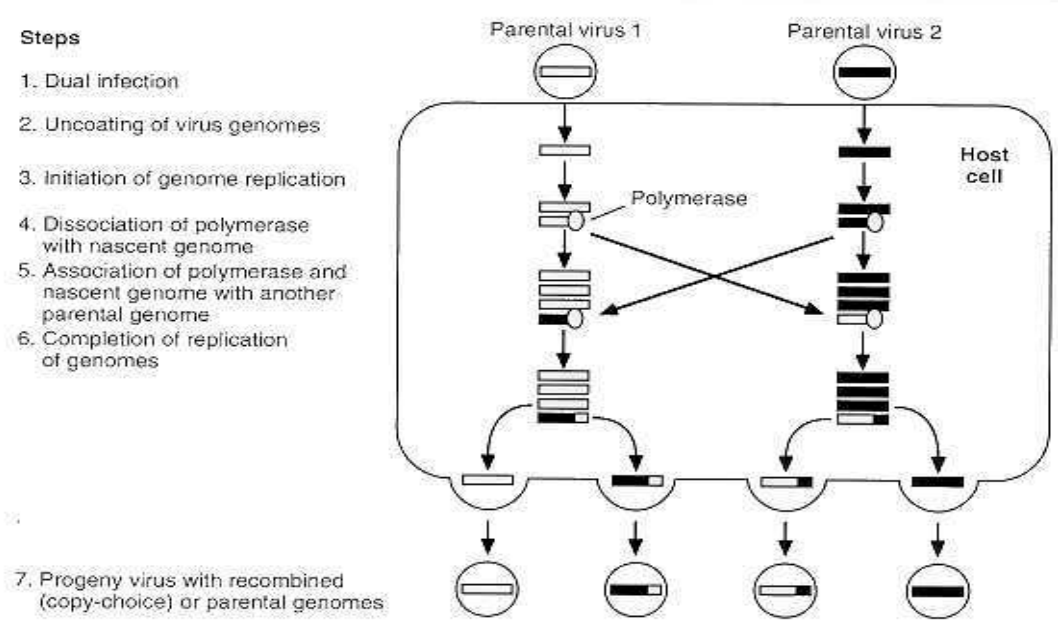


Fig.2 Recombination by copy-choice of incompletely linked genes

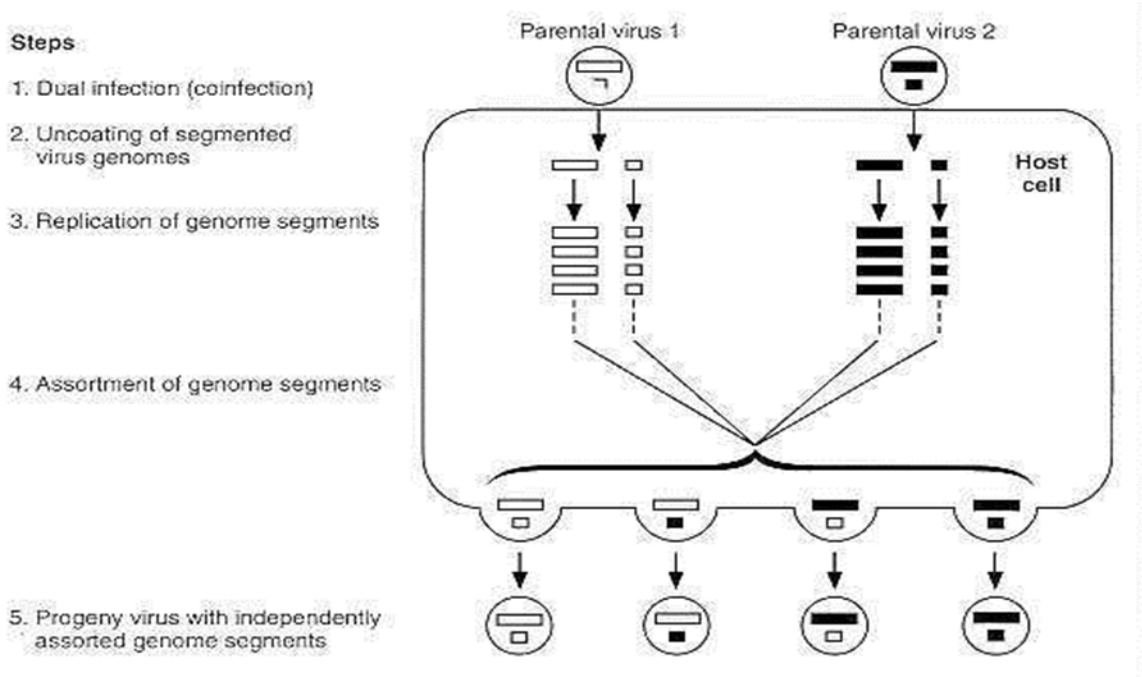


Fig.3 Recombination by independent assortment during dual infection

Beneficial Use of Viruses

While viruses are primarily known as pathogens, they can also be used for the benefit of humans. There are a number of ways in which viruses may produce direct benefits for human health.

1- Vaccines: The most obvious of these is as vaccines and vaccine vectors, vaccines do not simply protect against infection with the same virus. Relatively harmless viruses are often used to provide protection from their more dangerous relatives (for example, the use of vaccinia virus to protect against smallpox, or Shope fibroma virus to protect against myxomatosis) and viral vectors may be used to develop candidate vaccines against a range of diseases both viral and non-viral in nature.

2- Viruses in bacteriophage therapy

These are highly specific viruses that can target, infect, and (if correctly selected) destroy pathogenic bacteria. Bacteriophages are believed to be the most numerous types of viruses accounting for the majority of the viruses present on Earth. These are basic tools in molecular biology. They have been researched for their use in therapy.

3- Gene therapy: The key element of gene therapy is the introduction of functioning genes into the cells of a human patient, to express desired functions or to correct defective or non-operational genes within those cells. The original concept behind gene therapy was the treatment of individuals with an inherited genetic disorder, but applications in this area have been limited. The most common target has been cancers, accounting for almost two-thirds of all clinical trials to date. It is also possible to target infectious diseases by introducing specific inhibitory genes, including those producing antisense or small interfering (si) RNAs.

- **Virus vector systems**

Viruses naturally exhibit *cell tropism*, where the requirements of the virus for specific receptors along with other factors can be used to ensure that specific types of cells are infected. While most viruses used for gene delivery will infect many types of cell, careful selection (and, where appropriate, genetic modification) of the virus vector can favor the delivery

of the therapeutic gene to the required location. Adenoviruses are widely used as vectors, and can be engineered both to enhance specificity and to minimize unwanted effects. Enhancement of specificity can involve either altering the surface receptors of the virus, or using cell type-specific promoters to control the expression of inserted genes. Approval of the first gene therapy product in Europe (Colybera® for pancreatitis) may occur in 2011. This uses an adeno-associated virus vector.

4- Cancer prevention and control:

Some viruses are innately able to target and destroy cancer cells, while other methods use molecular approaches based on viral vector systems to create specific therapeutics.

Table 1: Use of viruses in the prevention or control of cancers

Approach	Mode of action	Examples
Prophylactic vaccine*	Stimulation of immune system to prevent a cancer, typically one associated with a virus infection	Existing subunit vaccines for hepatitis B virus, human papillomaviruses
Therapeutic vaccine*	Stimulation of the immune system to control an existing cancer	Experimental approaches under evaluation, e.g. using adenovirus vectors or papillomavirus DNA
Replication-competent virus	Preferential killing of cancer cells by virus	Adenovirus, Newcastle disease paramyxovirus
Modified replication-competent virus	As above, with enhanced killing of cancer cells	Adenovirus with enhanced receptor binding
Nonreplicating virally derived vector	Transfer into cancer cells of a cytotoxic gene	Rexin-G (retrovirus core with cytocidal cyclin G gene)
Virus-directed enzyme prodrug therapy (VDEPT)	Virus-mediated delivery of enzyme combined with systemic administration of prodrug	Recombinant adenovirus expressing herpes simplex enzyme, plus treatment with ganciclovir

5- Control of harmful or damaging organisms, in both agriculture and medicine:

The use of biological organisms to control damaging pests is broadly known as **biological control**, or biocontrol. Traditionally this has been used in agriculture, but applications exist in the control of agents important to human health as well. There are four basic approaches:

- Predators, which prey on the target species
- Parasites or parasitoids (insects that lay their eggs inside or on the host)
- Pathogens, which cause disease in the target species
- Competing species (antagonists)

viruses are used for the control of multiple species of insects and also for rabbits. Biological agents can produce long-lasting effects and in some cases are able to spread among the target population. They have also been recognized as inherently less toxic than conventional pesticides by the US. Environmental Protection Agency. Their disadvantages include limited range of action, slow effects compared to chemical agents, high costs of initial treatment, low environmental stability, particularly in sunlight etc.

Table 2: Viruses used as pest control agents

Virus type	Number In use	Target
Baculoviruses (various)	13	Caterpillars, sawflies
Oryctes rhinoceros virus	1	Rhinoceros beetle
Myxoma poxvirus	1	Rabbit
Rabbit hemorrhagic disease calicivirus	1	Rabbit