Virology

Fourth Class

College of science/*University of Baghdad*

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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).

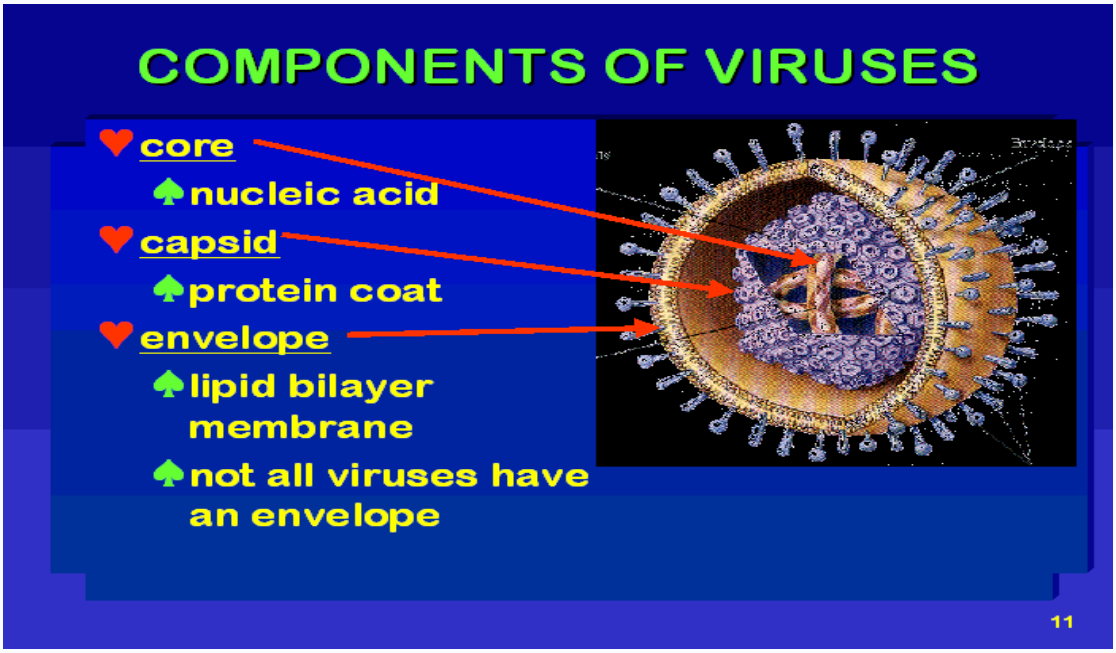
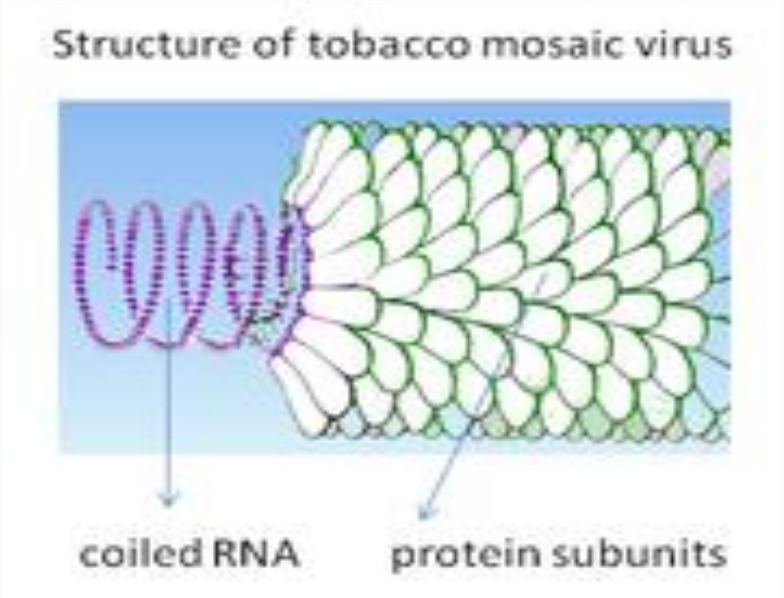


Figure 1: Component of viruses.

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.

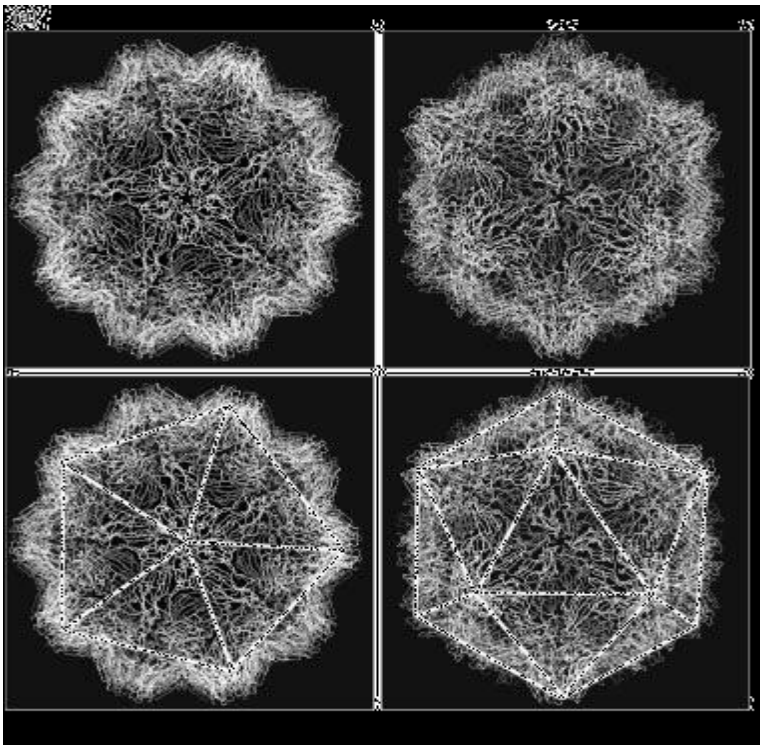
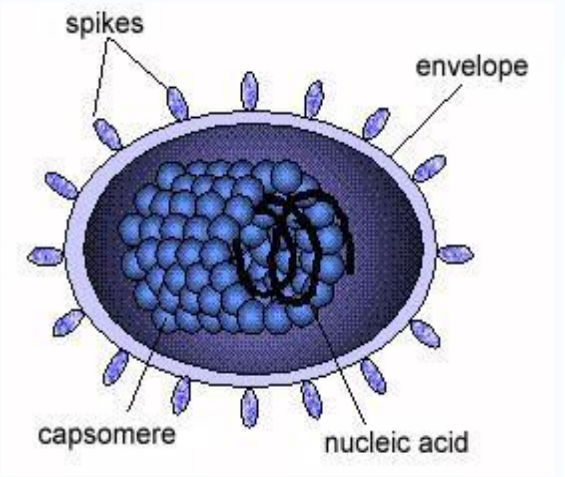


Figure 3 :Electron micrograph of icosahedral adenovirus.

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.



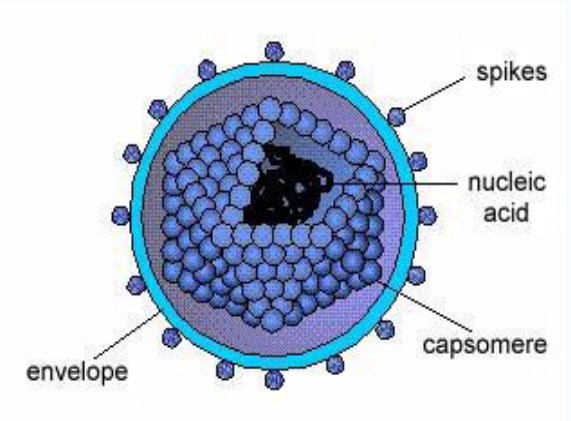


Figure 4: Enveloped helical virus **Enveloped icosahedral virus**

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.

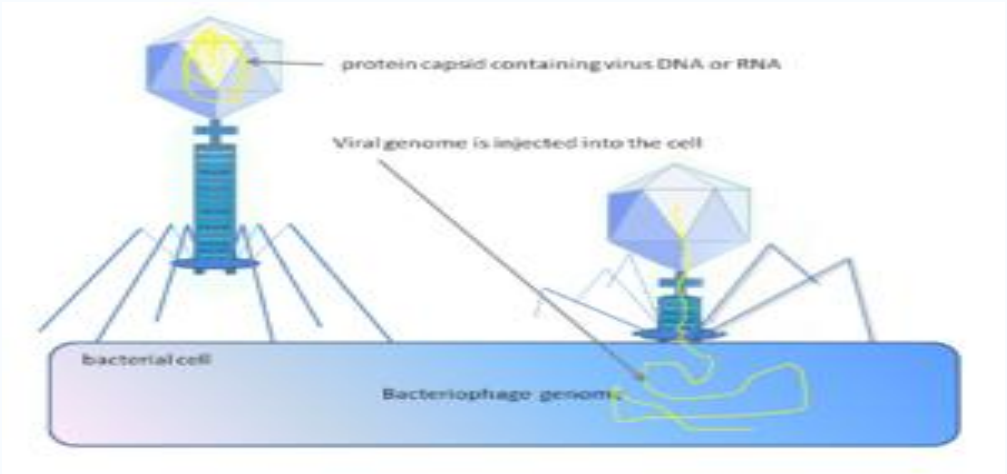


Figure 5: Some bacteriophages inject their genomes into bacterial cells.

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.

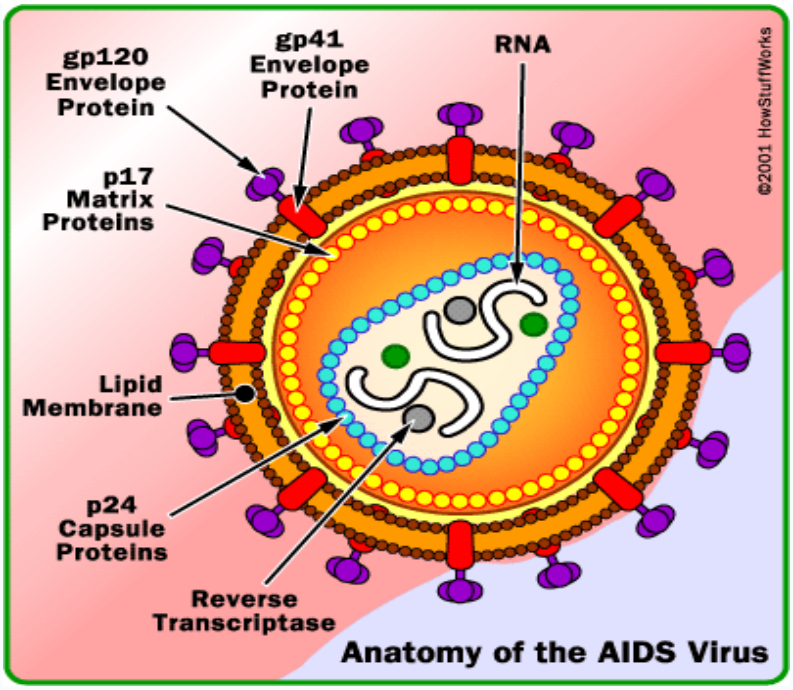


Figure 6: HIV virus

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).

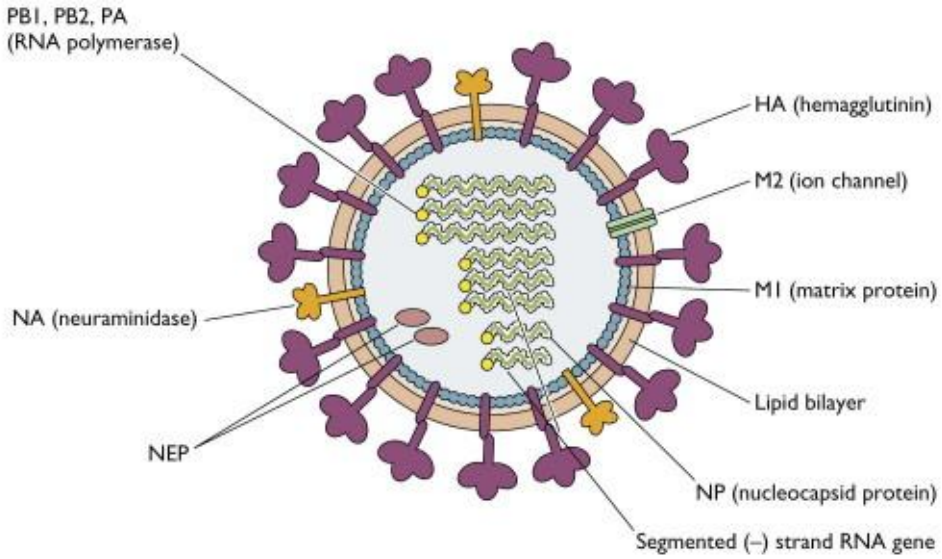


Figure 7: Influenza virus.

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**

Multiplication of animal viruses:

A virus needs a living cell to multiply. It invades the host cell and takes over metabolic machinery of the host. Consequently, depending on virus types, cell death occurs releasing thousands of similar viral particles.

General Steps in Viral Replication Cycles

A variety of different viral strategies have evolved for accomplishing multiplication in parasitized host cells. Although the details vary from group to group, the general outline of the replication cycles is similar.

A) Attachment

The first step in viral infection is attachment, interaction of a virion with a specific receptor site on the surface of a cell. Receptor molecules differ for different viruses but are generally glycoproteins. In some cases the virus binds protein sequences (eg, picornaviruses) and in others oligosaccharides (eg, orthomyxoviruses and paramyxoviruses). Receptor binding is believed to reflect fortuitous configurational homologies between a virion surface structure and a cell surface component. For example, human immunodeficiency virus binds to the CD4 receptor on cells of the immune system, rhinoviruses bind ICAM-1, and Epstein-Barr virus recognizes the CD21 receptor on B cells. The presence or absence of

receptors plays an important determining role in cell tropism and viral pathogenesis. Not all cells in a susceptible host will express the necessary receptors; for example, poliovirus is able to attach only to cells in the central nervous system and intestinal tract of primates. Each susceptible cell may contain up to 100,000 receptor sites for a given virus. The attachment step may initiate irreversible structural changes in the virion.

B) Penetration

After binding, the virus particle is taken up inside the cell. This step is referred to as penetration or engulfment. In some systems, this is accomplished by receptor-mediated endocytosis, with uptake of the ingested virus particles within endosomes. There are also examples of direct penetration of virus particles across the plasma membrane. In other cases, there is fusion of the virion envelope with the plasma membrane of the cell. Those systems involve the interaction of a viral fusion protein with a second cellular receptor or "coreceptor" (eg, chemokine receptors for human immunodeficiency virus).

C) Uncoating

Uncoating occurs concomitantly with or shortly after penetration. Uncoating is the physical separation of the viral nucleic acid from the outer structural components of the virion so that it can function. The genome may be released as free nucleic acid (picornaviruses) or as a nucleocapsid (reoviruses). The nucleocapsids usually contain polymerases. Uncoating may require acidic pH in the endosome. The infectivity of the parental virus is lost at the uncoating stage. Viruses are the only infectious agents for which dissolution of the infecting agent is an obligatory step in the replicative pathway.

D) Expression of Viral Genomes and Synthesis of Viral Components

The synthetic phase of the viral replicative cycle ensues after uncoating of the viral genome. The essential theme in viral replication is that specific mRNAs must be transcribed from the viral nucleic acid for successful expression and duplication of genetic information. Once this is accomplished, viruses use cell components to translate the mRNA. Various classes of viruses use different pathways to synthesize the mRNAs depending upon the structure of the viral nucleic acid. (Table 1) summarizes the various pathways of transcription (but not necessarily those of replication) of the nucleic acids of different classes of viruses. Some

viruses (eg, rhabdoviruses) carry RNA polymerases to synthesize mRNAs. RNA viruses of this type are called negative-strand (negative-sense) viruses, as their single-strand RNA genome is complementary to mRNA, which is conventionally designated positive-strand (positive-sense). The negative-strand viruses must supply their own RNA polymerase, as eukaryotic cells lack enzymes able to synthesize mRNA off an RNA template.

In the course of viral replication, all the virus-specified macromolecules are synthesized in a highly organized sequence. In some viral infections, notably those involving double-stranded, DNA-containing viruses, early viral proteins are synthesized soon after infection and late proteins are made only late in infection, after viral DNA synthesis. Early genes may or may not be shut off when late products are made. In contrast, most if not all of the genetic information of RNA-containing viruses is expressed at the same time. In addition to these temporal controls, quantitative controls also exist, since not all viral proteins are made in the same amounts. Virus-specific proteins may regulate the extent of transcription of the genome or the translation of viral mRNA.

Small animal viruses and bacteriophages are good models for studies of gene expression. The total nucleotide sequences of many viruses have been elucidated. This led to the discovery of overlapping genes in which some sequences in DNA are utilized in the synthesis of two different polypeptides, either by the use of two different reading frames or by two mRNA molecules using the same reading frame but different starting points. A viral system (adenovirus) first revealed the mRNA processing phenomenon called "splicing," whereby the mRNA sequences that code for a given protein are generated from separated sequences in the template, with noncoding intervening sequences spliced out of the transcript. Recently, several DNA viruses (herpesviruses, adenovirus, polyomavirus) were found to encode microRNAs; these small (~22 nucleotide) RNAs function at a new level of post-transcriptional gene regulation, either by mediating degradation of target mRNAs or by inducing inhibition of translation of those mRNAs.

The widest variation in strategies of gene expression is found among RNA-containing viruses (Table 2). Some virions carry polymerases (orthomyxoviruses, reoviruses); some systems utilize subgenomic messages, sometimes generated by splicing (orthomyxoviruses, retroviruses); and some viruses synthesize large polyprotein precursors that are processed and cleaved to generate the final gene products (picornaviruses, retroviruses). The viral protease of human

immunodeficiency virus is what is inhibited by the class of antiviral drugs called protease inhibitors.

The extent to which virus-specific enzymes are involved in these processes varies from group to group. DNA viruses that replicate in the nucleus generally use host cell DNA and RNA polymerases and processing enzymes. The larger viruses (herpesviruses, poxviruses) are more independent of cellular functions than are the smaller viruses. This is one reason the larger viruses are more susceptible to antiviral chemotherapy because more virus-specific processes are available as targets for drug action.

The intracellular sites where the different events in viral replication take place vary from group to group (Table 3). A few generalizations are possible. Viral protein is synthesized in the cytoplasm on polyribosomes composed of virus-specific mRNA and host cell ribosomes. Many viral proteins undergo modifications (glycosylation, acylation, cleavages, etc). Viral DNA is usually replicated in the nucleus. Viral genomic RNA is generally duplicated in the cell cytoplasm, though there are exceptions.

E) Morphogenesis and Release

Newly synthesized viral genomes and capsid polypeptides assemble together to form progeny viruses. Icosahedral capsids can condense in the absence of nucleic acid, whereas nucleocapsids of viruses with helical symmetry cannot form without viral RNA. In general, non enveloped viruses accumulate in infected cells, and the cells eventually lyse and release the virus particles.

Enveloped viruses mature by a budding process. Virus-specific envelope glycoproteins are inserted into cellular membranes; viral nucleocapsids then bud through the membrane at these modified sites and in so doing acquire an envelope. Budding frequently occurs at the plasma membrane but may involve other membranes in the cell. Enveloped viruses are not infectious until they have acquired their envelopes. Therefore, infectious progeny virions typically do not accumulate within the infected cell.

Viral maturation is sometimes an inefficient process. Excess amounts of viral components may accumulate and be involved in the formation of inclusion bodies in the cell. As a result of the profound deleterious effects of viral replication, cellular cytopathic effects eventually develop and the cell dies. However, there are

instances in which the cell is not damaged by the virus and long-term, persistent infections evolve Virus-induced mechanisms may regulate apoptosis, a genetically programmed event that makes cells undergo self-destruction. Some virus infections delay early apoptosis, which allows time for the production of high yields of progeny virus. Additionally, some viruses actively induce apoptosis at late stages which would facilitate spread of progeny virus to new cells (figure 1, 2).

Viroids:

Until 1970s, viruses were considered as the smallest infectious agent. The discovery of viroids has proved that the infectious entities smaller than viruses exist in nature.

Viroids are plant pathogens that consist of a short stretch (a few hundred nucleobases) of highly complementary, circular, single-stranded RNA without the protein coat that is typical for viruses. The smallest discovered is a 220 nucleobase scRNA (small cytoplasmic RNA) associated with the rice yellow mottle sobemovirus (RYMV). In comparison, the genome of the smallest known viruses capable of causing an infection by themselves are around 2 kilobases in size. The human pathogen hepatitis D is similar to viroids.

Viroids were discovered and given this name by Theodor Otto Diener, a plant pathologist at the Agricultural Research Service in Maryland, in 1971.

Viroid RNA does not code for any protein. The replication mechanism involves RNA polymerase II, an enzyme normally associated with synthesis of messenger RNA from DNA, which instead catalyzes "rolling circle" synthesis of new RNA using the viroid's RNA as template. Some viroids are ribozymes, having catalytic properties which allow self-cleavage and ligation of unit-size genomes from larger replication intermediates.

The first viroid to be identified was the potato spindle tuber viroid (PSTVd). Some 33 species have been identified

Virusoids:

Virusoids are circular single-stranded RNAs dependent on plant viruses for replication and encapsidation. The genome of virusoids consist of several hundred nucleotides and only encodes structural proteins.

Virusoids are similar to viroids in size, structure and means of replication (rolling-circle replication)

Virusoids, while being studied in virology, are not considered as viruses but as subviral particles. Since they depend on helper viruses, they are classified as satellites. In the virological taxonomy they appear as Satellites/Satellite nucleic acids.

The term virusoid is also sometimes used more generally to refer to all satellites.

Prion:

A prion is an infectious agent that is composed primarily of protein. To date, all such agents that have been discovered propagate by transmitting a mis-folded protein state; as with viruses the protein itself does not self-replicate, rather it induces existing polypeptides in the host organism to take on the rogue form. The misfolded form of the prion protein has been implicated in a number of diseases in a variety of mammals, including bovine spongiform encephalopathy (BSE, also known as "mad cow disease") in cattle and Creutzfeldt–Jakob disease (CJD) in humans. All known prion diseases affect the structure of the brain or other neural tissue, and all are currently untreatable and universally fatal. In general usage, prion refers to the theoretical unit of infection. The precise composition of the prion is not known, though they can be formed by combining PrPC, polyadenylic acid, and lipids.

Prions are hypothesized to infect and propagate by refolding abnormally into a structure which is able to convert normal molecules of the protein into the abnormally structured form. All known prions induce the formation of an amyloid fold, in which the protein polymerises into an aggregate consisting of tightly packed beta sheets. This altered structure is extremely stable and accumulates in infected tissue, causing tissue damage and cell death. This structural stability means that prions are resistant to denaturation by chemical and physical agents, making disposal and containment of these particles difficult. Evolutionarily, prion replication has been shown to be subject to mutation and natural selection just like other forms of replication.

Proteins showing prion-type behavior are also found in some fungi, which has been useful in helping to understand mammalian prions. Fungal prions,

however, do not appear to cause disease in their hosts and may even confer an evolutionary advantage through a form of protein-based inheritance. The word prion is a portmanteau derived from the initial and final letters of the words proteinaceous and infection.

Transmission of viruses:

Viruses are known to infect both plant cells and animal cells. Since viruses are obligate intracellular parasites they must develop direct methods of transmission, between hosts, in order to survive. The mobility of animals increases the mechanisms of viral transmission that have evolved, whereas plants remain immobile and thus viruses must rely on environmental factors to be transmitted between hosts.

a- Transmission mode of plant viruses:

1- Mechanical transmission by rubbing leaves together, injecting plant extract, by cation of animals,etc.
2- Vegetative and graft transmission: viruses will be transmitted to the progeny, if any part of infected mother plants in used for vegetative propagation through rhizomes, bulbs,corns,tubers, etc.
3- Pollen transmission; when pollens consisting for viruses fall on stigma of female plants, they germinate and eventually facilitate the virus to infect the ovules of plants.
4- Seed transmission; very rare.
5- Nematode transmission; some nematodes that feed roots of plant act as vector for some viral pathogens.
6- Fungal transmission
7- Insect vector transmission
8- Dodder transmission; dodder are the trailer or climber parasitic plant which grow forming bridge between two plants.

Transmission mode of animal viruses:

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**:

a) Contact. The major means of transmission may be by droplet or aerosol infection (eg, influenza, measles, smallpox).
b) by the fecal-oral route (eg, enteroviruses, rotaviruses, infectious hepatitis A).
c) by sexual contact (eg, hepatitis B, herpes simplex type 2, human immunodeficiency virus).
d) by hand-mouth, hand-eye, or mouth-mouth contact (eg, herpes simplex, rhinovirus, Epstein-Barr virus).
e) 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.

Arthropod

Human Human

Arthropod

(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.

Arthropod

Low vertebrate low vertebrate

Arthropod human

(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.

Arthropod

Human Low vertebrate

Arthropod

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.

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 :

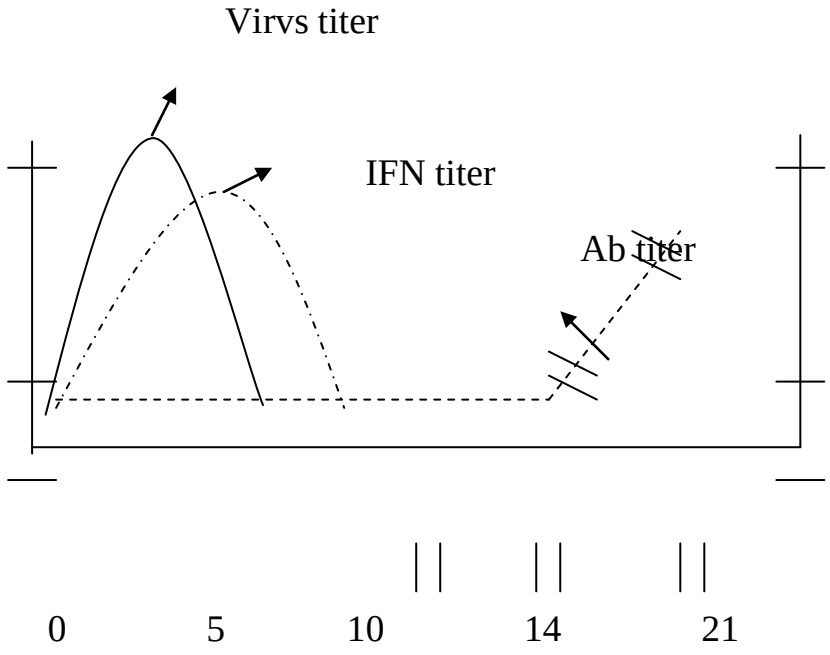
- These cytokines are the most important to virologists.
- They discovered by Isaacs and Lindenmann in 1957.
- They are host – coded proteins that inhibit viral replication and are produced by intact animals or cultured cells in response to viral infection or other inducers.
- They are produced by all 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.

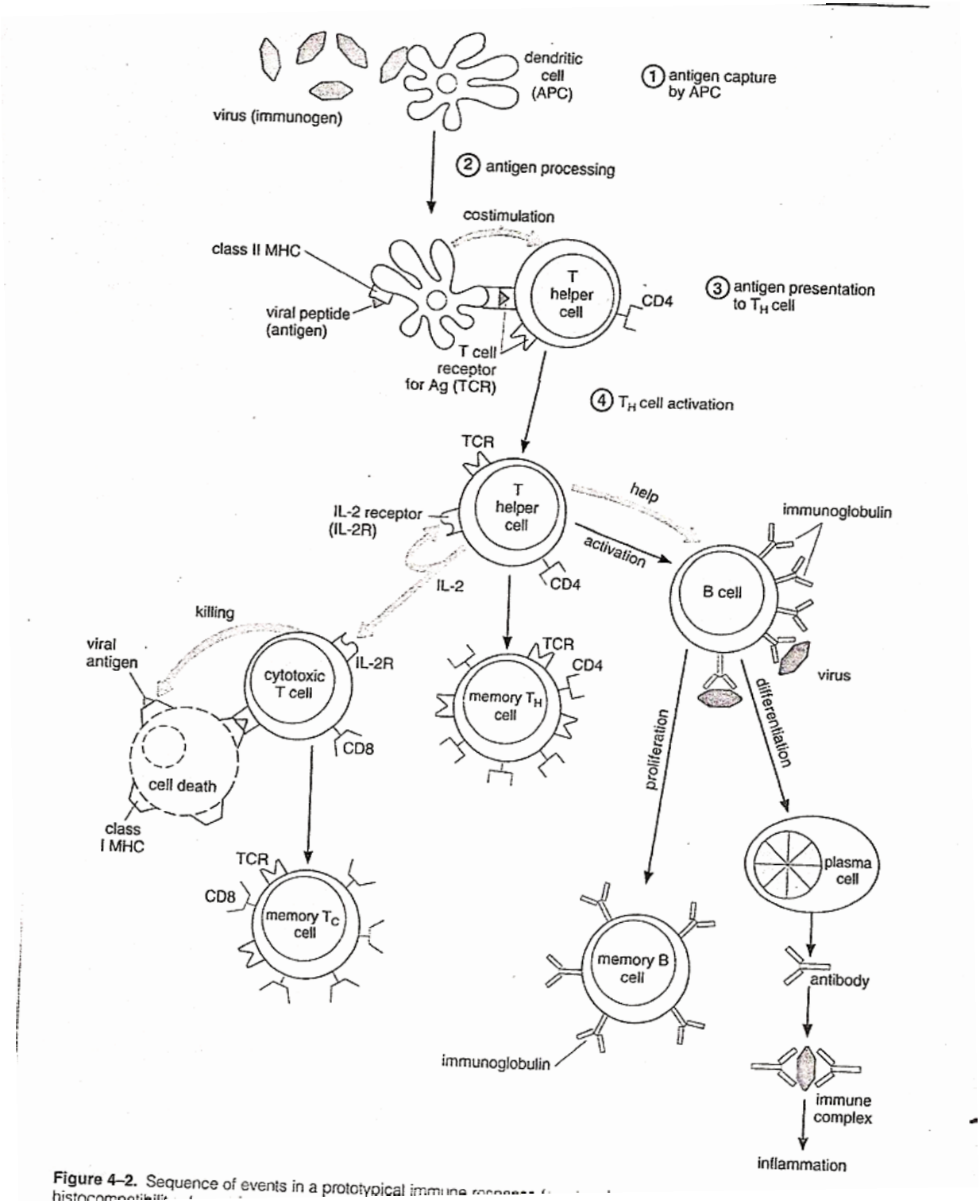
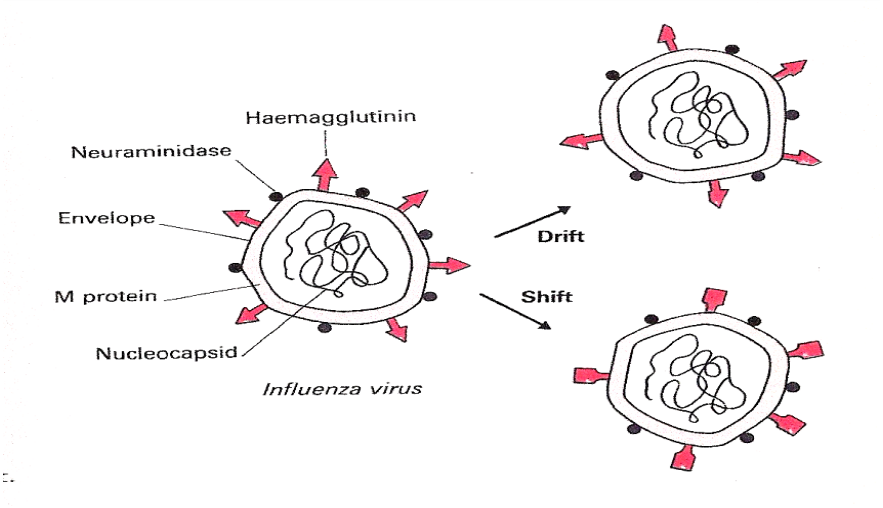


Figure 4–2. Sequence of events in a prototypical immune response (

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.

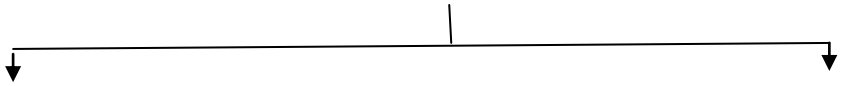
Viral disease varies in severity, depending on virulence of the virus and age, health, and habitat of the human host. Lifelong immunity develops to some but not all viral agents. Virus infection can be diagnosed by overt symptoms, cultures, antigen detection, and nucleic acid probes.

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 and

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 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.
gastroenteritis

***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

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 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.