Brief History of Virology

Viruses are still a major cause of most human diseases.

We will begin of with a few examples of common viruses. One should note that viruses affect every " living" creature including bacterium, protozoa,and yeast**.**

Animal viruses	Plant viruses	Other
Rabies	Tobacco Mosaic	bacteirophage lambda
Smallpox	cucumber mosaic	T-even phages
Polio	Brome Mosaic	yeast viruses
hepatitis A,B,C		
yellow Fever		Scrapie (prion)
Herpes		Mad Cow Disease (prion)
Foor and Mouth Disease		Plant Viroids
AIDS (HIV)		Hepatitis Delta.
Human T-cell leukemia		

Note: Some of these viruses such as kuru are "slow-viruses," and are models for degenerative diseases: These are caused by prions. Alzheimer's disease may be of a similar origin. .Diabetes, and rheumatoid arthritis may be viral related. This is quite controversial.

The majority of viral infections occur without any symptoms, they are subclinical. There may be virus replication without symptoms. In other cases virus replication always leads to disease, e.g. measles.

Some viruses may cause more than one type of disease state ,e.g. measles, chicken pox. in other cases same symptoms may result from different virus infections (hepatitis).

Viruses are:

- submicroscopic, obligate intracellular parasites.

- particles produced from the assembly of preformed components

- particles (**virions**) themselves do not grow or undergo division.

- lacking the genetic information that encodes apparatus necessary for the generation of metabolic energy or for protein synthesis (ribosomes).

They are therefore absolutely dependent on the host cell for this function

- One view said that inside the host cell viruses are alive, whereas outside it they are merely complex assemblages of metabolically inert chemicals.

- Viruses are smallest entities in most cases. While this is true, the largest known virus (Mimivirus, for 'mimicking microbe') is 400 nm in diameter, while the smallest mycoplasma (e.g., *Mycoplasma*, *Ralstonia pickettii*) is only 200-300 nm long.

Exceptional Entities:

A number of pathogenic entities are clearly more similar to viruses than other organisms. Known entities are:

- **Viroids:** Viroids are very small (200–400 nucleotides), circular RNA molecules with a rod-like secondary structure. They have no **capsid** or **envelope** and are associated with certain plant diseases. Their replication strategy is like that of viruses—they are obligate intracellular parasites.

- **Virusoids:** Virusoids are satellite, viroid-like molecules, almost larger than viroids (e.g., approximately 1000 nucleotides); they depend on the presence of virus replication for multiplication (e.g. '**satellite**'); they are packaged into virus capsids as passengers.

- **Prions**: are infectious agents believed to consist of a single type of protein molecule with no nucleic acid component. Confusion arises that the prion protein and the gene that encodes it are also found in normal 'uninfected' cells. These agents are associated with 'slow' virus diseases such as Creutzfeldt–Jakob disease in humans, scrapie in sheep, and bovine spongiform encephalopathy (BSE) in cattle

History of Viruses:

Events Helped in Virus Discovery:

- the first record of a virus infection consists of a hieroglyph

from Memphis, the capital of ancient Egypt, drawn in 3700 BC, which depicts a temple priest showing typical clinical signs of paralytic poliomyelitis. Pharaoh Ramses V, who died in 1196 BC and whose extraordinarily well-preserved mummified

body is believed to have succumbed to smallpox—a comparison between the pustular lesions on the face of the

mummy and those of more recent patients is startling.

- Smallpox was **endemic** in China by 1000 BC and practice of

variolation (similar to Vaccination) was developed. Survivors of smallpox outbreaks were protected from subsequent infection, the Chinese inhaled the dried crusts from smallpox lesions like snuff or, in later modifications, inoculated the pus from a lesion into a scratch on the forearm.

- Invention of microscope by Antony van Leeuwenhoek

(1632–1723), a Dutch merchant, constructed the first simple microscopes and with these identified bacteria as the 'animalcules' he saw in his specimens.

- However, it was not until Robert Koch and Louis Pasteur in the 1880s jointly proposed the 'germ theory' of disease that the significance of these organisms became apparent.

- **Koch's Postulates** (proof that an infectious agent is responsible for a specific disease:

1. The agent must be present in every case of the disease

2. The agent must be isolated from the host and grown *in vitro*

3. The disease must be reproduced when a pure culture of the agent is inoculated into a healthy susceptible host.

4. The same agent must be recovered once again from the experimentally infected host.

- Pasteur worked extensively on rabies, which he identified as being caused by a 'virus' but despite this he did not discriminate between bacteria and other agents of disease.

First real evidence on virus identity

- In 1892, Dimitri Iwanowski, a Russian botanist, showed that extracts from diseased tobacco plants could transmit disease to other plants after passage through ceramic filters fine enough to

retain the smallest known bacteria.

- A few years later (1898), Martinus Beijerinick confirmed

and extended Iwanowski's results on tobacco mosaic virus (TMV) and was the first to develop the modern idea of the virus, which he referred to as *contagium vivum fluidum* ('soluble living germ').

- Freidrich Loeffler and Paul Frosch (1898) showed that a similar agent was responsible for foot-and-mouth disease in cattle, but, despite the realization that these new-found agents caused disease in animals as well as plants, people would not accept the idea that they might have anything to do with human diseases.

- This resistance was finally dispelled in 1909 by Karl Landsteiner and Erwin Popper, who showed that poliomyelitis was caused by a 'filterable agent'—the first human disease to be recognized as being caused by a virus.

New Virus infecting Bacteria:

- Frederick Twort (1915) and Felix d'Herelle (1917) were the first to recognize viruses that infect bacteria, which d'Herelle called **bacteriophages** ('eaters of bacteria').

- In the 1930s and subsequent decades, pioneering virologists such as Salvador Luria, Max Delbruck, and many others used these viruses as model systems to investigate many aspects of virology, including virus structure, genetics and replication.

- These relatively simple agents have since proven to be very important to our understanding of all types of viruses, including those of humans which are much more difficult to propagate and study.

- During the Spanish–American War of the late nineteenth century and the subsequent building of the Panama Canal, the number of American deaths due to yellow fever was colossal. The disease also appeared to be spreading slowly northward into the continental United States. In 1902, through experimental

transmission to mice, Walter Reed demonstrated that yellow fever was caused by a virus spread by mosquitoes. This discovery eventually enabled Max Theiler in 1937 to propagate the virus in chick embryos and to produce an attenuated vaccine—the17D strain—which is still in use today.

-The success of this approach led many other investigators from the 1930s to the 1950s to develop animal systems to identify

and propagate pathogenic viruses.

- **Eukaryotic** cells can be grown *in vitro* (tissue culture) and viruses can be propagated in these cultures, but these techniques are expensive and technically quite demanding.

Nevertheless, they are increasingly being discarded for the following reasons:

1. Breeding and maintenance of animals infected with pathogenic viruses is expensive.

2. Whole animals are complex systems in which it is sometimes difficult to discern events.

3. Results obtained are not always reproducible due to host variation.

4. Unnecessary or wasteful use of experimental animals is morally repugnant.

5. They are rapidly being overtaken by 'modern science'—cell culture and molecular biology.

In recent years, an entirely new technology has been employed to study the effects of viruses on host organisms. This involves the creation of **transgenic** animals and plants by inserting all or part of the virus **genome** into the DNA of the experimental organism, resulting in expression of virus **mRNA** and proteins

in somatic cells (and sometimes in the cells of the germ line). Thus, the pathogenic effects of virus proteins, individually and in various combinations, can be studied in living hosts. 'SCID-hu' mice have been constructed from immunodeficient lines of animals transplanted with human tissue.

These mice form an intriguing model to study the pathogenesis of human immunodeficiency virus (HIV) as there is no real alternative to study the properties of this important virus *in vivo*. While these techniques often raise the same moral objections as 'old-fashioned' experimental infection of animals by viruses, they are powerful new tools for the study of virus pathogenicity. This method

will become widely used after solving technical difficulties associated with the construction of **transgenic** organisms.

CELL CULTURE METHODS

They began early in the twentieth century with whole-organ cultures, then progressed to methods involving individual cells, either **primary cell** cultures (somatic cells from an experimental animal or taken from a human patient which can be maintained for a short period in culture) or **immortalized** cell lines, which, given appropriate conditions, continue to grow in culture indefinitely.

In 1949, John Enders and his colleagues were able to propagate poliovirus in primary human cell cultures. This achievement regarded as the 'Golden Age of Virology' and led to the identification and isolation during the1950s and 1960s of many viruses and their association with human diseases.

Plaque Assay

Renato Dulbecco in 1952 was the first to quantify accurately animal viruses using a **plaque** assay.

In this technique, dilutions of the virus are used to infect a cultured cell **monolayer**, which is then covered with soft agar to restrict diffusion of the virus, resulting in localized cell killing and the appearance of plaques after the monolayer is stained (Figure 1.1). Counting the number of plaques directly determines the number of infectious virus particles applied to the plate.

The same Plaque technique can also be used biologically to clone a virus (i.e., isolate a pure form from a mixture of types). This technique had been in use for some time to quantify the number of infectious virus particles in **bacteriophage** suspensions applied to confluent 'lawns' of bacterial cells on agar plates, but its application to viruses of **eukaryotes** enabled rapid advances in the study of virus replication to be made.

Plaque assays largely replaced earlier endpoint dilution techniques, such as the tissue culture infectious dose (TCID50) assay, which are statistical means of measuring virus populations in culture; however, endpoint techniques may still be used in certain circumstances—for example, for viruses that do not replicate in culture or are not cytopathic and do not produce plaques, (e.g., human immunodeficiency virus)

\- George Hirst, in 1941, observed **haemagglutination** of red blood cells by influenza virus (see Chapter 4). This proved to be an important tool in the study of not only influenza but also several other groups of viruses—for example, rubella virus. In addition to measuring the **titre** (i.e., relative amount) of virus present in any preparation, this technique can also be used to determine the antigenic type of the virus. Haemagglutination will not occur in the presence of antibodies that bind to and block the virus haemagglutinin. If an antiserum is titrated against a given number of haemagglutinating units, the haemagglutination inhibition titre and specificity of the antiserum can be determined.

In the 1960s and subsequent years, many improved detection methods for viruses were developed, such as:

- Complement fixation tests

- Radioimmunoassays

- Immunofluorescence (direct detection of virus antigens in infected cells or tissue)

- Enzyme-linked immunosorbent assays (ELISAs)

- Radioimmune precipitation

- Western blot assays

- PCR techniques

These techniques are sensitive, quick, and quantitative.

Monoclonal Antibodies (MA) Technology

In 1975, George Kohler and Cesar Milstein isolated the first MA from clones of cells selected *in vitro* to produce an antibody of a single specificity directed against a particular antigenic target. This enabled virologists to look not only at the whole virus, but at specific regions—epitopes—of individual virus antigens as well function of individual virus proteins. MA techniques have more applications in other types of serological assays (e.g., ELISAs) to increase their reproducibility, sensitivity, and specificity

- MA are produced by immunization of an animal with an antigen that usually contains a complex mixture of epitopes. Immature B-cells are later prepared from the spleen of the animal, and these are

fused with a myeloma cell line, resulting in the formation of transformed cells continuously secreting antibodies. A small proportion of these will make a single type of monoclonal antibody against the desired epitope. Recently, *in vitro* molecular techniques have been developed to speed up the selection of monoclonal antibodies, although these have not yet replaced the original approach shown here

Ultrastructural & Physical Testing

- Physical measurements of virus particles began in the 1930s with the earliest determinations of their proportions by filtration through colloidal membranes of various pore sizes-The first electron micrograph of a virus (TMV) was published in 1939. Over subsequent years, techniques were developed that allowed the direct examination of viruses at magnifications of over 100,000 times.The two fundamental types of electron microscope are the transmission electron microscope (TEM) and the scanning electron microscope (SEM) - Studies of the sedimentation properties of viruses in ultracentrifuges in the 1960s in obtaining purified and highly concentrated preparations of many different viruses, free of contamination from host cell components that can be subjected to chemical analysis. The relative density of particles, measured in solutions of sucrose or CsClvirus

Molecular Biology Technology

- The term 'molecular biology' has taken on the new and different meaning of 'genetic engineering' or 'genetic manipulation.'

These techniques for manipulating nucleic acids *in vitro (that is, outside living cells* or organisms)

- This powerful new technology has revolutionized virology and, to a large extent, has shifted the focus of attention away from the virus particle onto the virus **genome.**

Initially, any investigation of a virus genome will usually include questions about the following:

- Composition—DNA or RNA, single-stranded or double-stranded, linear or circular

- Size and number of segments

- Terminal structures

- Nucleotide sequence

- Coding capacity—open reading frames

- Regulatory signals—transcription **enhancers**, **promoters**, and **terminators**

Theories on Origin of viruses:

1. Regressive evolution: This theory states that viruses are degenerate life forms that have lost many functions that other organisms possess and have only retained the genetic information essential to their parasitic way of life.

2. **Cellular origins:** In this theory, viruses are thought to be subcellular, functional assemblies of macromolecules that have escaped their origins inside cells.

3. **Independent entities:** This theory suggests that viruses evolved on a parallel course to cellular organisms from the self-replicating molecules believed to have existed in the primitive, prebiotic RNA world. This is similar to what spontaneous generation stated that viruses created from primitive cellular molecules have replication properties such as plasmids.

Basic characteristics of Viruses

1-Although viruses are very heterogeneous, there is a unity of structure, basically protein and nucleic acid (RNA or DNA).
2- They are reproduced by replication..
3- Size: viruses are "filterable" agents.
4- Obligate (genetic) parasites--dependent on host cell genetic material.
5- Virus genome is either DNA or RNA not both.

Viruses have probably been around as long as life has existed.

In human history there are references to viruses in Homer. He writes of " rabid dogs". Also rabid dogs were known in Mesopotamia. In drawings from ancient Egypt, etc. drawings of people with withered legs, which could have been the result of polio. Smallpox probably played an important role in history of S. and Central America. Yellow fever was endemic, " Flying Dutchman" may have been due to this cause.
In looking at the economic history of the tulip trade in Hlooand, valuable tulips were variagated, which was the result of virus infection

Experimental virology really begins with the experiments of Jenner in 1798.The idea of vaccination was not truly novel It had been practiced by the Turks and possibly also in China. See paper by Langer, Immunization against Smallpox before Jenner in Scientific American reprints. Jenner did not know causative agent or reason for immunity, but noted that individuals exposed to cow pox did not suffer from small pox. Probably other peoples such as the Chinese were also aware of the technique of scarification. Known as variolation.

It is of interest that the virus we use today in the vaccination against small pox, is not the same as that used by Jenner. Sequence analysis indicates that it is not cow-pox, but a variant that arose during the last few hundred years. It is speculated that it may be of horse origin.

Perhaps the most important paradigm for microbiology was proposed by Koch and Henle, although known as Koch's postulates about this time. There was great difficult in applying these Koch's postulates to viral disease. This postulate requires a stop of in vitro growth, which is not always possible with animal viruses. Indeed even today we have had trouble applying these postulates to HIV and the AIDS epidemic.

Koch's postulates: Definition of a pathogen

1. The organism must regularly be found in the lesions of the disease.
2. The organism must be isolated from diseased host and grown in pure culture
3. The inoculation of such a pure organism into a host should initiate the disease
4. The organism must be recovered once again from the organism.

Two other important landmarks were the proving by Pasteur that spontaneous generation of organisms did not occur, and the development of limiting dilution by Lister.
It was also Lister who developed the concept of sterility to obtain pure cultures.

1881-1885, Pasteur. Use of animals as model for growing and studying viruses. Passage of rabies virus through the brain of rabbits, produced an attenuated vaccine. When infected into dogs produced mild infection, with increased latent period. However Pasteur did not try

to identify the infectious agent.

This method of attenuation, by producing attenuated virus in tissue culture still used today. Importance of Pasteur's work was not only the characterization of rabies, but also the whole concept of using animals to develop model systems for the study of viruses.

Discovery Period. 1886-1903.
Plant virology

Knowledge of variegation in tulips dates from 16th century.

- In 1886 Mayer (in Wegeningen, Holland) demonstrated infectivity of TMV. One could get disease spread from tobacco pulp or sap. However Koch's postulates could not be satisfied.

Ivanowski observed/looked for bacteria like substance. 1898, Beijerink demonstrated filterable characteristic of the virus and thinks virus was obligate parasite. Chamberlain filter-candles of unglazed porcelain had been invented for water purification. These filters retained bacterium, and had a pore size of 0.1-0.5 micron. Filters were made of diatomaceous earth (clay)-kieselguhr. Also substance could pass through a layer of agar--contagium vivum fluidum "contagious living liquid." Boiling, or treating with formaldehyde abolished infection. The term for such agents was coined--virus, Latin from Greek, toxin.

In the 1930's Elford--"collodion" membranes, and could show that viruses are particulate and of discrete size (10 nm for FMDV)

10-9 meter = 1 n meter. Range of size.

Animal virology
Loeffler and Frosch (1898) reported that the infectious agent of foot and mouth diseases virus was a filterable agent. This could have been a toxin, however since on dilution one still obtained material, suggest that it was a replicating agent.
In 1900 first human disease shown to be caused by a filterable agent was Yellow Fever by Walter Reed. He established that yellow fever virus was present in the blood of patients during the febrile period, and that the virus could be transmitted by mosquitoes. Yellow

Fever had a very high mortality rate. In 1853 there was an epidemic in New Orleans with mortality of 28%.
Infectivity controlled by destroying mosquito population.
There were many human volunteers in the study of yellow fever, with many deaths. Thus the basic concept arose about this time of a filterable agent too small to be observed in light microscope but able to cause disease by multiplying in living cell.

1908 Ellerman and Bang demonstrated that certain types of tumors (leukemia of chicken) were infectious, and that the infectious material had characteristics of cell free agent.

1911 Peyton Rous discovered that non-cellular agent could transmit solid tumors: virus now known as the Rous Sarcoma virus (RSV).

Bacteriophage Era

Twort (1915) working with vaccinia virus, attempting to grow the virus in medium, got bacterial contamination, micrococcus noted the existence of a substance that cleared bacterial cultures, termed this substance bacteriophage. Twort abandoned this work after World War I and reported it in a short paper 1917 D'Herelle, a Canadian working at the Pasteur made same discovery with the Dysentery bacillus. Developed limiting dilutions, plaque assays, and proposed that virus was particulate in nature.
Note: Novel by Sinclair Lewis: Arrowsmith; idea was to use bacteriophage to destroy bacterial infections. This idea constantly re-occurs.

Plant virology

Chemists had shown that virus could be purified using all the techniques of protein chemistry.
1935: Wendell Stanley, an organic chemist, reported the crystallization of T.M.V. This material was infectious.
Analysis of the crystals showed them to be predominantly proteins in nature of very high molecular weight (- 90% protein). The observation that viruses could be crystallized gave rise to controversy of whether TMV was a living organism, or a "pure" inert chemical substance. 0.5% phosphorus and 5% RNA.
Stanley defined TMV as an "autocatalytic" protein, which may be assumed to require the presence of living cells for multiplication cf. with trypsinogen-trypsin.

1938-1970. Development of the phage group and Molecular Biology

The 1940's and 1950's was the era of the Bacteriophage and the animal virus. The great surge in virology occurred as a result of the work with bacteriophage in the 1940's by Delbruck and co-workers. Delbruck considered father of modern molecular biology although really was a physicist interested in genetic structure.

About the same time identification or correlation was found between tumor viruses and tumors in mice.

Delbruck and Ellis (1940) found the replication cycle of the bacteriophage using the one step growth curve experiment, and in 1952 Hershey and Chase showed that it was the nucleic acid portion that was responsible for the infectivity and carried the genetic material.

Delbruck worked with Luria to form the phage group. The first phage CSH meeting took place in 1947 with 8 participants. From this meeting and group developed the whole field of molecular biology.

In 1954 Watson and Crick elucidated the structure of DNA.

Discovery of lysogeny by Lwoff in 1949, and later zygotic induction was an important milestone in tumor biology.

1. It showed that virus could behave like a bacterial gene on the chromosome.
2. Showed quiescent negative regulation
3. Led to Jacob/Monod model of gene induction and repression, the foundation of the operon model.

The development of lambda genetics is one of the great intellectual adventures of our time. Work on lysogeny led to the idea that genetic material (foreign and host) could be transferred by viruses.

Animal Virology and tissue -Culture

Simultaneously with this work there was the development of tissue culture techniques. Alex Carel in 1910 had already shown that it is possible to grow chick embryo fibroblasts in culture, and in the 1930's chick embryos were using for growing viruses such as pox virus. By 1940 Earle and associates had developed media for the growth of cell lines.

1949 Enders et al. worked out human tissue culture--used for growth of poliovirus. In 1954 received Nobel Prize. Era of polio research extremely important in virology led to quantitative methods of measuring animal viruses--development of defined media for tissue culture, and eventually animal virus plaque assays.

1953 Salk vaccine (killed poliovirus) introduced and by 1955 poliovirus had been crystallized. Later Sabin introduced attenuated polio vaccine. Dulbecco in 1950's described animal virus plaque assays similar to phage plaque assays, and viral transformation analogous to tumor formation in vitro.

1965 Spiegleman and coworkers obtained complete replication of nucleic acid of QB phage in a cell free system; thus showing the RNA was also genetic material.

1970 Temin and Baltimore independently demonstrated the presence of reverse transcriptase in RNA tumor viruses (RNA --> DNA --> RNA).

1980's Cloning of viral genes.
- Sequencing of complete genomes
- Production of hybridomas.
- Isolation of AIDS virus.
- HTLV series.
- Oncogene characterization and relationship of virus to cancer.
- Monoclonal antibodies.
- Discovery of cytokines and growth factors.
- Knowledge of immunology.
- Development of PCR techniques.

Gene therapy a product of virus, with the development of vector systems. By 1977 we have the complete eradication of smallpox. Last natural case. What should we do with smallpox in labs? we wil discuss the threat of bioterrosim at a later time.

Definition of a Virus

Lwoff in 1957 proposed to define a virus as potentially pathogenic entities with an infectious phase and: (1) possessing only one type of nucleic acid, (2) multiplying in the form of their genetic material (3) unable to undergo binary fission and (4) devoid of a Lipmann system. This is basically a negative definition, and stresses the non-cellular nature of viruses.

Viruses are infectious entities whose genomes are either RNA or DNA, and that replicate

inside living cells using the cellular synthetic machinery and causing the synthesis of specialized components that can transfer the viral genome to other cells.

Thus viruses are intracellular parasites at the genetic level. They are obligatory parasites--cannot be grown outside of the cell. Absolutely dependent on host cell energy yielding and protein synthetic apparatus.

Viruses persist in two stages:

1) dormant phase--extracellular; this phase is neither "alive nor dead" rather should be described as functionally active or inactive.

2) Vegetative phase--intracellular.

One should note that the nucleic acid of the virus, in some cases, is infectious.

All viruses consist of RNA or DNA and a protein coat. Some viruses are enclosed within envelopes that contain both proteins and lipid.

An interesting question: Is a virus an organism? Is it more of an organism than a chromosome? Could viruses have evolved from chromosomes or some other organelle? What about transposons?

Recent diagnosis method

New single virus detection techniques for faster disease diagnosis

Date: May 30, 2013

Source: The Optical Society

http://www.sciencedaily.com/releases/2013/05/130530111309.htm

Summary:

Two independent teams have developed new optics-based methods for determining the exact viral load of a sample by counting individual virus particles. These new methods are faster and cheaper than standard tests and they offer the potential to conduct the measurements in a medical office or hospital instead of a laboratory.

Comparison between Viruses and other microorganisms:

TABLE 13.1 Viruses and Bacteria Compared

	Bacteria		Viruses
	Typical Bacteria	Rickettsias/ Chlamydias	
Intracellular parasite	No	Yes	Yes
Plasma membrane	Yes	Yes	No
Binary fission	Yes	Yes	No
Pass through bacteriological filters	No	No/Yes	Yes
Possess both DNA and RNA	Yes	Yes	No
ATP-generating metabolism	Yes	Yes/No	No
Ribosomes	Yes	Yes	No
Sensitive to antibiotics	Yes	Yes	No
Sensitive to interferon	No	No	Yes

Chemistry of Viruses:

Virus Particle:

- Submicroscopic entity measured in nanometer (nm) = 1/1000000000, ranged from 20-250 nm
- consists of a nucleic acid covered with a protective protein coat or lipoprotein.
- The protein coat called capsid consists from smaller subunit called capsomer.
- Able to organize its own replication within host cell
- It is dependent on the host's protein- synthesizing system
- They have receptor binding-protein for attaching to cellsNucleic Acids:
- Ribonucleic (RNA) and Deoxyribonucleic (DNA) acids are important genetic materials in both virus and host.
- RNA may take enzyme role during amino acids synthesis to form polypeptides in protein production

- Most plant viruses are RNA and in human and animals are DNA viruses but RNA viruses are dominant.

- Both are unbranched macromolecules polymers that differ primarily in the structure of their monomers (repeating unit).

- Each monomer of N.A. is a nucleotide consists of 3 major parts:

1. Phosphates (PO4-3)
2. Pentose Sugar (Deoxyribose or Ribose)
3. Nitrogenous Bases:

Adenine (A), Guanine (G), Cytosine (C), Thymine (T) in RNA and Uracil (U) in DNA.

- Bases A + G= purines (double ringed molecule) and

C + T or U= pyrmidines (single ringed molecule).

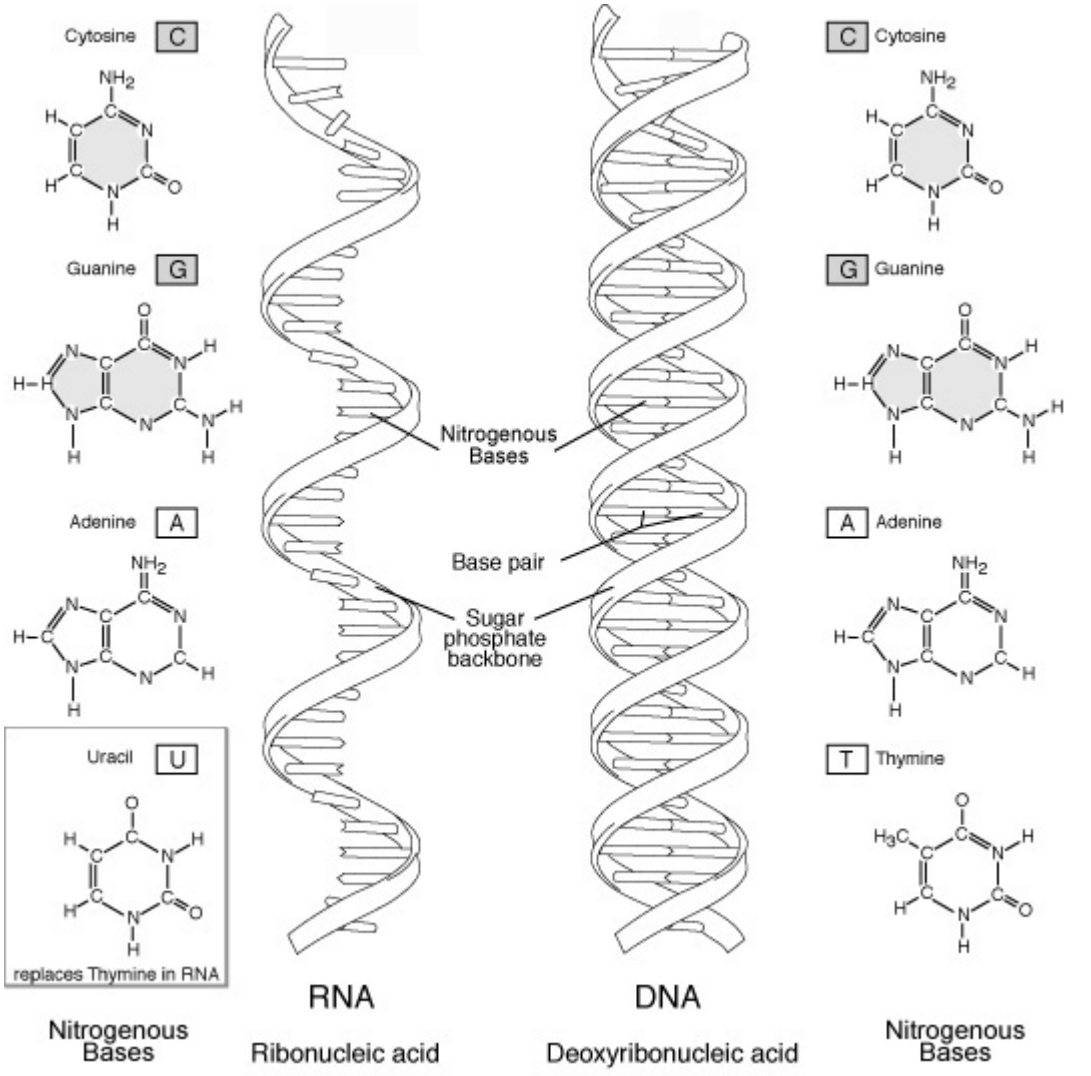
- Nucleotide lacks phosphate root (PO_4^{-3}) called Nucleoside.

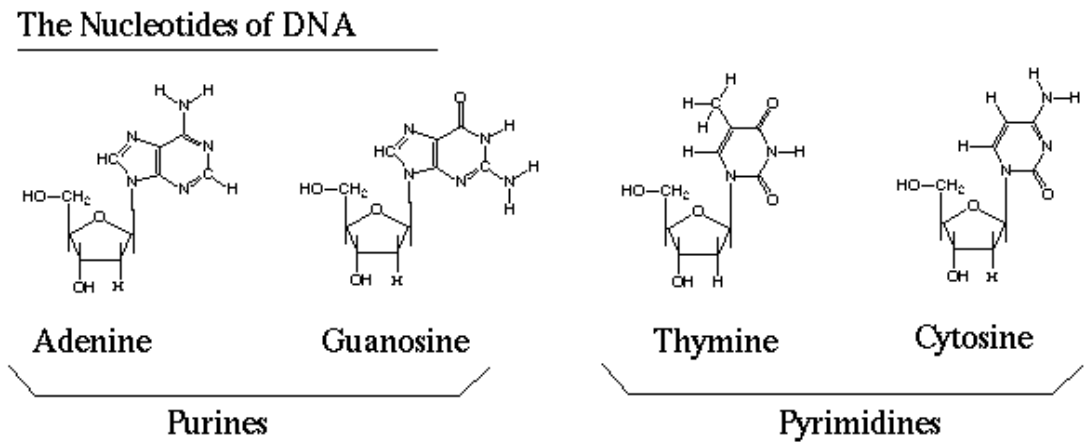
Relationship between RNA role and amino acids synthesis:

- Triplet Code or 3 letter code first suggested by the Physicist Gamow in 1954.

- It is called now Codon which specify each amino acid: Example: AGA

- Synthesis of 20 amino acids are determined by 64 bases (4X4x4) of purine or pyramidine bases which makes distinct triplets (codon) with assistance of transfer RNA.





Proteins:

- Are macromolecules consists of amino acids connected by polypeptides to form the protein coat
- The protein coat of virus particle which called capsid consists of capsomers which may be covered by a lipid layer.
- Sometimes, there are protein spikes originate from the capsid.

- Protein represent the major part of the virus particle about 95% of the size.
- Amino acids are the repeating units in the protein synthesis using the genetic code or codon (triplet letters) as described earlier.
- The gene expression process includes:
  1. Transcription: dsDNA orders to make a complimentary copy of RNA

GTG CAT CTG ACT CCT GAG GAG AAG
GUG CAU CUG ACU CCU GAG GAG AAG
Valine Histidin Lucine Trypto Phenyl Gluta Gluta Lys

2. Translation: amino acids formation and protein synthesis

Virus Morphology and Symmetry:

helical symmetry A form of symmetry in which many RNA virus capsids are constructed.
Each capsomere on the helix consists of a single polypeptide molecule and establishes bonds with two capsomeres on each of the adjacent turns, giving stability to the capsid.
The overall length of the helix is determined by the length of the RNA molecule. In all animal viruses with helical symmetry the nucleocapsid is folded and packed within a lipoprotein envelope, e.g. *Bunyaviridae*,*Orthomyxoviridae*, *Paramyxoviridae* and *Rhabdoviridae*.

helical viruses Viruses whose morphology displays helical symmetry

icosahedral symmetry One of the two types of symmetry found in viral capsids, the other being helical symmetry. Crystallographic considerations prescribe that the identical units forming the capsid of an isometric particle must be arranged with cubic symmetry. Of the possible forms that this may take, icosahedral symmetry provides the facility to make a range of viral capsids with different numbers of structural units. An icosahedron has 20 triangular faces and 12 vertices.
The simplest has 60 identical structural units in regular relation to each other, three to a triangular face. To make a large virus in this simple form from 60 units would require a large protein, which raises difficulties with genome coding capacity, and an alternative is to use a larger number of small units (i.e. more than 60). This inevitably means that the units cannot all have identical relationships to each other.
Those not surrounding a vertex form groups of six called ‘hexons’, and those at each vertex are in groups of five called ‘pentons’. Only certain multiples of 60 units are possible, and the numbers which make up different viral capsid structures are defined by the triangulation number,
T. There are always 60*T* units, where $T = h2 + hk + k2$ (*h* and *k* are integers having no common factors).
Examples are $T = 3$ (caliciviruses), $T = 4$ (alphaviruses),

T = 13 (rotaviruses and orbiviruses) and T = 16 (herpesviruses).
The structural units form into morphological units on the virus surface.
In general, the number of morphological units (capsomeres) which can be visualized on the surface of an icosahedral virion is $10T + 2$ (e.g. 162 for herpesviruses).

icosahedron A solid with 20 triangular faces and 12 vertices. In a regular icosahedrons the faces are equilateral triangles and there are axes of two-fold, three-fold and five-fold rotational symmetry.

isometric particle Particles with identical linear dimensions, distinct from the rodshaped and bullet-shaped virus particles and viruses enclosed by irregular capsules. They appear spherical; however, their capsids are constructed with icosahedral symmetry.

quasi-equivalence: A theory invoked to account for the surface morphology of spherical viruses. It requires that subunits forming the icosahedral capsid should be capable of assembling into both hexamers and pentamers. The insertion of 12 pentamers produces curvature in the sheet of hexamers where they are inserted, resulting in a closed icosahedral shell that is not strictly equivalent, but forms a more stable structure. Thus icosahedral viruses have a capsid composed of 12 pentamers and a variable number of hexamers, e.g. herpesviruses have 150 hexamers and 12 pentamers, making up the capsid; adenoviruses have 240 hexamers and 12 pentamers.

quasi-species A term that describes the nature of most RNA viruses, which are populations of genetic variants within which one (the quasi-species) predominates.

Viruses Classification:

Virus classification is the process of naming viruses and placing them into a taxonomic system. There are two classification systems

1. Traditional System:

This is the system was set by the International Committee on Taxonomy of Viruses. (ICTV). According to this system, viruses are mainly classified by phenotypic characteristics, such as morphology, nucleic acid type, mode of replication, host organisms, and the type of disease they cause.

Viral classification starts at the level of order and continues to the species as follows, with the taxon suffixes given in *italics*:

Order (-*virales*)

Family (-*viridae*)

Subfamily (*-virinae*)

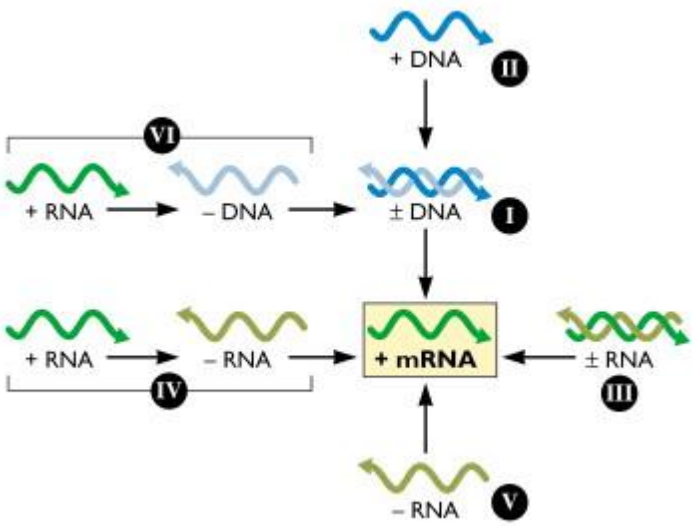
Genus (*-virus*)

Species

Species names generally take the form of *[Disease] virus*

The ICTV defined "A species is a monophyletic group of viruses whose properties can be distinguished from those of other species by multiple criteria.

2. The Baltimore system



Although many viruses are classified into individual families based on a variety of physical and biological criteria, they may also be placed in groups according to the type of genome in the virion. Over 30 years ago virologist David Baltimore devised an alternative classification scheme that takes into account the nature of the viral nucleic acid.

One of the most significant advances in virology of the past 30 years has been the understanding of how viral genomes are expressed. Cellular genes are encoded in dsDNA, from which mRNAs are produced to direct the synthesis of protein. Francis Crick conceptualized this flow of information as the central dogma of molecular biology:

DNA —> RNA —> protein

All viruses must direct the synthesis of mRNA to produce proteins. No viral genome encodes a complete system for translating proteins; therefore all viral protein synthesis is completely dependent upon the translational machinery of the cell. Baltimore created his virus classification scheme based on the central role of the translational machinery and the importance of viral mRNAs in programming viral protein synthesis. In this scheme, he placed mRNA in the center, and described the pathways to mRNA from DNA or RNA genomes. This arrangement highlights the obligatory relationship between the viral genome and its mRNA.

By convention, mRNA is defined as a positive (+) strand because it is the template for protein synthesis. A strand of DNA of the equivalent sequence is also called the (+) strand. RNA and DNA strands that are complementary to the (+) strand are, of course, called negative (-) strands.

According to Baltimore classification, viruses can be placed in one of the seven following groups

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