1- Historical background

Viral diseases have been known for thousands of years. Under the Babylonians, rabies was known to be transmitted by the bite of rabid dogs. Smallpox stigmata were also found on Egyptian mummies. But it wasn't until the end of the 19th century that viruses as such were identified, and the science of viruses was born: virology. Progress in virology was slower than in bacteriology and mycology. Viruses are not visible under light microscopy, nor can they be cultivated in the laboratory on standard media. It was not until the second half of the 20th century that their intracellular replication became known.

Tobacco mosaic, a plant disease, has served as a model for the study of viruses. It is described as a transmissible disease, but its infectious agent is unknown. In 1884, Charles Chamberland developed an ultrafiltration system to eliminate microorganisms. The filtrates obtained were normally sterile, but in 1892, Dimitri Iossifovitch Ivanovski demonstrated that the agent responsible for the disease was much smaller than the microorganisms. He also demonstrated that the factor responsible for mosaic was an ultra-filterable and transmissible agent.

2- Introduction

Viruses (Latin, poison) form a unique group of infectious agents whose genome is a nucleic acid element, deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), which reproduce inside living cells and use their synthesis machinery to direct the synthesis of specialized particles called virions. Viruses differ from living cells in at least 3 ways: their simple, cell-free organization, the absence of DNA and RNA together in the same virion and their inability to multiply independently of cells, and their ability to reproduce solely from their own genetic material.

3- Structure

Virus morphology is determined by electron microscopy, X-ray diffraction, biochemical and immunological analyses.

3-1- Virus size

Viruses range in size from 10 to 300 or 400 nm in diameter. The smallest viruses are slightly larger than ribosomes (e.g. parvovirus), while the largest viruses (poxvirus) are close to the smallest bacteria.

3-2- General properties of viruses (Figure 1)

The virus is composed of:

- a nucleic acid, DNA or RNA, carrying the genetic information ;
- a capsid, which is a protein structure that protects the genetic material of a virus. The nucleic acid-capsid complex is called the nucleocapsid. For some viruses, the nucleocapsid is called the core;
- sometimes an envelope.

There are 4 morphological types of capsid and virus:

1- The protein subunits making up the capsid are distributed on an icosahedron (a regular polyhedron with 20 triangular faces and 12 vertices). On the faces, the protein sub-units are grouped by 6, and on the edges to form capsomeres called hexons. At the apex of each triangle, 5 different planes emerge. The sub-units are grouped by 5, and the capsomere at the top is called a penton. The number of capsomeres varies from virus to virus, but not the number of pentons. Ex. parvovirus.

2- Helical capsids in the form of hollow protein cylinders. The rotomeres, all identical, combine in a spiral arrangement to form a rigid tube (tobacco mosaic virus) or a flexible tube (influenza virus).

3- Some viruses have an envelope surrounding the nucleocapsid. These enveloped viruses are spherical, even if the nucleocapsid is icosahedral or helical.

The viral envelope or peplos (coat) is acquired at the end of the multiplication cycle by nucleocapsid budding through the host cell's membranes (cytoplasmic, nuclear, endoplasmic reticulum, etc.). The host cell provides the lipid bilayer, while the spicules are of viral origin.

Spicules are viral glycoproteins, also known as peplomers, which enable viruses to recognize and bind to host cell receptors.

4- Complex viruses are those whose nucleocapsid is neither icosahedral nor helical:

- Poxviruses

These are the largest known animal viruses. In the case of smallpox viruses, the surface is covered by a series of tubes composed of a double row of spherical units distributed at random (figure 2).

- Bacteriophage

Phages T2, T4 and T6 infect *E. coli* and have a head attached by a collar to a tail consisting of a rigid hollow central tube, a mantle or sheath surrounding the tube and a basal plate. The latter is hexagonal, with a hook at each corner and articular fibers responsible for attachment.

Complex bacterial viruses with head and tail are called binary.

3-3- Nucleic acid (or genome)

A virus has a genome made up of DNA or RNA. This genome may be single-stranded or double-stranded. Genome size varies considerably among DNA viruses (3 to 300 kpb), whereas it is between 10 and 20 kb for most RNA viruses.

The genetic material of most DNA viruses is double-stranded and linear. It can also be circular double-stranded (hepatitis B virus), single-stranded and circular (bacteriophage X174), and phage lambda has linear double-stranded DNA ending in sticky ends.

The genetic material of RNA viruses is single-stranded. When the genomic RNA is identical to the mRNA, the RNA is said to be positive chain (or plus) or, on the contrary, complementary to the mRNA, negative chain (or minus). Reoviruses are double-stranded. The retroviridae genome is made up of two identical, linear, single-stranded RNA molecules, linked by covalent bonds at their 5' ends.

3-4- Viral envelopes and enzymes

Around the nucleocapsid, some viral families have a structure or set of optional peripheral structures known as the envelope. Viruses with an envelope are called enveloped; others are called naked.

All animal RNA viruses with helically symmetrical nucleocapsids are enveloped: orthomyxoviruses, paramyxoviruses, rhabdoviruses. Some icosahedral RNA viruses (togaviruses) and DNA viruses (herpesviruses, poxviruses) also have envelopes.

Viral envelopes have a complex macromolecular, lipido-glucido-protein composition. The lipid-protein structure makes envelopes highly sensitive to physico-chemical actions, to the action of lipid solvents and in particular to ether, detergents, bile salts and pH variations. It also makes the virion thermosensitive. As a result, the presence of an envelope, far from being an additional element of protection for the nucleocapsid, actually makes enveloped viruses more fragile in the external environment, where they survive for a short time, and in the body's hostile environments (faeces).

Most animal viral envelopes originate from the membrane systems of the host cell (known as peplos). There are three possible membrane origins: the inner leaflet of the nuclear membrane (herpes virus), intra-cytoplasmic membrane systems such as the endoplasmic reticulum or Golgi apparatus, and the plasma membrane (myxovirus). Envelope sugars and lipids come from host cells, while proteins are encoded by viral genes. Proteins can protrude from the envelope as projections or spicules. These structures enable the virus to attach to the host cell surface.

In addition to structural proteins, enzymes are associated with the capsid and envelope.

4- Virus classification and nomenclature

Virus classification is based on:

- The nature of the nucleic acid, making it possible to distinguish DNA viruses (D) from RNA viruses;
- Nucleocapsid symmetry: helical (H), cubic (C) or mixed;
- The presence (E) or absence (N) of an envelope;

Viruses are classified into orders, families, subfamilies and genera:

Order (highest taxon) : virales
Families: viridae
Subfamilies: virinae
Genera: virus

These names are written in:

- capital and italics for families, e.g. PARAMYXOVIRIDAE
- italics without capitals for subfamilies and genera.
- for species common names, roman without capital, e.g. measles.

4-1- Classification et multiplication des bactériophages

Les caractères les plus importants pour la caractérisation des bactériophages sont la morphologie de la particule et le type d'acide nucléique. Le matériel génétique est de l'ADN ou de l'ARN et la majorité possède un ADN bicaténaire. Ils sont placés dans les groupes morphologiques suivants : icosaédrique sans queue, à queue contractile, à queue non contractile et virus filamenteux.

4-1-1- Multiplication of double-stranded DNA phages (lytic cycle)

The lytic cycle: the case of E. coli phage T2. Phage multiplication is faster than that of animal and plant viruses. It begins with :

- adsorption: the phage attaches itself to specific receptors (which may be wall proteins or lipopolysaccharides, teichoic acid, flagella or pili). Initially, fibers come into contact with the receptor, and the basal plate approaches the surface. The lysozyme in the phage tail depolymerizes the mucocomplex of the bacterial wall, cutting the glycosidic bonds. The sheath reorganizes, shortening and widening. The central tube is propelled through the wall and DNA is injected into the bacteria. The virion, having injected its DNA, ceases to exist as an independent infectious particle.

- synthesis of nucleic acids and phage proteins: this phase begins with a halt in all host cell synthesis. RNA polymerase begins to synthesize phage mRNA. These direct the synthesis of proteins and enzymes needed to build the phage nucleic acid and degrade the bacterial genome. The structural proteins (head and tail) appear around 9 minutes after infection, and this synthesis is directed by phage DNA and messenger RNAs.
- Maturation and release phase: phage DNA condenses, then surrounds itself with protein units reconstituting the phage head. The elements of the tail then associate. New virions are formed. The virions formed during maturation number between 100 and 200, and act through endolysin on the bacterial wall. The bacterium bursts and releases its contents around the 24th minute. The multiplication of virions is called the vegetative phase.

4-1-2- RNA phage (phage MS-2)

- RNA phages bind to the F pili of male bacteria, which are the only sensitive ones.
- Genomic RNA serves as messenger for the synthesis of 3 proteins corresponding to its triple information: capsid protein, protein A, replicase. The RNA then serves as a template for the synthesis of new RNA chains in the presence of the replicase, as shown below:

* Complementary chains (negative chains) are synthesized from genomic RNA (positive chain);
* The negative chain is used to synthesize positive chains.

- Maturation and release of virions.

4-1-3- Lysogenesis of temperate bacteriophages

Lytic infection is specific to virulent bacteriophages. There is a 2nd type of bacteriophage called temperate. When a susceptible bacterium is infected by such phages, two responses can occur:

- the phage triggers the same lytic cycle as before.
- the bacteria resist the phages; this is a lysogenic infection, as under certain conditions, the cells can lyse and release phages.

Lysogenic bacteria

These are bacteria that harbor the viral genome and can transmit it to their descendants. An example is the *E. coli* K12 phage lambda, whose genome is a double-stranded strand with cohesive ends. It can either follow the lytic or lysogenic cycle. In the latter form, it integrates into the bacterial chromosome, forming a prophage. The prophage behaves like a bacterial gene, which is passed on to the progeny. The bacterium has become immune, and the prophage rarely detaches to trigger the lytic cycle.

There are consequences of lysogenesis, as in the case of conversion. Bacteria carrying a prophage can acquire new properties. One example is the *Corynebacterium diphteriae* species, which by harboring a prophage becomes capable of toxin production.

4-2- Virus-animal cell interaction

Infection of an animal cell by a virus can give rise to several possible responses:

* Productive interaction: penetration of the viral genome into the cell leads to the formation and release of virions.

* Abortive interaction: infection of the cell by a virus does not result in the production of virions. The cell does not allow them to develop.

* Integrative interaction: the virus integrates into the host cell genome (by covalent linkage): provirus or free plasmid. It is thus transmitted after cell division.

4-2-1- RNA virus multiplication cycle (poliovirus model):

- adsorption and penetration :

Adsorption takes place at membrane sites in the cell and at certain surface constituents of the virus. Polioviruses bind to membrane glycoproteins, then their RNA penetrates by pinocytosis.

- synthesis of viral constituents :

For 2 to 3 hours, the cell synthesizes viral constituents, while its own synthesis is stopped. Viral mRNA is a positive chain, and its role is to (i) transcribe its information for the synthesis of viral proteins, a replicase, capsidal proteins (ii) give its complement (negative chain) and from the latter, positive chains are obtained.

- encapsidation: the synthesized viral components assemble by incorporating an RNA molecule.

4-2-2- DNA virus multiplication cycle (adenovirus model, cubic virus)

With the exception of poxviruses, DNA viruses multiply in the cell nucleus.

- adsorption and penetration :

The virus is adsorbed by its hemagglutinating fibers and specific receptors in the cell. It penetrates by pinocytosis and decapsidation takes place as it passes the nuclear membrane.

- synthesis and replication :

DNA gives rise to mRNAs encoding proteins and enzymes. DNA replication is a semi-conservative process.

- encapsidation: virions are assembled in the nucleus, cross the nuclear membrane and then the cytoplasmic membrane by cell lysis.

4-3- Main human pathogenic viruses

Today, many diseases remain worrying, to say the least, even if vaccinations have made it possible to curb the onset or severity of some of them (rubella, influenza, poliomyelitis). What's more, the emergence of new viral strains is responsible for some highly unusual pathological syndromes (Ebola fever, Acquired Immune Deficiency Syndrome virus.....) (Table 1). Generally speaking, the infecting virus targets a particular cell family within the organism, exerting a cytopathogenic power that disrupts the metabolism of the affected cell to the benefit of the single, rapidly expanding viral population.

Table 1. Examples of human viruses.

Virus	Infection
Herpes virus	Varicella, shingles, various herpes
Pox virus	Smallpox, vaccinia
Poliovirus	Poliomyelitis
Influenza virus	Influenza
Paramyxovirus	Mumps
Rhabdovirus	Rabies
Togavirus	Rubella
Retrovirus	Acquired immune deficiency syndrome

5- Methods for studying viruses

Viruses can only multiply in living cells. 3 types of culture can be used:

5-1- Animal inoculation

Initially, the only way to culture viruses was to inoculate susceptible animals. Poliomyelitis, for example, could be reproduced in monkeys by intracerebral inoculation. Rabies virus by intracerebral inoculation in monkeys.

5-2- culture on embryonated eggs

Several types of inoculation are possible, depending on the viruses studied.

- inoculation on the chorio-allantoic membrane: this is carried out on 10 to 12-day-old embryonated eggs. A small fragment of the shell and shell membrane is removed, a drop of

inoculate is applied and closed. Poxviruses and Herpes viruses multiply on the chorioallantoic membrane, forming lesions.

- inoculation in the amniotic sac: 7-day-old embryos are used. Myxovirus influenzae A, B and Myxovirus para-influenzae can multiply.
- inoculation into the allantoic cavity: 7 to 10-day-old embryos are used.
- inoculation into the yolk sac: 5 to 7-day-old embryos are used. Virus multiplication in the yolk sac is accompanied by embryo death (herpes virus, arbovirus).

5-3- Cultivation on animal cells

Viruses are grown in vitro on animal cells. The cells are suspended in a growth medium contained in a glass container. The cells are suspended in a growth medium contained in a glass vessel, and grow on the wall in a single layer. Three types of cell are used:

- cells obtained from tissues under the action of enzymes, e.g. monkey kidney cells, human cells such as thyroid cells harvested during surgery.
- continuous lineage cells: these are cancer cells of the Hela lineage obtained from cervical carcinoma of the uterus and KB lineage obtained from squamous epithelioma of the mouth.
- diploid cells: derived from human embryonic tissues (lung, heart, kidney, thyroid).

6- Sensitivity to physical and chemical agents

Generally speaking, viruses are more resistant than bacteria to physical agents such as heat, UV and X-rays. They are also highly resistant to desiccation, particularly freeze-drying (low-temperature, vacuum drying).

Certain antibacterial substances are also active against viruses (ether, chlorine and derivatives).

7- Fighting viruses

Virus control is prophylactic, and is of 2 types:

7-1- Chemoprophylaxis

The role of chemical substances is either to modify the virus shell, rendering it unable to bind to receptors on the sensitive cell. They can also modify the surface structure of the sensitive cell, and thus the cell receptors, preventing the virus from attaching to them.

7-2- Immunological prophylaxis

This consists of using non-virulent virus material with antigenic properties. This may be killed (inactive) viruses or live viruses with attenuated virulence.

- Killed viruses are obtained by culturing viruses on living tissue. They are collected, purified and then treated with heat or formalin. These viruses are killed by these agents, then adjuvants are added to promote the appearance of antiviral antibodies after administration to the body.
- Live viruses: these vaccines are made up of either spontaneously-attenuated or artificially-attenuated strains.

7-3- Chemotherapy

There are many antiviral chemical substances, but few of them are used therapeutically. They act at 2 levels: either to prevent virions from multiplying by preventing replication of their genome (no synthesis of their constituents, denaturation of nucleic acid), or to prevent the infected cell from passing into a healthy cell.