The MEGA Sheet

DNA and RNA viruses

By: BAKIR JABER

جديد فايروس كل ابدا كان يعملها فمته التي اترتيبات بعض مستلزم العزيزه فغمتي
لادي فايروس اي عن لاحق ذكرت التي المعلومات بعض بنقل فمته و جديدة بصفحة
القيمة المعلومات عدا ما موجود الدكتور ذكره ما كل يعني , الفايروس صفحه في مكانها
تضيع تبعت الاستله أو القادمة بالفصل تاخذ رج انه يمكى بعين و يحكيها كان الي
بعض توضيح و بشرح فمته كما .. (!!! بدونهم طويله الشيت بصراحه لأنه) الوقت
الجميع انصح .. ما شينا مهمة بطريقة الدكتور شرحها التي الويكيبيديا من المواضيع
!! الأقل على قراءتها
DNA Viruses

We will start talking about 3 families: **Parvoviruses**, **Papovaviruses** and **Adenoviruses**.

As we know the viruses are classified into: DNA and RNA viruses. "we will start with DNA viruses".. but there are certain viruses that have a different classification (it is better to classify them in groups) like **hepatitis** and **arboviruses** because they may contain subtypes that are DNA or RNA viruses.

Note: the discussion will be followed from the simplest to the most complex viruses.

DON’T MEMORIZE NUMBERS! WE WILL MEMORIZE THEM AT THE END OF EACH FAMILY!!

**Parvoviruses (or the viruses of a Parvoviridae family):**

- They are the simplest of all DNA viruses.
- Have a single-stranded DNA genome.
- Totally dependant on the infected cell (don't code for any enzymes or proteins necessary for their replication).
- Classified into:
  1. **Densivirinae**:
     - Include members that infect invertebrates.
  2. **Parvovirinae**: - The letter D comes before N in alphabet this will help you to remember that ParoviririDae is the Family Name and ParoviririNae is the subfamily -
     - Include members that infect vertebrates (our main concern).
- Classified into viruses that:
  1. **Parvovirus**: (confusing because this genus name is the same as the family): infect animals like Feline PV "cats", Canine PV "dogs", Porcine PV "pigs", Mice PV "mice"..
  2. **Dependoviruses**: can't replicate in their own so they require a help which is usually provided by another viruses like 1.-**Adenoviruses** in most cases and that is why the name is Adeno Associated Viruses (AAV)

**2-Herpesviruses** (**HSV**), 3.**Human Papilloma virus** (**HPV**) and 4.**Vaccinia viruses** (note: all of this viruses are DNA viruses.. so the help must be provided by a related viruses).

Mimic: Aden (اسم بني ادم) Have P.S Vaccine, to Help him cessating video games. (P.S =play station)

Aden = adenovirus, HPV and HSV, vaccine = vaccinia
**Dependoviruses** commonly infect humans, if they find the helper viruses they will continue. If they don't then they usually become integrated in the q arm of chromosome number 19 and their integration is not associated with any effects. SO they fail to continue their replication cycle and become integrated in the genome of the infected cell doing nothing.

-(integrated Paroviruses "dependoviruses" is not associated with any pathology and it’s a DEAD end for the virus .( it cant be reactivated if a helper virus infect the host after integration of the genome )

**3-Erythroviruses**: their target is the immature erythrocytes and we have two members in this genus which infect humans and animals -**B19 parovirus** (infect humans), -**Semian parovirus** (infect monkeys).

Both Dependoviruses and Erythroviruses are two subfamilies of the viruses that infect the humans.

**4-Bocavirus**: which was discovered in 2005 as a member of this family that infect the respiratory tract of humans.

SO the Paroviruses are:

-very simple in their structure .. they contain an icosahedral capsid (protein coat) with a minimum number of capsomers = 60 capsomers .. they contain a single stranded DNA genome .. their size is 20 nm (18-26 nm).

-each of the capsomer is made of two proteins known as **VP1** (viral peptide 1) and **VP2** (viral peptide 2) ..and the VP2 constitutes 80% of the total protein mass of the virus.

-VP1 and VP2 share significant homologic sequence of their amino acids because they are coded for by overlapping sequence → the same sequence is utilized by the virus to produce these two proteins .. they differ in small amount of amino acids that make this proteins .. meaning that the overlapping of the reading frame is utilized to transcribe the genome . (See next) . (The above paragraph have the same idea of Apo B48 and Apo B100 proteins in biochemistry , in which a non sense codon stop the synthesis of the Apo B48 and this non sense codon is not produced in synthesis of Apo B100 so synthesis of the protein continues .. ) just change the name Apo B48 to VP1 and Apo B100 to VP2 !

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**Adeno associated virus** (Dependovirus)
- VP1 although is less in quantity (20% of the total protein mass of the virus) is longer than VP2 and have a unique region external to the capsid which is essential for binding to the antibodies as for binding to the susceptible cells which is Erythrocytes .. and this protein is necessary to stabilize the conformation of the virus and this regions are accessible to antibody binding .. the fact that is accessible in the immune system which allows the induction and production of the antibodies that can neutralize the affectivity of the virus .. so the antibodies that are against the VP1 protein neutralize the affectivity of the virus !

Now we will talk about the **B19 Parvovirus**

**B19 parvovirus :**

- Erythroivirus that targets the Erythrocyte cells.

- The genome of this virus is 5.6 kilobase in length (we said kilobase not kilo basepair because it is single stranded DNA virus) .. it have 5600 nucleotides make up the whole sequence of DNA ..

- With molecular weight about 1.5-1.8 x10^6 Daltons.

- The receptor used by parvovirus B19 (remember viruses have anti-receptors ) is antigen P (known as globoside which is blood group antigen) present in the surface of Erythrocyte of most individual (more than 90% and in the range of 99% of individuals have P+ blood group antigen meaning that they can be infected with parvovirus but thus who lacks it or have a P- group is naturally resistant to infection by this viruses.

- Of all DNA viruses , Paroviruses seems to be among the most dependent on cellular function (because even the simple DNA viruses which is Papovaviruses code at least for the protein that initiate the replcative cycle which act as a helicase ) .. but Paroviruses lack DNA polymerase and transcriptase so they dependent in cellular enzymes and proteins and that is why replication of Paroviruses is dependent in the replcative cycle of the infected cell so the virus that replicates in the cell passes through the S phase of its growth cycle where all enzymes and proteins are available because it lacks all proteins and enzymes necessary for the replication ..

SO it relies on the cell for its replication and that is why it infect mitotically active cell .. that is the reason for the fact that the Paroviruses replicate only in the mitotically active cell (dividing cell) .. they don't replicate in resting cell , simply because they cannot force it to enter the S phase !
-as a naked viruses the only way for this viruses repressive is by its destruction of Erythrocyte in which they replicate and that is a consequence leads to Anemia so they cause cessation (stop) of Erythropoiesis (synthesis of RBC) for a while which is the time required for the replication, and when the host make a body response as a consequence of infection, the antibodies will clear the virus and the Erythropoiesis starts again and back normal.

So in those infective individuals due to the viruses replication in mitotically active cells, the Erythropoiesis stops and it take about few days to the body and host to make a response that clears the virus, and once the virus is cleared from the circulation the normal Erythropoiesis process back normally. However in individuals that lack the ability to clear the virus, they develop interassistant type of infection and in that case they become dependent in transfusion. Those individual who fail to produce a new response to clear the virus (because of immunosuppression, immunosuppression therapy or because a congenital immune defects) develop interassistant type of infection which is known as pure red cell aplasia (failure to function normally) that is again caused by Parvoviruses as a consequence of failing to clear the virus from the circulation.

-B19 Parvovirus: is the most important human pathogen that was the single human pathogen known until 2005, when the Bocavirus was discovered, and B19 Parvovirus was discovered by Yvonne cossart in London in 1975. This scientist was working in labs in London trying to diagnosis hepatitis B virus using a developing method to diagnosis the virus infection and one of the individual showed a positive reaction in the test and this specimen was in raw B, well number 19, and this virus was not the hepatitis B virus as he expected, and after the studying it was noticed that it is a new virus therefore he called it B19 Parvovirus. At this time this virus was not known to cause an infection, but in 1981 it was linked to transient aplastic crisis (TAC) and in 1983 it was first linked with the fifth disease.

Transient Aplastic Crisis (TAC):

Individuals with underlining chronic hemolytic conditions like thalassemia, sickle cell disease, enzymatic defects of red blood cells associated with abnormality on the membrane of this cells such individuals are known to develop a condition known as transient aplastic crisis which was known but the etiologic agent wasn't so in 1981, B19 was discovered as a cause of this condition which is crisis of hemolysis in individual who is already suffer a hemolytic anemia. So acute hemolytic superimpose with chronic hemolytic condition and such individuals may need blood transfusion to treat the anemia that developed in those individuals.
Fifth disease:
It was known in the 19th century diseases of childhood were named by numbers, first, second, third, fourth and fifth disease (measles was the first disease). The fifth disease is characterized by a skin rash that might mature which last for few days. The etiology of the fifth disease also was unknown until 1983 when they discovered that the B19 is actually the cause of fifth disease also known as Erythema infectiosum or (different name that describe the nature of the illness which characterized by redness erythema of the skin specially of the face.

SO Parvoviruses cause:

* **Normal individual fifth disease** (mostly children are infected early in the life).

* **Transint Aplastic Cirisis** (TAC) in individuals with hemolytic condition.

* **Pure red cell Aplasia** for immune-compromised patients.

* it also can cause a congenital infection; B19 can infect susceptible female (if she was not infected in her life) –if she does not have antibodies- and remains susceptible until she is pregnant, she can be infected, and if infection develops early it can be transmitted to the fetus through the placenta and that is can be serious and may lead to abortion because of the sever hemolysis which can take place in this individual.

TIME TO MEMORIZE NUMBERS:

LENGTH 18-26, CAPSOMERS: 60, VP1: 20%, VP2: 80%, 5.6 Kbase, 1.5-1.8 Daltons

1 - المستقبل: اعتذر واحد انتا بتعرفه مولود سنة 1918 او حولي و بعد ما تدخين صورته اكتب على وجهه رقم 2 و اكتب على بطنه رقم 6 ...
2 - البيضاوي: اتخيل انه علامتك كانو 60 و 20 و 80 اخيلهم على ...
3 - المثلث: اتخيل حالك بالسوبر ماركت شو بتقدر اشي ب 5 دنانير و 60 قرش – 5.6
4 - قلب الحب: الساعة 18 يعني 3:18 pm شو بتكون بتعمل ؟؟ المفروض يبتغذى, اخيلت صورة الغذاء ؟؟

خلاص ممتاز

ولا قوم خذلك بريك ..

Take kitkat ..

و سمع الارقام لأنه المفروض عنقل خزتهم ..
The SECOND FAMILY:

**Papovaviruses or Papovaviridae:**

**Introduction:**

-the name is derived from the members:

1. **Papilloma** (cause Papilla: warts growth and abnormal hypertrophy of tissue).
2. **Polyoma** (cause multiple tumors).
3. **Vacouliating viruses** (cause a vacuole in the cytoplasm in the infected cell, they are not a cause for any human illnesses).

-ONLY **Papilloma** and **Polyoma** viruses are the two members that associate with infection in humans.

-are naked icosahedral with a double stranded superhelical (circular) closed DNA genome.

-the range in diameter from 40 to 45 nm for Polyomaviruses and from 52 to 55 nm for Papillomaviruses SO they slightly differ in their size which reflect a difference in their genome size.

-their icosahedral capsid is composed of 72 capsomers (60 make the equilateral triangles and 12 are in the vertices(corner).

-each capsomers is composed of 2(L1, L2) peptide for Papillomaviruses or 3(VP1,2 and 3)peptides for Polyomaviruses (L=late..so this peptides are made in the late phase of the transcription which has two phases; early and late)

-their genome is 5-8 Kbp.

-this viruses are known to cause different type of infection (all known viral infectious can be caused by this viruses)

-infection by this family must start at the basal layer .. they can't infect other layer and the virus need a differentiated factor which is usually the keratin.

-they cause lytic type of infection – like bacteriophages - in the most differentiated layer SO cells that are not terminally differentiated can't support a productive infection or can't support a complete replicative cycle which is necessary for the lysis of the cell .. that is why lysis is the result of the most differentiated cell because this cell contains all proteins necessary for the replication of this viruses and that is a consequence for the viral protein production and killing the cell because they are naked viruses.
- in other cell rather than the basal layer the proteins are not available for the completion of the lytic cycle and that is why they remain inside the cell until it reaches the most differentiated state then they cause lysis of the cell ,, and that is why it cause chronic infection ( in this regard ) .. and cause latent infection in the basal layer .. and some of them can cause the expression of certain protein that are associated with a malignant transformation of the cell so in this case they can cause a cancer.

SO depending in the host cell different infections can take place lytic , chronic , latent , and transformation infections.

Starting with Papillomaviruses:

-Papillomaviruses are significant because they are the cause of adenocarcinoma of the cervix.
-cause warts (papillomas) in animals and humans.
- the viral nature of human warts was first indicated in 1907 by Ciuffo .. he used a culture filtrate of warts.
->100 different HPVs have been described on basis of DNA sequence homology (>50%) which fall into 16(A-P) groups that differ antigenically.
- genome: is divided into TWO main region or operating frames:

1-early region

- two large (E1 and E2 .. E = early .. meaning that they produce its proteins during the early phase of transcription) and several smaller (E4-E7) ORFs .. which are associated with the regulatory proteins and code for them in the replicative cycle .. SO they concerned with the DNA replication transcription and transformation.

2-late region

- with two large genes (L1 and L2) which code for the structural proteins(the capsid) and they are proteins that essential for replication , remember papilloma capsomer is made of L1 and L2 protiens ;)
- the interaction of long control region (LCR) is concerned with the control of transcription.
Transformation

As we mentioned that the Papillomaviruses are the cause of the Adenocarcinoma in the cervix and that happen as following:

- binding of the E2 protein to an enhancer site on the LCR (long control region) then this site can up regulate transcription of E6 and E7 proteins (the key proteins in the transformation of the infected cell).

- integration of the viral genome results in disruption of E1 and E2 with subsequent increase in expression of E6 and E7.

- E7 binds Rb (P 105) and E6 binds to the tumor suppressor gene product P53 causing its rapid degradation.

- P105 and P53 are known to be growth regulated proteins. They are responsible for the normal growth of the cell. If these proteins are inhibited to performing their function (by the binding with E6 and E7) then the normal control of growth is lost and the cell undergoes non regulated or uncontrolled growth (=cancer like cervical cancer). So this result in transformation which then leads to Adenocarcinoma of the cell.

-The most important disease associated with Papillomavirus is cervical cancer because that warts are usually normal and can be treated surgically and tumors regress spontaneously after several months. Although they can be treated by surgery or cryotherapy.

Now we are going to talk about Polyomaviruses:

- they were named so because of their capacity to cause different types of tumors in different animals. (Note: no tumors are associated with Polyomaviruses in humans. It is restricted to the animals, although this virus can cause another infection in humans).

- most of them display a narrow host range and do not productively infect other species.

- they have two viruses are definitely associated with human disease:

  1. JC virus (JCV): derived its name from the patient that was detected in his body. In 1971 and that patient was suffering from a fetal disease known as a Progressive Multifocal Leukoencephalopathy (PML). So JC virus cause a disease in immune-compromised patients and usually the infection is early in life. That infection is followed of no ill effect but the virus remains latent in such individuals until immune decline, or until they suffer from an infection, or by aging, they develop immune decline where its activation lead to JC disease which is characterized by a progressive in coordination and patient usually die within a year.
2- **BK virus**: it causes urinary tract diseases (hemorrhagic cystitis and interstitial nephritis). (note: in rare cases BK virus maybe found in the case of PML disease) but usually it is associated with a renal infection specially after renal transcription or in immune-compromised patients.

-the genome of Polyomaviruses code for large T and small t antigens.

-Antigens accumulate in the nucleus and stimulate cellular growth and are important for replication.

-the early proteins are associated with immortalization and transformation of infected in animals

-large T antigen binds to both Rb and P53 and prevents the induction of cell death.

*TIME TO MEMORIZE NUMBERS:

Polyoma Length: 40-45nm, Papilloma Length: 52-55nm, 72: capsomers, genome: 5-8 Kbp

1 - المستطيغ: بني ادم ات ما بتعرفه مولود 40 او حوله و اكتب على وجهه 4 و على بطقه 5.
2 - الدائرة: بني ادم ات ما بتعرفه مولود 52 او حوله و اكتب على وجهه 5 و على بطقه 5.
3 - المثلث: بني ادم ات ما بتعرفه مولود 72 او حوله و اكتب على وجهه 5 و على بطقه 8.

جرب سمع الأرقام هالي و الي قبليها😊
The THIRD FAMILY:

**Adenoviruses:**

-they are very important human pathogen. first isolated in the 1953 by Rowe and colleagues (they were investigating the use of adenoidal tissue (Definition: tissue from the lymph mass present between the back of the nose and the throat. wiki) that is removed from the patient. they used this tissue as a culture for this viruses, but they discovered that the tissue itself contains a viruses with DNA (without a replication of the tissue) so they call the isolated virus ADENO because they were isolated from adenoidal tissue. after that Hillman and Werner were studying acute respiratory disease they isolate the same virus. and in 1956 they agreed to use the same name used by Rowe = adenoviruses because they were isolated from the adenoidal tissue.)

-Today well over 100 members of the adenovirus group have been identified which infect a wide range of mammalian and avian (birds) host. they divided into groups depending on the hemagglutination activity.

1- **Mastadenoviruses**: infect mammals.

2- **Aviadenoviruses**: infect birds.

-humans can be infected with 49 adenovirus serotypes and most of human diseases due to the lower number (six group A-F).

- 40, 41 associated with DNA diseases, and there are 8 types were lately discovered.

-Naked icosahedral viruses with a diameter of 70-75 nm.

-they have a characteristic Sputnik appearance (related to Russian satellite).

-capsid is composed of 252 capsomeres (240 hexons and 12 pentons). hexone make up the triangles and each triangle is composed of 20 in this case. and penton make up the vertices.

-of the hexons 60 are peripentons. because the penton has 5 edges so each edge is associated with hexone so in each vertices we have 5 hexons and 1 penton.

-each penton contains a base and a projecting fiber from the penton (10-30 nm) we have 12 fibers because we have 12 vertices. and adenoviruses bind to the cell by this fibers.
- The penton base and fiber are cytotoxic and contain type-specific antigen. They kill the infected cell. Certain viruses kill the infected cell by production of this structural components (pentons and fibers) which cause lysis to the cell.

- The fiber contains the VAP (viral attachment peptide of the virus) and acts as a hemagglutinin.

- Contain at least 11 polypeptide.

- The outer shell is composed of seven of this known polypeptides. Of which polypeptide II is the most abundant because it makes the hexon which is the most abundant also.

- The hexon protein is comprised of three tightly associated molecules of polypeptide II.

- Polypeptides VI, VIII, and IX are associated with the hexon protein as they likely stabilize the hexon capsomere lattice.

- Five copies of polypeptide III associate to form the penton base protein.

- Polypeptide IV forms the trimeric fiber protein.

- Polypeptide IIIa is penton associated.

**So the external seven peptides = 2, 6, 8, 9 and 3, 3a, 4**

- Polypeptide V bridges the core to the capsid.

- Polypeptide VII is a major core protein around which DNA is wrapped forming a histone-like center.

- Polypeptide Mu (unknown function).

- A terminal protein which is attached to the 5'end of viral DNA (two copies per virion) and serves as a primer for DNA replication.

**So the internal four are: The TERMINAtor V MUVii, MUVii = Movie**

- Terminal, 5, MU, 7

- DNA polymerase uses the terminal protein and a cytosine monophosphate as a primer. The virus does not have its transcriptase so it depends on the cell for its transcription but it has its own DNA polymerase so it can replicate by its own.

**-the genome:**

- ds DNA of 34-45 Kbp with a molecular weight of 20-25 x 10^6 Daltons.

- A terminal protein (55kd) covalently attached to the genome of the viruses.
Gene expression

occurs in three phases termed pre-early, early, and late.

note: these phases are dependent on each other; the products of the expression of pre-early phase are needed for the expression of the early phase and so on …

-most regulatory events in adenovirus gene expression occur at transcriptional or posttranscriptional steps.

-Pre-early phase: Transcription of E1a(early 1a) … The E1a transcript is spliced to yield two E1a mRNAs that are translated to proteins that necessary for the expression of the early proteins … One of the proteins is a transcriptional activator that induces transcription of the early phase proteins.

-Early phase: transcription of (E1b, E2, E3, E4) and (L1) followed by splicing of RNA transcripts. Progression to the late phase of gene expression with the help of protein products of at least 6 early genes then takes place. The first five proteins come from the immediate transcription of E1b, E2, E3, E4 and L1. After this, splicing of these mRNA transcripts takes place to produce more proteins. At least 6 proteins are required in this phase (actually more than six proteins can be produced, but a minimum of 6 are required to continue the replication of adenovirus).

-Late phase: Coincident with DNA replication and directed by the so-called major late promoter (20 distinct viral mRNAs). Transport of mRNAs to the cytoplasm. Splicing and transport involves proteins produced in the early phase.

Proteins function

-adenoviruses employ both virally encoded and host proteins in replication.

-E1A and virus-associated RNAs (VA RNAs) afford protection from α and β interferons.

-E1A and E1B activate host cell growth (S phase) and mediate transformation of cells in vitro.

E1A inhibits apoptosis whereas E2 activates viral DNA replication and E3 antagonizes TNF and CTLs.

Behavior of adenoviruses in cell culture

- The adenoviruses grow best in epithelial cells; they cause rounding and clustering of the cell culture infected.

- We can identify adenoviruses growing in by a ( group-specific ) antigen which’s present in the hexon; it’s an antigen specific for all adenoviruses. We also have a ( type-specific ) antigen present on the penton that can be used to determine the type that causes infection.

Take A DEEP Breath

Then EAT A bar of MARS TO INCREASE GLUCOSE IN YOUR BLOOD
Because the Next Family will require a Full Concentration MODE ;)

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The FOURTH FAMILY:

Herpesviridae

Introduction:

✓ The Herpesviridae family is one of the complex DNA viral families. The most complex DNA viral family is probably the Poxviridae because poxviruses can replicate in the cytoplasm with the absence of help from the cell.

✓ All herpes viruses replicate in the nucleus. They don't require much help from the cell; they have all necessary proteins and enzymes to proceed in infected cells and produce virus particles, so replication can take place because of the availability of all proteins and enzymes necessary for replication. However, they require the cell as the protein synthesizing apparatus; ribosomes and others are needed from the infected cell to produce viral proteins.

✓ Herpes viruses can replicate their genomes in a test tube if they're supplied with the necessary nucleotides; usually they do so in the cell.

✓ Herpes viruses are spherical in nature.

✓ Their core is composed of a tower structure, fibrous, dumbbell-like and spool-like structure. Around it, the linear double-stranded DNA is wrapped and this is surrounded by an icosahedral capsid. This capsid has a groove that runs along its longitudinal axis. The capsid is surrounded by a layer that is not present in any other virus called the tegument; tegument is composed of about 30 protein types, so its a protein layer between the capsid and the envelope. The envelope then surrounds the virus; the envelope is a phospholipid bilayer that is incorporated with a large number of short proteins (glycoproteins) unlike other viruses where the glycoproteins are fewer in number and larger in size.

✓ The difference between the average size of the capsid (100-110 nm) and the average size of the virus (200 nm) is accounted for the tegument layer, so the tegument is responsible for the variation in size between herpes viruses. Herpes viruses size ranges from 120-300 nm; the tegument could be very thin or thick and that’s why this variation in size. You can figure that the average size of the virus is double the average size of the capsid.

✓ Almost every animal examined has its own herpes virus; at least one herpes virus for each animal examined so far.

✓ (HSV-1, HSV-2 VZV, HCMV, EBV, HHV-6, HHV-7 and HHV-8) These 8 herpes viruses (out of the 100 herpes viruses that have been identified) were originally given names depending on the disease they cause, then they start to give them numbers (this is common for many viruses: Enteroviruses…etc). Originally the name was given according to the disease they cause or the geographical area of isolation or the tissue of origin…etc
The first herpes virus was called **Herpes simplex virus (HSV)**. It was the first to be discovered and it was known since ancient time. Greek were aware of the herpes viruses and the herpes name is derived for the Greek word to **herpein** (to creep, to crawl) because of the spreading nature of the lesions of herpes viruses, so the lesion spreads on the area that is affected; that's why the name (to herpein) because herpes simplex virus was first recognized by ancient Greek.

**Herpes simplex viruses** were found to be of **two types**: one that usually causes orofacial lesions and the other causes genital lesions. The first which causes orofacial lesions is known as Herpes simplex virus type1 (**HSV-1**) and the other is Herpes simplex virus type2 (**HSV-2**).

The third herpes virus that is related to these viruses is called **Varicella Zoster Virus (VZV)**; the name is derived from the fact that this virus causes 2 diseases: primary infection is in the form of Varicella or chicken pox and the second is the Zoster (the fire-belt).

The fourth of these viruses is **EBV (Epstein - Barr virus)** given the names of the scientists who discovered the virus: Epstein and Barr.

Fifth Human herpes virus is the **Cytomegalovirus (HCMV)**; cytomegalo because it causes enlargement of the cell (cytomegalia).

After these five viruses, they discovered new herpes viruses that mostly they are not associated with any illness until recently they have been recognized to cause diseases; that's why they were given numbers: **Human Herpes Viruses 6, 7 and 8 (HHV-6, HHV-7, HHV-8)**.

These viruses have tissue tropism. Some of them have neurotropism: they cause latent infection in sensory ganglia, and others have lymphotropism: they have tropism or they attack targets of lymphocytes; B or T-lymphocytes are infected with these viruses.

**shape of herpes virus:**

You can see the envelope which's irregularly spherical, and the icosahedral capsid and the layer that lies between is the tegument with the globular proteins that may reach up to 30 proteins.
Here you can see the core which has a spool, dumbbell-like structure and which's also fibrous in nature; it's composed of proteins. Around which a linear double stranded DNA is wrapped, so this spool is like the histon in this case. Then this is surrounded by the icosahedral capsid and this capsid is surrounded by the tegument and finally the envelope; as you can see the envelope is decorated with a large number of different types of glycoproteins that are short and numerous unlike other viruses.

✓ The genome weight ranges from 80-150 x10^6 Daltons. The smallest of these viruses is Varicella Zoster virus and the largest is the Cytomegalovirus. The range in size is significant: some viruses have double the size of the genome of other viruses which's reflected also in double the number of neocleotides (120-230 Kbp).

✓ The genome is originally linear, but once it enters the nucleus it becomes circular.

✓ In brief, The Replication of Herpes Viruses:
Fusion between the viral envelope and the cell membrane takes place; it's followed by the entry of the capsid and the capsid is transferred from the cytoplasm towards the nucleus to the nuclear pores; at the nuclear pore it injects the DNA. Uncoating takes place with the release of the viral genome which's linear in nature, but immediately upon release the genome assumes a circular shape (circularization takes place).
In some of the cases integration of the viral genome in the cell genome takes place; also the viral genome can be present as a plasmid in the cell so it's a plasmid-like structure that can be present in the nucleus of the cell where it's expressed.
Expression of the genome takes place by the rolling circle mechanism (definition: A model of DNA replication that accounts for a circular DNA molecule producing linear daughter double helices. wiki) with the production of DNA strands complementary to the template that is utilized for the synthesis of DNA. Of course transcription of the genome takes place by host cell transcriptases because the virus doesn't have its own transcriptase. They utilize the transcriptase of the cell to produce their own proteins and large number of genes are expressed (almost 100 genes are expressed for certain herpes viruses).
Biological Properties

Herpes viruses are classified as herpes viruses on the basis of architecture, but they share some biological features with other virus families.

Four biological characteristics are shared by all herpes viruses which include:

1- **Specifying a large number of enzymes** that include DNA synthesizing enzymes (DNA polymerase, DNA helicases and primases…etc) that are required for any linear synthesis of DNA and super coiling the genome. These also include nucleotide metabolizing enzymes like (thymidine kinases and dinucleotide reductase) which are different types of enzymes that metabolize the nucleotides.

   **Definition of THYMIDINE KINASE**

   An enzyme that catalyzes the phosphorylation of thymidine in a pathway leading to DNA synthesis, that is active especially in tissues undergoing growth or regeneration, and that is the key enzyme mediating replication in certain viruses (as the herpesvirus causing herpes simplex).

   They also have protein metabolizing enzymes (glycoproteases…etc), so herpes viruses specify a large number of enzymes with different functions.

2- **The synthesis of viral DNA and assembly of capsids occur in the nucleus**, so all steps of replication take place in the nucleus including assembly, and these viruses acquire an envelope while leaving the nucleus: some believe that they acquire the envelope at the inner lamella of the nuclear membrane then they lose it to acquire it from the outer lamella of the membrane, but irrespectively the envelope is acquired from the nuclear membrane, then they are coated within a vesicle and transferred across certain paths of the cytoskeleton of the cytoplasm and exocytosed at the cytoplasmic membrane and they are released from the infected cell.

3- **The irreversible destruction of the infected cell**. Their release from the infected cell is invariably followed by destruction of the cell, so if a cell supports productive replication of a herpes virus it will be killed. Because the infection in many of the cases is not productive but is latent, the virus remains latent in the cell, but if the cell supports productive replication, it will die. Death of the cell is due to different reasons (we’ll come to this but there are nuclear as well as membrane changes that take place which lead to the killing of the cell), so if a cell is infected with a herpes virus and produce viral particles (like epithelial cells) they will be killed, but if the infection is latent (like in sensory ganglia) they won't be killed. However, this is dependent on the type of the infection (productive or latent): productive leading to killing of the cell, or latent leads to no influence on the cell that's infected with these viruses.
4- **They are able to remain latent in their natural hosts.** Latency is established for the lifetime of the individual in the natural host. Once an individual is infected with a herpes virus (any herpes virus) this is followed by a *lifelong latency*; the virus will remain with that individual for his lifetime. However, the *site of latency differs* from one virus to the other:

- Herpes simplex and Varicella Zoster viruses establish latency in sensory ganglia.
- EBV establishes it in B-lymphocytes.
- Cytomegalovirus establishes it in salivary gland or in the kidney or in lymphocytes.
- Other herpes viruses (HHV-6, HHV-7 and HHV-8) establish latency in lymphocytes.

So all herpes viruses are capable of causing primary infection that's followed by establishment of latency and those latent viruses can be reactivated from one time to the other: it can be very rare or doesn't take place during the lifetime of an individual like reactivation a secondary disease in the case of Varicella Zoster virus, but it can be so frequent that reactivation takes place monthly or every two weeks like in the case of herpes simplex virus. So site and frequency are variable, but these viruses share the characteristic of establishing latency in infected cells.

- Some herpes viruses have a wide or broad host cell range, while others have a narrow range as they infect certain cell types.

- Efficiency and speed of replication: some require weeks while other within days. Herpes simplex and Varicella Zoster viruses are efficient and rapid in their replication; however, Cytomegalovirus is very slow as it may take from 2-4 weeks for replication to continue.

- Clinical manifestations: each causes a different disease:
  - It's mucocutaneous vesicular eruption in herpes simplex viruses.
  - It's infectious mononucleosis for EBV.
  - It's opportunistic infections that affect any organ in the body (the brain, they eye, the lung and the heart) in the case of cytomegalovirus.
  - It can be malignancy like in the case of human herpes virus-8 causes Kaposi's sarcoma.

So as you can see they vary with respect to their efficiency in biological properties as well.

**Classification**

- Classification into 3 subfamilies (Alphaherpesvirinae, Betaherpesvirinae and Gammaherpesvirinae) is based on biological properties of these viruses.
- Within the subfamilies, herpes viruses are classified into genera.
  - Alphaherpesvirinae has 3 genera: the herpes simplex viruses type 1 and 2 and Varicella Zoster virus;
  - Betaherpesvirinae includes Cytomegalovirus and human herpes viruses 6 and 7;
  - Gammaherpesvirinae includes EBV and human herpes virus 8.
Classification is based on:

i. DNA sequence homology: the more sequence homology between viruses then they will be classified together.

ii. Similarities in genome sequence rearrangement: rearrangement can take place depending on the presence of certain sequences (reiterated sequences). (reiterated definition: Say something again)

iii. Relatedness of viral proteins.

Alphaherpesvirinae

** HSV –1, HSV-2 and VZV**

- It includes the first 3 herpes viruses
- **Classified on the basis of:**
  - A variable host range usually The host range is broad.
  - Relative short reproductive cycle
  - Rapid spread in culture
  - So These viruses have rapid replication so they spread rapidly in culture.
  - Efficient destruction of infected cells
  - Capacity to establish latency primarily but not exclusively in sensory ganglia

Betaherpesvirinae

** CMV, HHV-6, HHV-7**

- **Classified on the basis of:**
  - Restricted host range
  - Long reproductive cycle
  - Slow progress of infection in culture
  - Enlargement of infected cells (cytomegalia)
  - Latency in secretory glands, lymphoreticular cells, kidneys and other tissues.

The name Cytomegalovirus is due the enlargement of infected cells (cytomegalia): enlargement of the cell with the formation of inclusion bodies inside both the cytoplasm and the nucleus (intranuclear and intracytoplasmic).

Gammaherpesvirinae

** EBV, HHV-8**

**Classified on the basis of:**

- Limited host range.
- Replication In vitro in lymphoblastoid cells
- Cause lytic infections in some types of epitheloid cells and fibroblasts
- Specificity for either T or B lymphocytes
- Latent virus is frequently demonstrated in lymphoid tissue
Replication in vitro is limited to the lymphoblastoid cells. These viruses don't grow in other cell types, and that's why it's difficult to grow these viruses in vitro.

These viruses cause lytic infection in some types of cells in vivo; epithelial cells are lysed (killed) with EBV. However, B-lymphocytes are immortalized (transformed) with EBV. So they cause different types of infection: productive infection which's mainly seen in epithelial cells, and latent infection which's established in B-lymphocytes, but a small proportion of B-lymphocytes may develop a productive type of infection.

**Now we'll start with the viruses one by one and discuss the most important features of these viruses.**

By This we have FINISHED The First Record ‘first lecture’

**Herpes Simplex Viruses 1 and 2**

- The most intensively studied, and the most important feature that was under investigation is the ability to establish latency and become reactivated.

- Surprisingly: The number of researches on herpes simplex virus and number of publications are far more than the number of its nucleotides that comprise the genome and yet the aspects of latency and reactivation are still unknown and not fully understood.

- Attractions of the virus are in its biological properties (specially the establishment of latency and reactivation).

- The herpes simplex virus 1 which's a cause of orofacial lesions and herpes simplex virus type 2 which's a cause of genital lesions are **identical in morphology** and they have **cross-reacting antigens**, but they also differ with respect to certain other antigens and that's how they are identified as two different viruses.

**Viral DNA**

- It is composed of about 150 kbp with a molecular weight of 100x106 Daltons.

- There are 4 isomeric forms for the genome: long and short segments alternating in each of the strands, so we have 2 strands; the possibilities are four.

- The genome of herpes simplex virus code for more than 70 proteins.
Gene Expression

We have Three gene classes:
- Alpha (immediate early)
- Beta (early)
- Gamma (late)

✓ Gene expression in herpes viruses is similar to that in adenoviruses passing through 3 phases. Immediate early (products are called alpha proteins) is equivalent to the pre-early phase in adenoviruses.

✓ As a result we have alpha, beta and gamma proteins that are encoded by viral DNA.
✓ A minimum of 5 genes are transcribed during the immediate early phase.
✓ Alpha genes are required to activate the expression of beta genes (the immediate early products activate early genes).

✓ Beta genes products include enzymes necessary for replication (Thymidine kinase), and the replication proteins.

✓ Gamma genes are large because they code for the structural components which are (30-35 proteins) present in the tegument, and we have 11 glycoproteins in the envelope of the virus, and there are capsid proteins and core proteins, so the number of proteins that are expressed during the late phase of transcription is huge.

Virion Polypeptides

✓ Virion polypeptides are the structural components of the virus.
✓ These 11 proteins (which are glycoproteins present in the envelope) were given names (glycoprotein B, gC, gD, gE, gG, gH, gI, gJ, gK, gL and gM), And many of them are not related to the entry or release from the infected cell.

\{A mimic – they are from B to M (BMW car) notice NO gF; I wish I can give an F grade for the person who named them for forgetting the ‘F’\}

✓ Glycoproteins B, D and H seem to be very important as they are essential for the production of infectious virions; actually scientists attempt to produce vaccine to prevent infection with herpes simplex viruses and they are concentrating thie studies on glycoproteins B and D because they are involved in adsorption and penetration into cells. Note that: prevent infection \(\rightarrow\) prevent adsorption and penetration!
But this doesn't mean that herpes viruses utilize only those glycoproteins for entry: in experiments, all of these proteins were removed by genetic mechanisms (knockout the genes coding for these glycoproteins); all of these genes were individually removed one after the other, and yet penetration takes place!! So we can see that penetration is not a function of a single gene; As you know complex viruses contain more than one antireceptor (more than one protein mediate entry into cells).

Glycoproteins G provides antigenic specificity between HSV-1 and HSV-2.

While gC and gE and gI seem to play a role in the protection of the virus from the immune attack. Immunity is very efficient against viral infections, but viruses have devised mechanisms to avoid the immune response in the host.

C3b is a very important opsonizing substance (opsonin bridges the Bacteria or the virus or any antigen towards the phagocytotic cell). The viruses cover themselves by binding to C3b, so the virus will be recognized as a cell in the infected individual because it's covered with the C3b in this regard.

Viruses can also cover themselves with immunoglobulins which are self molecules. This is by binding of glycoprotein E to the Fe of IgG.

The role of other glycoproteins (gJ, gK, gL and gM) is not well appreciated because as we mentioned they are still not to be important for entry or release from the cell.

A mimic: JacKaL MOM is not well appreciated in animal kingdom. when you read it sound the same as JKL MOM,

Replication

As mentioned before but remember that they utilize more than pathway for attachment and entry into the cell.
Fate of the infected cell

- Herpes simplex viruses kill cells that are productively infected with such viruses. The reason of killing of the cell is due to structural alterations that take place. Early changes are observed in the nucleolus of the cell in the form of enlargement of nucleolus and displacement towards the periphery of the nucleus. After that, chromatin changes take place, then fusion of adjacently infected cells, which's something known as the social behavior of the cells; they clink together forming multinucleated giant cells, accompanied with membrane permeability changes that lead to the death of the infected cell.

- In viral infection with herpes viruses, viruses immediately hack the mechanisms of the cell for their own benefit, so they stop macromolecular synthesis in the cell. This as such is incompatible with the viability of the cell; so cells are killed because of these structural changes and also because of functional changes as cells cannot synthesize their own proteins.

Latency

- Latency is very important aspect of herpes viruses. In the case of herpes simplex virus, it's established in sensory ganglia: it's in most of the cases the trigeminal ganglion for HSV-1 (Responsible for orofacial lesions), and it is sacral ganglia for HSV-2. Actually, these viruses can establish latency anywhere. If the infection was in the skin, they will establish latency in sensory ganglia that provide sensory nerves for that area. They travel back from the site of infection through retrograde: axoplasmic flow to reach the sensory ganglia where they become established. Usually the genome assumes the circular shape in the nucleus of the infected cell. After that, a population of latently infected cells will undergo reactivation leading to what's known as secondary lesions or reactivation lesions that the viruses travel back by axoplasmic flow within sensory nerves to the site that's innervated, and usually the site that witnesses the primary infection will have the reactivated or repeated infection.

- What governs the mechanism of latency application is largely unknown meaning that latency doesn't appear to depend on the synthesis of viral encoded proteins (no proteins are produced in the latently infected cell).

- A small amounts of RNA transcripts (latency associated-transcripts- LATs) have been found in latently infected cells, so latently infected cells expresses these transcripts and they may be involved in HSV latency.

- ICP0 is an alpha protein (produced by one of the five genes that are expressed very early). The blocking of this protein will block the reactivation of the virus so that the viral genome expression is inhibited by binding of LATs to this protein, and once this is removed reactivation can take place.

- Recently, there are evidence points to the involvement of Histone DeACetylases in the establishment of latency and reactivation in herpes simplex viruses, namely HDAC1 and HDAC2.

Hypothetically, by interfering with the HDAC enzymes' effectiveness, it may be possible to block the virus's ability to hide from the immune system, leading to a complete elimination of the virus by the immune system.
Varicella-Zoster Virus

✓ VZV is the 3rd member of alphasherpesvirinae, it has some morphological similarities to HSV1 and 2.
✓ Varicella Zoster virus particles don't have a cross-reacting antigens, and has minimal antigenic relatedness to HSV1 and 2.

✓ VZV has the smallest genome of all human herpes viruses (encodes ONLY 69 proteins).

✓ VZV has only one serotype this means that, individuals develop VZV infection once in his lifetime. Chicken pox is followed by a lifelong immunity to chickenpox; exogenous reinfection cannot take place (once you develop chickenpox, you won't develop the illness another time). However, chickenpox is followed by the establishment of latency in sensory ganglia, and the virus can be reactivated several decades after primary infection to cause the secondary form of the disease which's Zoster in this case.

Major Antigenic proteins

✓ The major antigenic proteins of Varicella Zoster virus are the surface glycoproteins. 
  \[ gE (Gp1), gB (GpII), gH (GpIII), gI (GP IV), and gC (GP V) \]
  These are glycoprotein 1 through glycoprotein 5; their old names in letters.

✓ The cells that are infected with Varicella Zoster virus express large amounts of glycoprotein E (gE that binds to the Fc of IgG here is similar to herpes simplex virus gE that also binds to the Fc of IgG). The neutralization in the case of using gE is complement dependent neutralization.

✓ gI (gpIV) is non covalently linked to gE in infected cells. induces neutralizing antibodies in the presence of complement. Relatedness of gE and gI here is similar to that for gE and gI in herpes simplex viruses.

✓ Glycoprotein B elicits complement independent neutralizing antibodies and also appears to have a role in virus entry (similar to herpes simplex virus glycoproteins B and D).
  As we see there are large number of structures that are similar and they have similar functions to these of herpes simplex virus proteins, and that's why they are within the same family; they have the same characteristic features of herpes simplex viruses. The difference is in the surface glycoproteins, but the lesions (pathology) and mechanisms of latency and reactivation are similar for Varicella Zoster virus.
Epstein-Barr virus

- Discovered by Epstein, Barr and Achong in 1964 in lymphoma cells provided by Burkitt. The name of Achong was dropped from the name of this virus, and actually Barr was the virologist who isolated the virus.
- EBV-1 is prevalent in the old world, and EBV-2 is prevalent in the developed countries. EBV 1 and 2 has a limited cross protection: an individual infected with EBV1 can be reinfected with EBV; the difference is significant to allow for the infection with these 2 types; immunity is specific for the type that caused the infection.
- EBV has a major surface glycoprotein (gp 350/220) that's utilized for binding to the susceptible cell and it's the target for the neutralizing antibodies, also a minor protein (gp 85) exists.

- EBV genome size (172 kilo base pairs) and it is considered as a large genome.
- Reiterated terminal repeats are very important. EBV transforms B-lymphocytes causing lymphoma (Burkitt's lymphoma, hodgkin disease…etc); it was found that the number of terminal repeats varies and it's very specific for the strain causing the malignancy, so we can determine whether this malignancy is polyclonal or monoclonal by determining the number of terminal repeats. For a clone of cells that are transformed with EBV the number of terminal repeats is the same, so if we found that more than number of terminal repeats exist for viruses that are isolated from the human, this indicates polyclonality (more than one clone of B-lymphocytes) of the transformation of the cell.
- The manner of dividing the genome into short and long unique is similar to herpes simplex viruses.

- The very limited host range is due to the limited distribution of their receptor which's CD21 (The CD21 is the complement receptor 2; it is specific for the complement protein C3d, and it is also the receptor for EBV surface glycoprotein gp350/220).
- This receptor presents only in B-lymphocytes and epithelial cells of the oropharynx and nasopharynx; this is why EBV can infect only those 2 cell types.
- The latent infection of B-lymphocytes is associated with the expression of a large number of proteins. Almost 11 proteins are expressed in latently infected cell;
  - EBNA proteins (Epstein-Barr Nuclear Antigens) 1, 2, 3A, 3B and 3C
  - Latent proteins or LPs (more than one protein).
  - LMPs: latent membrane proteins 1 and 2.
  - EBERs are two Epstein Barr related RNAs.
- As we see 11 proteins are expressed in latently infected cells, whereas at productive type of infection different proteins are expressed.
EBNAs and LPs are DNA binding proteins that are essential for establishing an infection (EBNA-1), immortalization (EBNA-2) so they are necessary for the establishment of latent infection and for the immortalizion of B-lymphocytes.

LMPs have oncogenic like activities.

The viral gene products maintain the latent infection and cause the previously resting B lymphocyte to continuously proliferate.

The protein that determines whether the infection is latent or productive is the ZEBRA peptide; if the zebra peptide is activated, this will result in productive infection. If the zebra peptide is suppressed, this results in latent infection (in this case the other 11 proteins are activated).

You can see in this pathway that either a productive infection takes place if the zebra peptide presents, or no expression of the zebra peptide and in this case, EBNAs (LMP1, LMP2, Latent proteins and EBERs) are expressed to the establishment of a latent infection.
The 5th HSV is the human cyto-megalo virus, or human herpes virus #5 "HHV-5", which is a wildly distributed virus and can infect a wide range of animals as well as human, and this virus is a species specific virus so that human cyto megalo virus can never infect animals and vice versa for animal viruses, this virus share a common growth characteristics between its serotypes as they all form inclusion bodies. During the replication of the virus so it causes enlargement in the cytoplasm of the cell and the name of the virus comes from this phenomenon (cyto-megalia is one of the effect of the virus in the cell).

cyto-megalia means the enlargement of the cell with formation of intra-cytoplasmic and intra-nuclear inclusion bodies.

Distinguishing characteristics of the virus are:

- **remarkable salivary gland tropism**: the virus start in latency in such cells as will as in kidney cells and monocytes.
- **species-specificity**, as mentioned “ma t’3ayart”.
- **slow replication in cultured cells**: take a 2-4 weeks in CPE to growth so we use of shill virus to enhance (speed up) the replication of the virus and by this we need only 48 hours to make a sample of antigen in this culture.

The viral genetic of this virus:

- The largest genome of all herpes viruses (240 kbp) that exists in four isomeric forms similar to the case of herpes simplex virus.
- Remember The smallest genome for VZV.
- This virus is rich in both, direct and inverted repeats codes at least for 67 proteins, 30 of it can be detectable, 2 of these composed the capsid and 8 envelope proteins and as many as 20 tegument proteins.

Envelope Glycoproteins:

The envelope of these virus is similar the herpes simplex and VZV and other herpes viruses.

**Glycoprotein B** and **Glycoprotein H (gP75)** and **Glycoprotein C II or gp47-52** are the three major glycoproteins in this virus and the 4th is **Glycoprotein 48** we will discuss them now:
**The First Glycoprotein is gB (150 kd)** is the major envelope glycoprotein of CMV that has the following functions:

+ Virion penetration into cells
+ Transmission from cell to cell
+ Fusion of infected cells.
+ A prominent target for neutralizing antibodies, which mean that the virus can be detected by antibodies through this protein so it use to be a vaccine to this virus.

**The Second Glycoprotein is Glycoprotein H (gP75)** has the following functions:

- Target for complement-independent neutralizing antibodies
- Cell-to-cell transmission of virus
- Membrane fusion.
- Essential for viral replication (entry).

So this glycoprotein (gH) is said to be similar or complementary function to glycoprotein B so that gB and gH have an overlap in there functions.

Synthesis of more than one protein have the same function is common in herpes viruses and this advantage make the virus able to cause infection even one of its protein is effected by a distortive agent.

**The Third Glycoprotein C II or gp47-52:**

- An abundant envelope glycoprotein
- Target for complement dependent neutralizing antibody.

**The Fourth Glycoprotein 48:** a minor envelope constituent.

- There is a variation in CMV that allow us to classify it to strains with an overall genomic DNA sequence homology of approximately 95% to 99% and that’s cause a cross protection to this virus.
- No other Exogenous infection is able to infect the individual because all strains of CMV have 99% homology so the immune defense produce for one strain is able to protect from other related strains keep in mind that the differences of the CMV strains is minor in nature.
- CMV cause a primary infection which is usually silent and consider as an asymptomatic clinical case.
If the infection still until the adolescence its associated with a mononucleosis this illness can produce symptoms.

No clinical symptoms is association with the primary infection of the CMV and if the CMV became in the latent period and if it reactivated again in the adolescence causing symptoms specially in immune-compromised patient so the CMV became a best example of opportunistic pathogens.

CMV is a opportunistic pathogens which mean that is have no effect in healthy individual and it can lead to a killing diseases like syphilites or interstitial pneumonia or cardaitis in people who have cancer or related other diseases.

The doctor then talk about the replication steps of CMV and said that they are similar to herpes simplex; So The CMV replicates in the nucleus of the infected cell, and added that is a slow replication and don’t lead to kill the cell immediately( unlike the other types of one time infected herpes viruses which take less time than CMV so this feature became a remarkable for this virus).

Other remarkable feature for CMV that the reproduction can be blocked after penetration of the infected cell as a result of release of (β2 Globulin) and this explains the narrow host range of this virus, although its receptors are widely distributed but NOT all infections lead to replication.

**There is three other herpes viruses, HHV-6,7 AND 8:** all of it was discovered after 1989, HHV-6 cause Rosulla infantum, HHV-7 cause no significant effect, while HHV-8 cause coposis sarcoma.
The FIFTH FAMILY:

**Poxviridae:**
- One of the largest and most complex viruses. Have its own enzymes especially polymerase and transcriptase. (so it don't rely on the cell to reproduction).
- The genome is composed of a single linear ds DNA of 130-260 Kbp with a terminal hairpin loop at each end (fused).
- They special thing about them is that they replicate on the cytoplasm of the infected cell.
- They have the largest size among DNA viruses which is (240-300nm) and they are most complex of animal viruses weather DNA or RNA
- Poxviruses can be seen under the (light) microscope, rakz **light**.
- It is a Brick – shaped in general and because its lake the right angle its better to describe it as a ovoid shape.
- Many of these viruses share antigenic determinants which is very important to control smallpox which the most latency viral infections that cause millions of death in the past.

- Poxviridae is the only virus with complex symmetry (the other either helical or icosahedral)
- Enveloped virus with biconcave core became between two lateral body (right pic.)
- The appearance of the outer membrane under EM shows a cress-cross appearance (left pic.)

- In genome is located on the core it a linear ds non-segmented DNA associating with a large number of histon-like proteins and the enzymes that transcript and replicate the virus.

Worth mentioning:
- There is two human pox viruses that can still cause infection which are moluscome contanusome and vaccinia virus.
- **moluscome contanusome** can use a skin disease.
- There are 8 animals poxviruses still can infect human called "zoonatic infections".

We Have Finished **ALL DNA Viruses** ...
RNA Viruses

We will start talking about:

**Picornaviridae:**

- Its The smallest and simplest RNA-containing viruses known ever.
- **Pico-rna-viridae**: pico, indicates for its small size, rna, means that it’s a RNA virus.
- Their size is similar to paroviruses and ranges form 24 to 30 nm
- This family includes the largest number of Members that can infect humans and animals. They are around 230 member.
- Can cause poliomyelitis and also can cause common cold.
- It can cause an agricultural loss, it can cause Foot–Mouth disease (الحمى القلاعية)
- The family is currently divided into five genera; Rhinoviruses, Enteroviruses, Aphthoviruses, Cardioviruses, and Hepatoviruses (REACH).
  - Aphthoviruses, Cardioviruses are animal viruses, Aphthoviruses are the pathogens of the Foot and Mouth disease which are occasionally infect humans and Cardiavirus Infects rodents (mice and rats).
  - Rhinoviruses, Enteroviruses, and Hepatoviruses are a primary human pathogens and they have a large number of serotypes:

<table>
<thead>
<tr>
<th>Genus</th>
<th>Virus</th>
<th>Serotype</th>
<th>The classification of the serotypes</th>
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<tbody>
<tr>
<td>Rhinoviruses</td>
<td>Polio viruses</td>
<td>&gt;100</td>
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<td></td>
<td>Coxsackieviruses</td>
<td>A 23</td>
<td>1-22, 24, <strong>(23= echoviruses 9)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B 6</td>
<td>1-6</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>Echoviruses</td>
<td>28</td>
<td>1-7,9,11-21, 24-27,29-33 Echo 8 = Echo 1 Echo 10 = Reovirus 1 Echo 28= Rhino 1A Echo 34 = Coxsackie A 24 Echo 22,23= Parechovirus</td>
</tr>
<tr>
<td></td>
<td><strong>Parechoviruses</strong></td>
<td>2</td>
<td>Previously Echo 22 and 23</td>
</tr>
<tr>
<td></td>
<td>***Enteroviruses 68-71</td>
<td>4</td>
<td>New naming system since 1967</td>
</tr>
<tr>
<td>Hepatoviruses</td>
<td>Hepatitis A virus</td>
<td>1</td>
<td>Previously enteroviruses 72</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>67</td>
</tr>
</tbody>
</table>
Notes for the Table:

** they classified Coxsackie viruses in to the Coxsackie viruses A and B, then A to 24 Coxsackie viruses, later they discovered that Coxsackie viruses A no# 23 was mistyped and its actually echoviruses no# 9.

** Echoviruses 22,23 have been classified recently as a new group called Parechoviruses.

** In 1967 they stop giving name to Enteroviruses and give a number for any newly discovered Echoviruses after that date so the we have Enteroviruses 68-71.

✓ Rhinoviruses have actually 100 serotypes, and that’s why we can't develop a vaccine for Rhinoviruses because it hard to obtain 100 vaccine need to control all serotype of this virus subgroup.

✓ Rhinoviruses cause the common cold, so it can't be vital

✓ Coxsackie viruses name derived from a village in New York.

✓ Coxsackie viruses divided in A and B according to pathogencity to animals specially to mice that one cause Casit paralysis and the other cause spactic paralysis. (Definition: a loss or deficiency of motor control with involuntary spasms caused by permanent brain damage.)

✓ Coxsackie viruses A and B cause different diseases in humans, Coxsackie viruses B is the most important cause of carditis and myocarditis.

✓ The Enteroviruses 72 discovered later that is Hepatitis A virus.

✓ Note that: The total no # of the Enteroviruses is 67, although the last number was given is 72 due to misclassification of these viruses.

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- Enteroviruses and Hepatovirus differ from Rhinoviruses in:
  - Stability at pH 3, which mean that Rhinoviruses is unstable in the stomach and can NOT cause diseases for the GI track. In construct Enteroviruses and Hepatovirus can NOT be inhibited by the pH of stomach and its can deal with even pH=1 !!!
  - Note that: Enteroviruses and Hepatovirus utilize the GI track as a route of entry to their target tissue in the host, Not to replicate in, for example Polioviruses go to the anterior horn of the spinal cord, Coxsackie A may go to the skin and Coxsackie B go to the heart and cause myocarditis, Echoviruses cause CNS infections.)
- Optimum T ° of growth, 35-37 ° to Enteroviruses and Hepatovirus and 33° to Rhinoviruses.

- Mode of transmission: Enteroviruses and Hepatovirus acts in case of contamination of drink and food and rarely in fingers, Rhinoviruses transmission is only by the direct spread from individual to another ( aerosols ).

- Diseases caused; myocarditis, CNS infections caused by Enteroviruses and Hepatovirus and common cold by Rhinoviruses.

Enterovirus:

✓ The virion is roughly spherical, naked, and range in diameter from 24 to 30 nm, seems that all shapes are roughly spherical for dr. Azme even a triangle!!

✓ Genome is a ss RNA (7500 nt) of positive polarity (can act as mRNA), polyadenylated at 3° and has a protein of 22 to 24 amino acids (VPg) at the 5° end.

✓ 60 subunits make up the icosahedral capsid each of which is composed of four viral polypeptide (VP) chains, VP1-VP4.

✓ VP1, 2 and 3 are exposed at the virion surface, whereas VP4 lies buried in close association with the RNA core.

✓ Of the four proteins, VP1 exhibits the greatest sequence variability and VP4 the least.

✓ Of the four proteins, VP1 is the most important due to its ability to bind to the cell surface.

✓ The uncoating if the virion is the result of the physical interaction of VP1 to the receptor.

✓ VP1 play role in immunity to this virus as a target to the antibodies.

✓ Antiviral agent that bind to VP1 can block the uncoating even if the virus was bind to the cell surface.

✓ Arildone (pleconaril) contains a 3-methyl- isoxazole group that binds to the floor of the VP1 canyon and alters its conformation to prevent the uncoating of the virus.

✓ Poliovirus produces a protease that degrades the 200,000 Dalton cap-binding protein of eukaryotic ribosomes, thereby blocking the translation of cellular mRNA. (this protein is utilized be eukaryotic for translation and transcription and Poliovirus products can degrade this protein causing cell death).
Picornaviruses receptors:

- They are all immunoglobulin superfamily.
- The structure of this receptor consists usually of two domains or subunit have all been mapped to human chromosome 19.
- Receptors can be of two families Immunoglobulin or Integrins

<table>
<thead>
<tr>
<th>Virus</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus (major)</td>
<td>ICAM-1</td>
</tr>
<tr>
<td>Rhinovirus (minor)</td>
<td>LDL-R</td>
</tr>
<tr>
<td>Polioviruses</td>
<td>PVR (similar to ICAM-1) CD155</td>
</tr>
<tr>
<td>Coxsackie A</td>
<td>ICAM-1</td>
</tr>
<tr>
<td>Coxsackie B</td>
<td>Unknown</td>
</tr>
<tr>
<td>Echovirus</td>
<td>DAF, VLA-2</td>
</tr>
</tbody>
</table>

Question: يمكننا نأخذ كمان 20 دقيقة نخلص فهيهم كمان، الموافق يرفع ايده؟
Answer: لالالآ و 5 رفعوا ايديهم انوه بذهم...
Outcome: No one Knows how, Dr. Azmi sees the majority of Students are raising their hands.. and he starts giving the Next FAMILY of RNA viruses.. ENJOY YA 7abaibi
This picture contains an influenza virus, that is a member of the family of Orthomyxoviridae that cause human diseases. The slide shows the EM appearance of influenza virus. It is roughly spherical with a helical segmented strand and an envelope that is decorated with two or more of the glycoprotein spirons.

This Picture shows more details about Orthomyxoviruses, notice that the virus is roughly spherical with a helical segmented single stranded RNA genome. The number of segments varies from 7-8 segments and these segments are associated with what is known as the **polymerase complex**. Four proteins are associated with the segments of the single stranded RNA genome of negative polarity (means that it doesn’t act as a messenger RNA) and this is known as the transcriptase complex, which is composed of three types of RNA polymerase and a nucleic protein, this is the core of the virus. The envelope of the virus is underlined by what is known as the Matrix protein (the M protein) which is very important for morphogenesis of the virus and for the acquisition of the envelope of the virus, so the virus acquires its envelope from the cytoplasmic membrane of the infected cell by the help of M protein, so M protein is a major protein in Orthomyxoviruses (Influenza viruses).
The envelope is composed of phospholipid bilayer, which is decorated with two types of glycoprotein; hemagglutinin (HA) and neuraminidase (NA). The total number of these glycoprotein spikes is 500. HA and NA are present in a ratio of (4-5:1); meaning that we have about up to 400 HA glycoproteins and about up to 100 NA glycoproteins. So HA is more abundant than NA.

- HA glycoprotein has a rod-like structure while NA has a mushroom-like structure and this nomenclature describes the function or the effect of this structure because it hemagglutinates erythrocytes from different species. HA is very important for infectivity of the virus, because the virus binds through this structure.

- NA glycoprotein has neuronic acid activity and it's very essential for the release of the virus from the infected cell; when this virus leaves the cell it leaves it by budding and this involves an interaction with sialic acid of the infected cell (there are bonds between the envelope of the virus and the sialic acid of the infected cell, NA acts by splitting these bonds so this will allow the release of the virus), so without this function of NA the virus will be unable to infect new cells because it will be unable to get out of the infected cell.

- NA also plays a major role during infection because it can liquefy/decrease the viscosity of the respiratory secretions. "Remember that the respiratory secretion is a non-specific type of body defense mechanisms" … These secretions in nature impede the Travel –movement (although viruses don’t move) - of viruses, NA liquefy these secretions facilitating the movement of the virus, so its important in establishing of the infection because if the virus doesn’t reach the respiratory epithelium it will be unable to cause infection, so the virus must overcome the secretions that cover the respiratory tract and this is partially achieved by NA.

**The structural proteins of the virus include:**

1. Nucleoproteins that are associated with the genome.
2. Matrix proteins that underline the envelope.
3. Two glycoprotein spikes:
   a. HA glycoproteins
   b. NA glycoproteins.

- There are differences between the different influenza viruses, influenza A has in addition to these two glycoproteins spikes what is known as M2 glycoprotein, M2 plays a major role in uncoating process; M2 facilitates the entry of Hydrogen ions through ion proton channels { the structure of these channels is responsible for the uncoating of the virus }, the acidity that results from the influx of Hydrogen ions via M2 structures will lead to uncoating of the virus and that’s why there are drugs that works by prevent the function of M2, such as Amantadine and remantadine, these drugs bind to M2 and block the function of it so these types of drugs are used for treatment of influenza. We have anti viral agents that target the NA of the virus; these anti viral agents prevent the release of infectious viral particles such as Zanamivir (Relenza) and Oseltamivir (Taniflue).
Viruses are classified within types (genera) and subtypes, the genera are distinguished on the basis of antigenicity of nucleoprotein (NP) and matrix (M) proteins, there are two genera:
- Influenza A and B viruses (the first genus includes two types of influenza; A and B)
- Influenza C virus.

Influenza A viruses are divided into subtypes based on the antigenicity of HA and NA glycoproteins, we have 16 HA types and 9 NA types.

Among the RNA viruses, influenza is very special in that all of its RNA synthesis takes place in the nucleus of the infected cell.

Remember all RNA viruses replicate within the cytoplasm except Influenza virus that start its replication within the nucleus of the infected cell, because it needs short capped primers/sequences that are generated from host cell RNAs and this is done by enzyme that can cut/steal short sequences 8-18 nucleotides of host cell mRNA, that’s why they require actively replicating cell in order to have mRNA available in the cell this enzyme is virus-encoded cap-dependent endonuclease.

Influenza virus mRNAs undergo splicing in the nucleus, and this is very essential because this enables the virus to produce more than one protein from the same transcript.

The most important type of influenza viruses is type A, influenza A has a wide variety to infect animals in addition to human, and that’s way influenza A can cause both pandemic and epidemic diseases. So influenza A viruses naturally infect humans, several other mammalian species and a wide variety of avian species whereas Influenza B and C are human pathogens.

Some Definitions:
- Epidemic: is an outbreak that spread in one area/country BUT if this outbreak spread to other countries/worldwide then it’s called Pandemic.
- Epidemic is annual {spread every year} whereas Pandemic every 10-40 years.

The surface glycoproteins of influenza A virus exhibit much greater amino acid sequence variability than their counterparts in influenza B virus and influenza C. Influenza A undergoes frequent changes involving the HA and NA glycoproteins spikes. Influenza B undergoes minor changes that are rare so Influenza B may cause Epidemic disease as a consequence of these changes. Influenza C is largely stable, it doesn’t undergo frequent changes. So Influenza A cause epidemic and pandemic diseases while Influenza B usually causes...
sporadic cases but it may cause small outbreak, Influenza C causes sporadic cases only, it doesn’t cause epidemic because the structure of the virus is stable and the immunity that presents prevails and prevent the spread of the virus among population (because its stability the change if it occur will be very small and the normal immunity of the body can prevails it) whereas the changes that appear in influenza A allow for the spread of the virus because the new virus will not be neutralized by antibodies present in the population {its completely new virus}.

✓ **Influenza A and B viruses contain 8 RNA segments, whereas influenza C contains 7 segments.** And this difference decrease the surface glycoproteins to one in Influenza C (which is HEF) while there are two surface glycoproteins in both A and B types (HA and NA), so the differences in the gene segments is reflected on the number of glycoproteins spikes that cover the virus.

✓ **Influenza C has a single multifunctional glycoprotein,** which is Hemagglutinin Esterase Fusion (HEF), so in influenza C insteade of having hemagglutinin (HA) and neuraminidase (NA), it has Hemagglutinin Esterase Fusion (HEF); so esterase replace the function of the neuraminidase and fusion which is the activity of HA is performed by the F part of the glycoprotein HEF.

**Virion Structure :**

✓ **Influenza A and B are morphologically indistinguishable** we cant differentiate between them by EM because they have the same structures, but the only way to differentiate between them is by immunological differences **but there are morphological features that distinguish influenza A and B viruses from influenza C virus,** because of the presence of a single glycoprotein spike in influenza C whereas there are at least two types of glycoprotein spike in both of A and B.

✓ **The RNPs (Ribonucleouprotein) consist of four protein species and the RNA genome which occurs in eight separate segments containing 10 genes;** RNPs is composed of four proteins {three polymerases; one acidic and two basic polymerases, plus a nucleuprotein} these proteins are associated with the genome segments; the 7-8 segments, These 8 segments will code for 10 proteins, because of the splicing that takes place in the nucleus.

✓ **The segments are complexed with nucleoprotein to from a nucleocapsid with helical symmetry .**

✓ **Genomic segments range in size from 890 to 2340 bases.** So the largest segment is almost three times the size of the smallest segments.
Replication:

Unlike replication of other RNA viruses, replication of orthomyxovirus depends on the presence of active host cell DNA synthesis. After the fusion of the envelope with the cell membrane, Hydrogen ions enter through M2 protein (in influenza A) and change the acidity that will result in the uncoating of the virus, then the genome is transferred to the nucleus; replication in the nucleus is necessary because the virus lacks capping and methylating enzymes activities, then the virus scavenges cap sequences from the nascent mRNA generated in the nucleus and attaches it to its own mRNA and this will prime replication and transcription of the virus, so transcription takes place with replication of the genome in the nucleus and as a consequence proteins are synthesized and these proteins will assemble with the genome of the virus in the cytoplasm into virions, which will acquire an envelope, and the acquisition of envelope occurs at the sites of budding and its usually proceeds by the synthesis of M proteins which is sent to vesicle with the Zip code to the site of budding. The site of budding in this case is the cytoplasmic membrane, here the nucleocapsid associates with the matrix protein and this is followed by budding of the virus from the infected cell.

Genome Organization:

The eight genome segments of Influenza A and Influenza B code for the following structures:

1. RNA segment 1 codes for PB2 (Polymerase Basic 2).
2. RNA segment 2 for codes PB1 (Polymerase Basic 1).
3. RNA segment 3 for codes PA (Polymerase Acidic).
4. RNA segment 4 for codes HA.
5. RNA segment 5 for codes NP (Nucleic Protein).
6. RNA segment 6 for codes NA.
7. RNA segment 7 for codes M1 and M2.
8. RNA segment 8 for codes NS1 (Non-Structural 1), and NS2 (Non-Structural 2).

* That is in Influenza A, but it is only M in Influenza B.

*The NS1 is truly non-structural, it's expressed in large amount in the cytoplasm of the infected cells and it functions to transfer mRNA from the nucleus to the cytoplasm. ** NS2 was found to be structural and it's associated with the M2 protein {they thought at the beginning that its non-structural, but they discovered later that this is a structural protein}, this protein is present in the association with M2 so it may has a function in uncoating process of the virus.
Virion Proteins:

- PB2, PB1 (Basic), PA (acidic):

These proteins have different functions, we have two types of polymerase one of them is acidic and the other is basic, but the function of polymerase is the synthesizing of RNA, so acidic polymerase works in acidic condition while the basic one works at basic conditions.

- NP:

Nuclear protein is the major protein associated with RNA, incapsidation of the genome is the function of NP, so it covers RNA protecting it from being degraded by ribonucleases, and it forms with the RNA the transcriptase complex, so the transcriptase complex is created by the association between the NP and the helical RNA segments of the virus.

- HA (16 subtypes):

HA is a surface glycoprotein, present in 16 subtypes and it is synthesized as HA0 and before the release of the virus, this protein should be cleaved into two segments, HA1 and HA2.

HA1 diffuses to the outside/the external side so it’s the hydrophilic part, while HA2 is the hydrophobic part. HA1 and HA2 remain attach to each other by S-S bond which is a covalent bond. Without the cleavage of HA0 to HA1 and HA2 the virus will not be able to infect cells, because it's necessary to expose HA1 which carries the viral attachment peptide (VAP) to the external side of the virus so that it can bind to a receptor.

The receptor of influenza viruses is sialic acid, so they connect to it via a peptide present in the HA1 of the virus. As we said the exposure of HA1 requires the cleavage of HA0, so that’s why cleavage which is achieved in the cytoplasm by proteases is important to create infectious viruses.

HA1 is responsible for the fusion of the envelope with the cytoplasmic membrane of the infected cell, and it acts as a target for neutralizing antibodies{ major target of antibodies}, so its very important in the function of influenza viruses that rely on intact HA to cause infection. Again HA is a main glycoprotein in influenza virus.

- NA (9 subtypes):

Has a function of splitting the neuron acidic bonds that have created during the release of the virus from the infected cell, so it's essential for the release of infectious viral particles.

Influenza are originally believed to be a primary pathogen of birds (avian species), and that’s why when we say avian influenza it's almost normal, because all influenza viruses infect avian species.

The 16 types of HA infect birds; also the 9 types of NA infect birds. So these types are primary pathogens of birds. Human can be infected only with three types of HA; that are HA1, HA2 and
HA3 while there are only two types of NA that can affect human and they are NA1 and NA2. So the remaining HA and NA types don’t infect human but they have the ability to do so.

H5N1 is the avian flu, but a human infected case by this virus was recorded, the prevailing that HA caused the pandemic because of the adaptation of this type of influenza, but natural adaptation didn’t take place {the spread of the disease doesn’t achieved certain level that is necessary to consider it as a human pathogen} so its not yet a natural human pathogen although some cases were recorded.

And in one occasions in 1900 N8 caused a human disease.

The types that can naturally cause human diseases are the combinations of H1N1, H2N2 and H3N2

- **HEF (Influenza C):**

Influenza C doesn’t cause epidemic and it has one structural glycoprotein (HEF) which has the function of HA and NA together.

- **M1 and M2.**

- **NS1 and NS2.**

**Genetics:**

- The most important aspect of influenza is it's genetic.
- Influenza can undergo variations, and there are three types of variations; one is minor and two are major, the minor source of variation is RNA recombination, but this is very rare whereas RNA changes in the form of RNA mutations are very common and they are called (antigenic drifts), drifts is to indicate minor change not replacement, so drifts are result from accumulated point mutations that take place over the time, So influenza A accumulate significant amount of mutations in their HA (in particular) and in their NA. Theses antigenic drifts cause epidemic diseases, why?? Because the immunity that present among individual will partially protect against infection, but not completely and that’s why this allows the spread of the virus. here RNA mutations result in epidemic not pandemic diseases because the bore of susceptible is limited so the spread is limited. But when RNA segment undergoes reassortment there is a possibility for major change in the influenza is referred to as (antigenic shifts). The antigenic shift mutation takes place when two influenza viruses infect the same cell, now in such cell all of the genome segments (the 8 segments) or the 10 proteins are present within the cytoplasm of the infected cell and they will assemble into viirons. The chance for different proteins from the two different viruses to assemble in one virus/strain is high, if this happen this is called antigenic shift; {reassortment of RNA segments from two different viruses} and this will create a new viruses.
The H1N1 which caused the pandemic in the last two years, had accumulated for antigenic shift, for reassortment process with involvement of birds, pigs and human strains, and this took place over time until it arising in a mixable strain, and then spread all over the world (almost every country in the world has recorded some cases of H1N1), the major change that happened here is reassortment or antigenic shift. So shifts cause pandemic while drifts cause epidemic and as we said epidemic occur annually while pandemic takes place every 10-40 years.

Nomenclature:

A/Swine / Iowa/15/30/H1N1:

Influenza A in particular is named according to a system that involves:

- The type ➔ A
- The origin of isolation (host) ➔ Swine.
- City of isolation ➔ Iowa.
- Number of strains ➔ 15.
- The year of isolation ➔ 1930.
- The composition of H and N ➔ H1N1.

A/ Bangkok/1/79/H3N2:

Look to this example and notice that it includes only 5 components; the origin of isolation isn’t included here! why ??

Because you can put the origin of isolation and the city of isolation together.

If you are STILL ALIVE and you are reading this !!! Then you are one of the 5% of our dof3a’s NERDS …

Best Wishes : BAKIR JABER