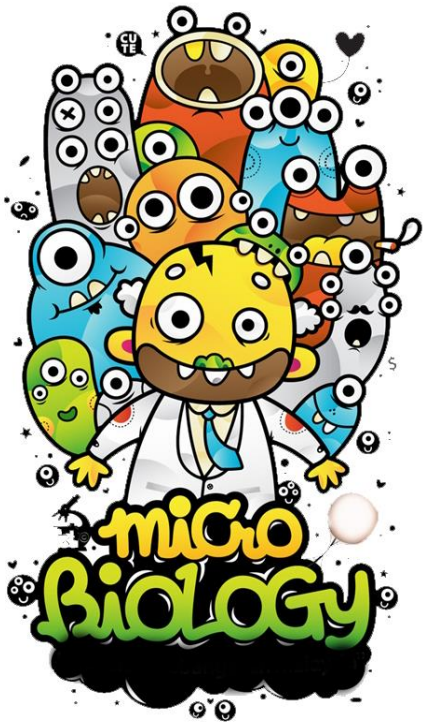

VIROLOGY

Subject: Pathogenesis

Lecture No.: 4

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Recap:

Endemic: present at a fairly low, constant level (mostly low but not always) in a certain geographical region (area).

Constant level: number of deaths equals number of new cases.

Epidemic: increase number of cases in a specific period of time at a certain geographical area (e.g. Influenza in winter months in Jordan)

Pandemic: happens on global level, characterized by increased number of cases in comparison to the base line (normal levels), and it is mostly associated with specific period of time such as winter months (e.g. MERS: Middle East respiratory syndrome).

We can say that pandemic is a global epidemic.

End of Recap.

What does a pathogen have to do?

1. Infect (infest) a host
2. Reproduce (replicate) itself
3. Ensure that its progeny are transmitted to another host

Infect – replicate - infect other cells

Now, how are viruses transmitted?

1. **Horizontal route**: person to person by:
   a. Inhalation (via the respiratory tract): aerosols and fluid droplets, examples: viruses that infect upper respiratory tract such as: influenza, rubella, measles, mumps, rhino, corona, varicella zoster.

b. Ingestion (via GI tract): fecal-oral route, contamination of water resources, and poor hygiene among children – as they usually pick up contaminated materials and put them in their mouths.

   Some viruses infect the GI tract and they cause the effect and the damage to the GIT itself in form of diarrhea and vomiting. However, other viruses might start their infection in the GIT but then move through blood to reach other organs and replicate in them.
   Keep in mind these two scenarios, they'll be explained later in this lecture. Examples:
   - Hepatitis A: infects the GI and spreads to the liver (not localized).
   - Rota, Astro, Calici viruses: primary localized infection to the GIT
   - Enteroviruses: infects the GI and spreads to several other organs, especially CNS at a certain point of their infection.

c. Inoculation, through: skin abrasions, mucous membranes (e.g. sexual transmission), IV transfusions & injections (especially between drug addicts who use the same syringe between them) and organs transplant.

2. **Vertical route**: from mother to fetus, and we have three possible cases:
   a. Trans placental (during pregnancy): Cytomegalo virus (CMV), Rubella, HIV, Herpes simplex virus.
   b. During delivery: Herpes simplex, Hepatitis B & C, HIV.
   c. During Breast feeding: Cytomegalo virus, HIV, Hepatitis B.

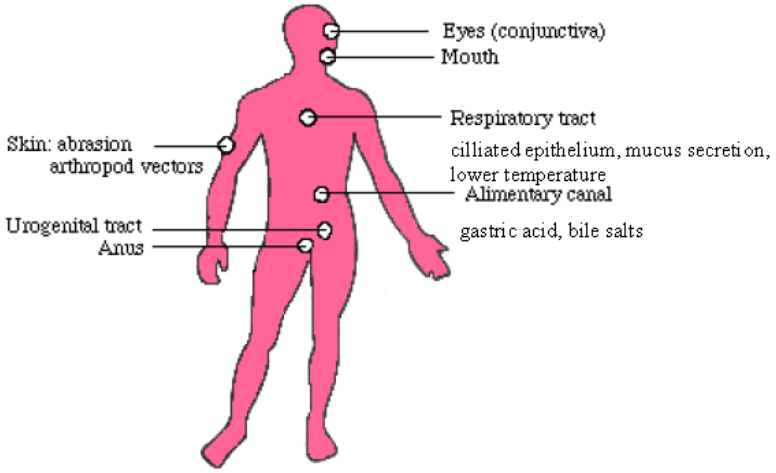
3. **Zoonotic route**: from animals to humans.
   a. Animal bite/scratch: Rabies by wild animals, cats, and dogs, the infection could occur through bite or saliva and could infect humans as well as animals.

      (Dr. Ashraf did not mention this)
      If rabies is passed through saliva, why are scratches a risk? Scratches from an infected animal may cause infection because saliva is sometimes present on claws - particularly if the disease is causing the animal to drool excessively (hyper-salivation). However, you can only get rabies by coming in contact with saliva and nervous bodily tissues of an infected animal.

b. Insect bite: Denge virus, Westnile virus, Eastern and Western Equine Eencephalitis virus.
   Mosquitoes are the vectors, they are not infected themselves. They spread these viruses by "transporting" them from the infected animals to humans.
c. Animals excreta: dried animal drooping; feces, mainly by rodents (rats, mice and bats), when these feces dry out, they become mobilized and may become airborne, then humans inhale them. Examples: Hanta and Arena viruses."Inhalation of dried animal feces"

Virus Entry:

Through eyes, respiratory tract, GIT, skin, urogenetial tract and anus.



GIT defensive methods: gastric acid and bile salts.

Respiratory tract defensive methods: ciliated epithelium and **mucus secretion**.

How could mucus secretion help in getting rid of viruses?

Presence of antibodies (immunoglobulins), specifically the IgA, which leads to neutralization of the foreign antigens (glycoproteins). Remember that neutralization is binding of antibodies to the viral antigens which are specific for the virus and not the cell, thus preventing its entry. Upon infection, the body produces antibodies and memory B cells, once there is a second exposure of the

virus later on, the process of neutralization will be much faster (it would take 2 days instead of 2 weeks for example).

Remember: glycoproteins are the most antigenic part of the virus.

Incubation period

It is the time between exposure and first symptoms of illness appearance.

General rule for viral infections:

Most viral infections are subclinical or asymptomatic. 60-70% of viral infections do not appear as symptomatic disease - you don't even know that the virus is there. Example: during winter months you feel tired and you think that you're getting ill, but you wake up next morning feeling okay.

This general rule depends on the virus itself, the immune system strength and many other factors.

The numbers here in this table represent incubation periods of some viruses, don't memorize them, but you should know for example that influenza virus has a very short incubation period, while HIV incubation is extremely long. Notice that they're divided them in 4 groups. Notice that the incubation period of respiratory diseases is relatively short. (You shouldn't memorize the table. Know the general characteristics)

Influenza	1-2d	Chickenpox	13-17d
Common cold	1-3d	Mumps	16-20d
Bronchiolitis,croup	3-5d	Rubella	17-20d
Acute respiratory disease	5-7d	Mononucleosis	30-50d
Dengue	5-8d	Hepatitis A	15-40d
Herpes simplex	5-8d	Hepatitis B	50-150d
Enteroviruses	6-12d	Rabies	30-100d
poliomyelitis	5-20d	Papilloma	50-150d
Measles	9-12d	HIV	1-10y

However, there are viruses that have a **varying incubation period**, e.g. Rabies virus which has an incubation period as short as one day only, and it could be as long as one year "usually from one month to a year". Rabies (as mentioned before) is transmitted to humans via animal bites/scratches, it could be transmitted by bat droppings inhalation but this theory is still under research. Rabies virus originally infects animals only, and it was transmitted to humans accidently. You should be highly suspicious when a patient shows up to you with an animal bite. You need to start him on rabies vaccination immediately, because once it passes the incubation period and the infection becomes clinical (symptomatic), the ultimate fate of the patient is death in just couple of days.

What determines the length of its incubation period (1 day-1 year)?

It is determined by how fast the virus reaches the CNS (its main site of action). If it reaches it, the incubation period is over and the patient will die. So, how far is the bite from the CNS? If it is in the neck, incubation period will be short, if it happens in the leg or foot, the incubation period will be much longer (numbers vary, but 1 day – 1 year is the range of possible cases).

Another virus we need to talk about is HIV. **HIV patients** are classified (labeled) as:

- HIV infected patients: immediately when the virus enters the body.
- AIDS patients: 10-20 years after getting the infection, exactly when CD4 count (receptor-containing cells) falls below 200 cells/mm^3

The time between the previous two stages is the incubation period for HIV. Remember that incubation period is asymptomatic. **HIV infection stages** are:

1. Acute phase of infection
   Within 2-4 weeks after HIV infection, many, but not all, people develop flu-like symptoms, often described as "the worst flu ever." During this early period of infection, large amounts of virus are being produced in your body. The virus uses CD4 count to replicate and destroys them in the process. Because of this, your CD4 cells can fall rapidly.

2. Clinical latency stage

Asymptomatic phase, the HIV continues to reproduce at very low levels *(plateau, also called viral set point),* the immune system CD4 count might rise just a little bit. This stage represents the incubation period. Keep in mind that in this stage, the immune system is fighting back the viral load and keeping it at a fairly constant level. This stage may cause mild symptoms only when the "constant" viral load increases slightly.

Antiretro therapy (ART) is given during this stage. As you know, there is no definitive treatment of HIV, the therapy only slows the further inevitable development of AIDS, you are essentially aiding the compromised immune system in his fight against the viral load, and as a result, the patient might have extra 10-15 years before being labeled as an AIDS patient.

3. AIDS
   Patient's immune system is badly damaged (collapsed) and his body becomes vulnerable to opportunistic infections. When the number of your CD4 cells falls below 200 cells per cubic millimeter of blood.

Important note: the virus is transmissible in all three stages.

Communicability: ability of virus to shed into secretions, e.g. in upper respiratory tract infections saliva of the patient contains viruses (any contact will lead to infections) fomites, personal belongings of the patient that can be contaminated by secretions or viruses (cup, towel).

Localized infection: infection limited to site of entry, e.g. influenza is localized to the upper respiratory tract even though its symptoms affect the whole body as well as "corona, rhino" viruses common cold viruses their infection in winter is more than influenza.

Disseminated infection: spread throughout the body.

Viremia: when viruses enter the bloodstream and hence have access to the rest of the body, it has two types:

1. Primary viremia: when the virus enters to the primary location of infection, then goes to the lymph nodes and then to the blood.
   site of entry ⟶ *regional lymph nodes* ⟶ *blood.*

2. Secondary viremia: associated with disseminated infections, the virus travels through blood to infect other organs and from these organs it travels to blood again.
   site of entry → *regional lymph nodes* → *blood* → *organs* → *blood again*

   Example: polio virus (from entero viruses) enters the body via fecal-oral route, then it goes to the GIT, then it uses the associated lymph nodes as a replication site "replication happens primarily in the gut", after that it travels via blood to CNS.

   Note: other entero viruses might infect other organs such as kidney, spleen, salivary glands, etc.

Replication

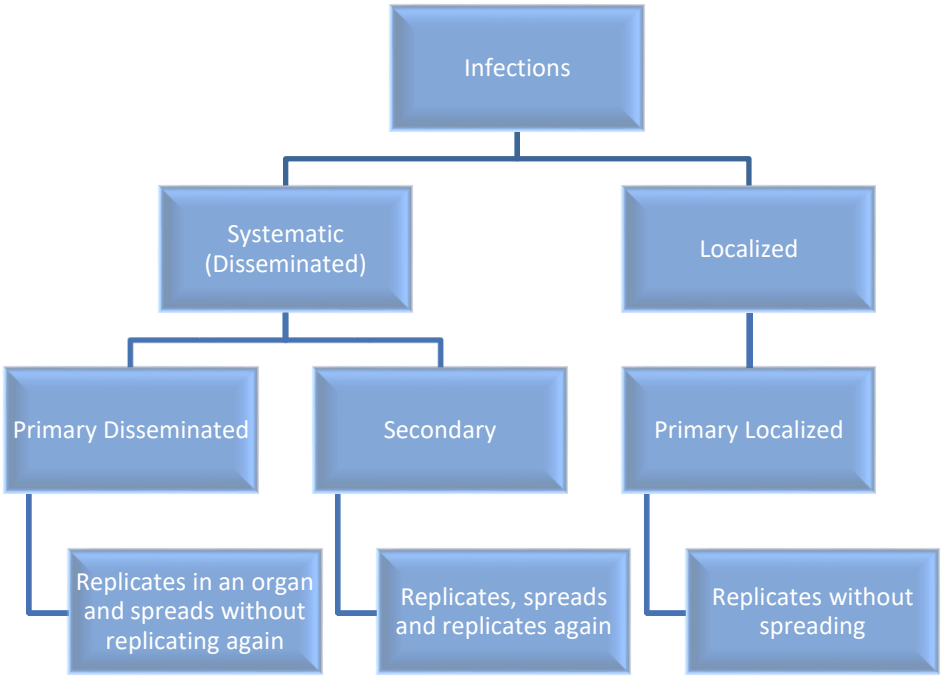
1. **Primary Replication**
   Having gained entry to a potential host, the virus must initiate an infection by entering a susceptible cell. This frequently determines whether the infection is "primary localized" or "primary disseminated". "Primary disseminated" means that the virus replicated in a specific organ and it traveled through blood but didn't infect other organs. "Primary localized" means that the virus replicated in a specific organ and stayed there. Example, corona or rhino viruses, causes symptoms only characterized to upper respiratory tract (rhino rhea, coughing).

2. **Secondary Replication**
   Occurs in systemic infections when a virus reaches other tissues in which it is capable of replication again in the new organ. Examples:
   - Poliovirus: first site of replication is gut epithelium, second site of replication is CNS).
   - Lentiviruses – A subfamily of retroviruses, first site of replication is the macrophages, second sites of replication are the CNS and many other tissues.

If a virus can be prevented from reaching tissues where secondary replication can occur, generally no disease results. To understand this sentence, we take a look at polio virus, its primary replication is in the GIT, it might cause vomiting and diarrhea, but generally these are considered as mild symptoms – you don't know that polio actually caused them. However, polio virus secondary replication is in the CNS, if it reaches it and starts replicating there, you will see the signs and symptoms of the infantile paralysis, so if we prevent it from reaching the secondary site of replication (CNS), no disease happens.

Note: 90-95% of polio infections are subclinical.

Localized Infections:		
Virus:	**Primary Replication:**	
Rhinoviruses	U.R.T.	
Rotaviruses	Intestinal epithelium	
Papillomaviruses	Epidermis	
Systemic Infections:		
Virus:	**Primary Replication:**	**Secondary Replication:**
Enteroviruses	Intestinal epithelium	Lymphoid tissues, C.N.S.
Herpesviruses	Oropharynx or G.U.tract	Lymphoid cells, C.N.S.



Spread Throughout the Host

Apart from **direct cell-cell contact (through gap junctions)**, there are 2 main mechanisms for spread throughout the host:

1. Via the **bloodstream,** the virus may travel:
   a. Free in plasma: Togaviruses, Enteroviruses.
   b. In association with red cells: Orbiviruses
   c. platelets (Herpes simplex virus)
   d. lymphocytes (EBV, Cytomegalo virus)
   e. Monocytes (Lentiviruses)

   Note: Dr. Ashraf said that these previous examples are not for memorizing.

2. Via the **nervous system.**
   Usually preceded by primary viremia. Virus travels from peripheral nerves to central neurons in axonal retrograde transport (opposite to the axon direction). Examples:

- Rabies (explained earlier) bite in the neck takes shorter time than a bite on the leg or foot.
- Herpes simplex viruses "DNA virus": characterized by latency, these viruses' primary infection is asymptomatic (subclinical) and they seek refuge (or hide) in the dorsal nerve ganglia peripherally. Once there is a drop in the immune system strength (due to stress, illness, fever, malnutrition, UV light, etc) the virus will reactivate now and then. But how does it hide? **(Conditions of latency: it infects the body, and once it's there, it never leaves nor gets eradicated) Latency discussed further ☺** :
  1. It acquires the shape of **episome** (similar to plasmids in bacteria) which is a circular extra chromosomal genome (could be the whole genome or part of it, mostly the whole genome).
  2. **Expression of early proteins only.** Viruses: Herpes simplex, papilloma, limited duration in adeno virus. *(Notice that they are DNA viruses).*

Virulence: the ability of the virus to cause disease in infected cell. Once the patient is infected what is the chance of developing a disease

Abortive infection: no viral replication, early viral proteins cause cell death.

Acutelytic infection: infection that lasts for a short period of time, kills target cells and causes short symptoms.

Persistent infection: chronic, latent and slow virus infections.

Virulent viruses: Kill target cell and cause disease.

Types of infected cells

1. **Non permissive cells**: virus has infected the cell accidently and it is unable to replicate within it which means that there is no production of new virions. The virus might produce its very early proteins, and the ultimate fate of these cells is either death (**abortive infection**) or transformation (cancerous cells). Infect (maybe by mistake) but cannot replicate.

2. **Permissive Cells**: virus is able infect the cell and replicated within it, kills target cell and causes disease (**productive response** by virulent viruses). Infect and replicate.

Cytopathic Effects: Virus-induced Damage to Cells

1. Changes in cell size and shape.
2. Cytoplasmic inclusion bodies
3. Nuclear inclusion bodies

   What are the **inclusion bodies**?
   They are remnants of replication of the virus (**capsid proteins**)"i.e. what does the virus leave behind?" They are essentially an aggregation of non functioning proteins or ones that were not used in the replication process. E.g. Rabies' Negri bodies which are of diagnostic importance.
   - **Nuclear inclusion bodies**: remnants for viruses that replicate inside the nucleus."General rule DNA viruses - with exceptions"
   - **Cytoplasmic inclusion bodies**: remnants of viruses that replicate in the cytoplasm."General rule RNA viruses – with exceptions"
   - **CMV** virus can leave both cytoplasmic and nuclear inclusion bodies

4. Cells fuse to form multinucleated cells:
   This happens in <u>enveloped viruses only</u>, because there is a chance that the left-over spikes or glycoproteins which are now bound to the cell membrane (after fusion of the enveloped virus), will bind to another intact susceptible cell that has the virus receptors at its surface, this will happen few times until it becomes one giant multinucleated cell."There are some forces between the receptor and glycoproteins so fusion might occur after adhesion." Example: HIV. Another name is syncytia formation.

   Note: To understand it better –not scientifically true, just to get you the picture, imagine as if the cell that has the left-over glycoproteins as a giant enveloped virus that fuses with another intact susceptible cell.

5. Cell Lysis
6. Alter DNA
7. Transformation (cancerous cells)
8. Virokines and viroreceptors; DNA viruses, cell proliferate and avoid host defenses.

-These were asked by the doctor-

Virokines, are proteins encoded by some large DNA viruses that are secreted by the host cell and serve to evade the host's immune system. They resemble cytokines, growth factors, or complement regulators.

Viroceptor, is used if the proteins encoded resemble cellular receptors.

TABLE 6.4

Cytopathic Changes in Selected Virus-Infected Animal Cells

Virus	Response in Animal Cell
Smallpox virus	Cells round up; inclusions appear in cytoplasm
Herpes simplex	Cells fuse to form multinucleated giant cells; nuclear inclusions
Adenovirus	Clumping of cells; nuclear inclusions
Poliovirus	Cell lysis; no inclusions
Reovirus	Cell enlargement; vacuoles and inclusions in cytoplasm
Influenza virus	Cells round up; no inclusions
Rabies virus	No change in cell shape; cytoplasmic inclusions (Negri bodies)
HIV	Giant cells with numerous nuclei (multinucleate)

Patterns of Viral Infections

1. Unapparent infection (Subclinical infection) no symptoms.

2. Apparent Infection:

a. Acute infection, primary infection mostly localized leads to site leads to lysis and death example influenza “why coughing lasts for weeks”
b. Persistent Infection:
    I. Chronic infection lasting for long periods of time (e.g. HEP B &C) HEP B 85% of the cases recover after acute phase of infection the remaining 15% go into persistent infection. HEP C is the opposite 15% recover while the remaining go into persistent infection. The virus replicate at a slower rate and is detectable, also causes an increase in liver enzymes.
    So when the liver enters this phase regeneration then lysis and then regeneration –what happens?- Cirrhosis on the short term and cancer of the liver on the long term.
    II. Latent Infection, Herpes viruses
    Latency, consider this herpes viruses are characterized by acute phase infection, it infects the patient becomes symptomatic and then it subsides but it does not leave the body it goes and seeks refuge (hides) in certain locations in the body. Hepes simplex virus(1,2,3 varicella zoster) hide in the dorsal nerve ganglia.
    -What is the difference from chronic infection?
    In chronic infection virus is there if you assay for it and causing harm to the target organ. In latent infection you cannot detect the virus there is no harm to any organ “lying dormant”

    Conditions of latency, lies as an episome (circular piece of DNA extra chromosomally like the plasmid) there is translation of the early proteins only. Any drop in immune system might lead to reactivation of the dormant ones.-Continued in the next lecture-
    III. Slow virus infection

“I don’t want to die without any scars”

Good Luck