Pathogenesis of Viral Infections

Today we will start the pathogenesis of viral infection, then the immunity of viral infection before going into the individual viruses.

Simple Fact:

1- viruses are the most common cause of infection.
   - They are more common than bacterial infection, parasitic infection, and fungal infection.
   - Example: in respiratory tract infection they comprise 75% of the infections and the remaining 25% are due to bacteria, fungi, etc.
   - However most of these infections are not very serious, some may cause fatal outcome but most of it are considered benign.

2- Normal Flora.
   - viruses do not comprise part of the normal flora of the body whereas bacteria are part of the normal flora.
   - it's important to mention here that the normal flora represent infections aids, which enter into association with the host (and that is the definition of infection).
   - so the infection is : the establishment of a relationship between the host and the organism, but if this relationship result in a disease that's a different story. (so this relationship may be beneficial or harmful causing disease). bacteria could be useful for human.

   - normal flora may provide protection against pathogenic organism because they occupy a space and they :
     1- utilize nutrition.
     2- produce substances that kill pathogenic organism.
     3- produce substances useful for the host like vitamin K (produced by certain bacteria).
viruses can't do what bacteria can do in the normal flora, they are always harmful to human, and even if they do not cause harm they can't do good.

Medawar has a nice description of viruses: "a virus a piece of bad news wrapped in a protein coat ".

**viral pathogenesis**

we said that viruses are harmful and foreign to the host, they may or may not cause a disease.

- **viral pathogenesis**: is the process by which a viral infection cause a disease, in other words it's the mechanism by which viruses cause a disease.

normal flora at one point may be harmful to the host and cause disease if an individual is devoid from its defense mechanism (cancer, HIV), so there is no absolute division of pathogenic and non-pathogenic for organism, any organism is potentially pathogenic(under certain circumstances) even the one in normal flora.

A) **Basic concept:**

- Disease has a prerequisite which is infection, so infection must be established first by viruses then there are certain mechanisms utilized by viruses to cause disease. And the factors that cause disease may be from both viral or host nature or origin.
- If the infection do not lead to disease it would be hard to detect the virus. so any one may look healthy but he may be carrying a virus, but there is no clinical manifestation.

- Diseases are abnormal situation of no value to the virus, because this stimulate host mechanism to eliminate and destroy the virus. so it's not in the interest of the virus to cause a disease and kill the host because this mean that their survival, presence, and perpetuation will be threatened, and that's why the majority of viruses infections are subclinical(asymptomatic).

- The consequences of viral infection usually depend on the interplay between host and viral factor.

- It's important to distinguish between disease and infection before studying pathogenesis of viral infection.
  
  - Infection: the entry of the virus in the body, and that can cause no symptoms or can produce transient symptoms due to the local irritation.
  - Disease: the virus present at target organs, signs and symptoms are associated with it (abnormal situation has taken place).

B) pathogenesis is the result of:

1- injury of discrete population of cells.

2- in a particular organ.

3- producing signs and symptoms of disease in a giving host.

Viruses replicate in cells, and this replication is attended by certain consequences that may reach to the degree of killing the cell (destruction of cell).

If this destruction is significant, the organ and its function will be affected due to the stimulation of the defense mechanism against viral infection which can lead to certain manifestation.
So the basic defect caused by viruses is at the level of the cells, because they replicate in cells and these cells are present in particular target organ (each virus has its target organ), and as a consequence of damaging the cells, disease signs and symptoms are apparent in the giving host depending on the degree of this function (the cell damage) caused by the virus.

- **poliomyelitis**: often called polio or infantile paralysis, is an acute, viral, infectious disease spread from person to person. (wiki)

- **Enteroviruses**: are a genus of positive-sense single-stranded RNA viruses associated with several human and mammalian diseases. (wiki)

**c) Extent of the disease depends on:**

1- **Virus dose:**

Certain dose is needed to establish the infection and this dose vary from one virus to another. The common dose which establish an infection (which is benign) is one particle which mean that one virus can cause a disease.

On the other hand, in some cases like poliomyelitis (it's an enterovirus), millions of viruses are needed to establish infection. And even if millions enter the body, most infections will remain asymptomatic. like if 100000 individuals are infected with poliomyelitis only one individual will develop a disease.

2- **Route of entry:**

Examples...

- Viruses that enter the GI tract or respiratory tract, find difficulty in establishing themselves and causing infection, because of the non-specificity of the virus and also due to the specific defense mechanisms.
• If the virus introduced directly to the blood stream as in the case of blood transfusion or contaminated needles or injection by arthropods, the chance of the viruses to cause infection increase because it has bypass many defense mechanisms.

• In mucous membrane the barriers (like secretions, antibodies, chemical substances), and the integrity of the barrier itself play an important role in the defense, because in order for the virus to establish an infections it must bypass (overcome) all these barriers.

So in the second case (blood stream) all the above barrier has been passed and it's easier to cause infection.

3) Replication efficiency:

Some viruses are more efficient in replication than other, and both the virus and the host once they enter a relationship they seek an advantage reproduction.

When viruses enter the host, they want to replicate and that's the only way of perpetuation of the virus to be sustained in nature. So they need the host to replicate in.

Natural selection favor viruses with low pathogenicity, (because will be no host to replicate at the end) and it's easy to eliminate the host and break the cycle of infection.

While viruses with low pathogenicity do not cause clear illness and the individuals who are ill continue their normal life, and they infect others (source of infection), and that's how an infection spreads in the community. This is applied in the case of common causes of disease because people do not take precautions, and they continue their life and infect other,(that's what makes a common cause common).

Whereas in individuals with rabies viruses(high pathogenicity), they are hospitalized, isolated, and usually in 100% of the cases death is the end...
result. So it's easy to break the cycle of transmission of rabies virus as compare to other viruses.

In conclusion natural selection will select only viruses with no virulence and that's why most of the viral infections are asymptomatic but diseases are an exception.

**D) Introduction to infection**

Viral pathogenesis concerns itself with the mechanisms by which viruses cause injury to cells in different tissues and organs to produce the signs and symptoms of disease.

If we consider these mechanisms there are two component:

- Direct effect to viral replication on the cell.
- Response of the host to the virus replicating in his body (indirect effect). In many cases most of the manifestations are due to this effect.

Viruses that are significant in disease as a cause of direct effect are few, those that cause damage especially naked viruses who has no option but to destroy the cell. But many viruses by themselves do not cause any of the manifestation. However most of the manifestations are due to the host cell response.

**Example:** hepatitis A, B, C, and E are associated with clinical manifestations in the minority of individuals (majority of individuals do not especially children) . However in certain individuals who mount a vigorous immune response to viral infections, this secondary indirect factor can lead to different vision. Sometimes it causes **hepatic conflict damage** which is a severe inflammation that cause necrosis and hepatic failure leading to death, which is due to the host response not the virus himself.

so the body response to the infection can be very serious and usually the cause of viral infection is determined by a delicate balance between these two mechanisms.
E) **Symptoms of infection:**

In some viral infections, most of the pathologic symptoms are due to the side effect of the immune response. And what is seen in almost all viral infection are labeled as non-specific manifestation.

- These non-specific manifestation are:
  1. fever.
  2. headache.
  3. malaise.
  4. loss of appetite.
  5. abdominal pain.
  6. nausea.
  7. skin rashes.
  8. inflammation.
  9. vomiting.

All infections have these manifestations which are due to certain cytokines that are released from the infected cells, mainly interferon and interleukins which are responsible for the majority of manifestation observed at the beginning of viral infections.

Virus infections made results in the development of.....( I couldn't get what he said) due to the virus himself. But the majority of manifestation seen early at infections are due to the interferon and interleukins and the majority of viral infection are limited to these non-specific manifestation.

Some viruses are considered symptomatic in the majority of cases such as influenza, small pox, rabies, measles, and sever illness . individual with these viruses show clinical manifestation but these clinical cases are few or do not exist.

It is perfectly possible to envisage or imagine viruses with a hit-and run strategy, usually viruses enter the host, cause some damage, then they are shed from the host and infect another host, and that's why they are
perpetuate in nature, and there is a clear tendency not to damage the host.

**Mechanism of cellular injury**

It's the mechanisms that are utilized to cause damage to the cellular level, and they are referred to as CPE (cytopathic effect), because they effect the cell.

viruses in cultured cells cause many effect:

1) **Altered shape (rounding):** cells are usually spindle in shape and viruses cause abnormal rounding of cells.

2) **Detachment of the cell from the substrate:** usually cells adhere to the substrate and as a consequences of viral infection they start to detach from the substrate.

3) **Membrane fusion(giant cells, syncytium, polycariods):** viruses can cause membrane fusion of adjacent cells which result in the formation of giant cells. This effect is known for measles, and herpes viruses, those that have glycoprotein in their envelope which promote the adhesion of membrane of adjacent cells.

4) **Increase membrane permeability:** the permeability of membrane can be influenced and that's why in herpes viruses it's considered a cause of cell death after the virus is released.

5) **Inclusion body formation:** this is probably the most common effect of viruses on cells. They cause inclusions bodies that can be:

   - intracytoplasmic or intranuclear.
   - basophilic or acidophilic.
   - multiple or single.
   - small or large.

different viruses cause different inclusion bodies and these bodies are used to utilize and identify the viruses (they are the agonistic marker of viruses).
6) **Lysis:** two things can lead to lysis of the virus, the virus itself or the previous effects. and this effect is considered as the accumulative effect or the collective effect of all the previous effects mentioned above.

Lysis may be a result of naked viruses because it's the only way by which they can leave the cell.

7) **Apoptosis:** viruses can activate apoptosis (programmed cell death) which lead to the stepladder, degeneration, calcium dependent bladder degeneration of the genome of the cell.

These effect require the binding of fast ligand to the cell, and this can be activated by viruses.

**Mechanism of infection**

Viruses start infection by implanting themselves at the body site (named the portal of entry) and then replication take place and the viruses gain access to either blood stream or neurons or lymphatics to reach the target organ.

From the site of entry, viruses must gain access in some way that allow them to transfer from the portal of entry to the target organ.

**Examples:**

1) Rabies viruses gain access to nerve endings, that are exposed as a consequence of a bit, because rabies virus is transmitted by dog bit or cat bit, so near exposed nervous endings are the portal of entry utilized by the virus, then after entry the virus travels back to the CNS, to the brain via retrofit axoplasmic fluid with nerves.

2) Viruses can gain access to the blood stream which transfer them to the target organ.

3) Viruses may gain access to the lymphatics and then from the lymphatics the reach the blood stream.

So the target organ is attacked by the virus, the virus replicate there and the outcome varies, some viruses cause severe damage and death of the
host and other do not, and they are shed from the target organ to the environment, to infect new individuals.

This whole process may be associated with clinical manifestations or may not, if no clinical manifestation are observed, this is known as subclinical infection, and the knowledge of subclinical infection come from serologic studies.

How do we know about a subclinical infection caused by viruses?

we can confirm this by detecting antibodies to the virus, and this antibodies has been detected in individuals who never complained from clinical manifestations (symptoms), which is an indication that the infection was subclinical (no history of disease among these individuals yet they have antibodies). And even the most lethal, serious infection like west nine virus which cause meningitis or encephalitis in individuals, and in a study named Cairo it was mentioned that more than 70% of those among the age of 40 have antibodies to the virus indicating that they were infected. so even this virus which is associated with serious illness like encephalitis can cause subclinical disease

Unapparent infection have great epidemiologic important because they are the major source for dissemination of virus through the population which result in immunity.

This immunity that spread among individuals unequivalently is known as herd immunity, and herd immunity is one of the most important factor in determining the spread of infection in the form of an epidemic.

if herd immunity is high no epidemic can be caused, because there isn't enough susceptible individuals in the population for an epidemic spread. and we know for example that we need at least 200,000 susceptible individuals for the spread of measles epidemic, so if most population have antibodies to the virus then the spread of measles in epidemic form is impossible and that's true for many viruses.
another example is influenza which causes a short lasting immunity and that's why influenza lasts ...(i couldnt hear what he said) ,that's why individuals who are infected with one type loses their immunity after 1 to 2 years and they become susceptible to infection and that's why influenza epidemics are annual because of the short lasting immunity, but in the case of immunization against certain viruses like polio or measles with high herd immunity the virus cannot spread in the community in the form of epidemics, but it may cause sporadic infection

Host factor that can modify viral pathogenesis

1.Viral receptor: this is very important, because if the receptor exist for the virus it can cause a disease, and if it doesn't exist then the virus can't cause a disease, this is genetically determined and could be due to the state of differentiation; meaning that there are markers that differentiate cells which are utilized by viruses.

2.Age: it's another important factor, generally speaking most infections are benign in children but very serious in adults.

examples:

- Polio, hepatitis viruses, brucella.

-EBV (herpes viruses) causes totally asymptomatic infection in children and in adults it can cause serious infection mononucleosis.

-Poliomyelitis is less likely to lead to paralytic illness in children while in adults it will occur.

-Hepatitis A: is an asymptomatic in the vast majority in the children and symptomatic in the vast majority in adults and lethal (fatal), it is unlikely
in an individual in the forty to survive from hepatitis A. Hepatitis A spreads in the community among children without causing illness, but the neonatal period in neonates maybe hardly hit by certain viruses.

Many viruses may cause severe illnesses in adults but subclinical, asymptomatic diseases in children.

3. Metabolic state: is another issue to be considered

- **Malnutrition** can predispose for severe illness in individuals
  For example: measles in malnourished children can cause kwashiorkor (severe illness that lead to a disease)
- **Vitamin A**: in those with vitamin a deficiency measles cause punctate keratitis that is the most common cause of ******* in certain countries like India, it leads to blindness (loss of vision) in cases where we have vitamin a deficiency in those individuals.
- Pregnancy is another state which can be affected and result in different effects of viral infection for example:
  1. varicella is very lethal among pregnant women, its serious in adults but it's very serious among pregnant women.
  2. hepatitis E has a mortality about 1% but among pregnant women the mortality is about 20% (20 times more).
  So pregnancy is a state of immuno suppression in addition to the hormonal factor associated with pregnancy.

4. Altered immune responses: can be in two forms:

- Impaired immune response which leads to infection with different viruses, whether deficiency is congenital or acquired, it leads to severe viral infection.
- In cases of enhanced immunity (auto-immunity) is associated to decrease infection, deviation from the normal range whether increase or decrease in the immune status of an individual can predispose for viral infection
  So auto immunity has been shown to be associated with increase in the rate of viral infection.
Routes of entry

1) Skin

- Skin can be penetrated by viruses as a result of:
  - Direct mechanical trauma e.g. human Papilloma virus which cause skin warts and they may cause cancer, HIV, herpes simplex virus, hepatitis B, poxvirus
    So mechanical trauma can allow these viruses to penetrate the skin.
  - Injection with a contaminated needle e.g. HBV, HIV
  - A bite of an infected mosquito where arboviruses are transmitted
  - A bite on an infected anima where like rabies
- Viruses don’t usually multiply in the skin because it’s the most resistant part to penetration of viruses, its first covered by a dead layer of cells and viruses can’t replicate in a dead layer that’s why reaching to the continent of the skin is required in all of these cases
- And that’s why viruses don’t usually replicate in the skin but it has been found that rabies virus can replicate transiently in the striated muscle that are exposed because part of the animal can expose striated muscle and in this case the virus gain access to their endings and may replicate in striated muscle
- Generally, viruses do not multiply locally but are carried away from site of infection and transferred to the target organ:
  - by bloodstream (HBV, arboviruses)
  - or migration along nerves (rabies)

2) Respiratory tract

- The major route of infection: 75% of infections affecting the respiratory tract are caused by viruses.
- Preferring route of viral infection and this can be followed by:
  - Local respiratory tract infection (the infection is limited to the respiratory tract) e.g. influenza, respiratory Syncytial Virus, parainfluenza virus, SARS, corona virus.
- but certain viruses can replicate initially in the respiratory tract but their target organ is different and they may or may not subsequently affect the respiratory tract like measles, mumps, chickenpox, enteroviruses. All of these utilize the respiratory tract route to enter and disseminate to other target organs e.g.

1. Measles: skin and mucus membrane
2. Mumps: parotid and other salivary glands
3. Chickenpox: skin and mucus membrane
4. Enterovirus: eye, heart, veins depending on the virus.
   Transmission is usually by droplets or aerosols and could be direct or indirect.

3) GI tract

• Can be infected by viruses contaminating either food or drink but also contaminated fingers especially among children can be the cause of GI tract infection, they contaminate their mouth and as a result viruses reach the GI tract and they may cause
  - Local infection (e.g. rotavirus, coronavirus, adenovirus)
  - they may spread to their target organs (e.g. enteroviruses, hepatitis A, picornavirus)
• Virus survival in the GI tract is influenced by several factors like:
  - Acid stability: stomach acidity is an important factor
  - Resistance to bile salts
  - Enzymes: GI tract enzymes may affect viruses, usually viruses are resistant except to pronase
• Viruses that cause GI infection are usually non-enveloped (naked) because these viruses are more resistant and more stable to acid.

4) the genitourinary tract

• Sexual transmission of viruses, tears or abrasions of mucosa will allow viral entry.
• Sexual transmitted viruses include: HIV, HSV mostly HSV 2, papilloma viruses causing genital warts and consequently cancer of the cervix, HBV
Nature of cervical mucus, the pH of vaginal secretions and the chemical composition of urine all play a role in host defense.

5) conjunctiva

Localization versus systemic spread

So viruses enter through different routes and they either cause localized infection or disseminated infection, for example:

- Respiratory infections – influenza, rhinoviruses and RSV cause localized infection
- Gastrointestinal infections caused by rotaviruses also cause localized infection.
- Dermatologic infections of the papillomaviruses (skin warts) cause localized.
- Whereas other infections like measles, mumps cause disseminated infection.

Now the site of budding in epithelial cells originally infected is an important determinant factor:

- If the virus is shed from the apical part of the cell the infection is usually localized.
- If the infection (the virus) is shed from the basolateral aspect of the cell the infection is usually disseminated.

So what determines the dissemination or the localization of the viral infections is usually the aspect of shedding of the virus form the infected cell.

Spread

✓ Types of spread:

1) cell to cell:

- skin warts.
- influenza in the respiratory tract.
- pox viruses.
2) blood stream: associated with viremia.

- Viremia can be either plasma free or cell associated (virus present within the cell).

Cell that are utilized are those circulating blood stream so they are: lymphocytes or monocytes. Mononuclear cells are the carriers of viruses that spread in the form of cell associated viremia but could be also plasma free viremia.

- Viremia could be primary or secondary: have primary phase of viremia and secondary (two phases or one phase of viremia).

for example:

- in the case of “Varicella chicken pox“ the virus replicates in the oropharynx, gate access to lymph nodes, where it cause primary viremia that disseminate the viruses to the “Reticuloendothelial system“ the virus replicate there for a while and then it’s released from the Reticuloendothelial system again to the blood stream where it cause secondary viremia, this secondary viremia disseminate the virus to its target organ (the skin and the mucus membrane).
- whereas in the case of poliomyelitis the virus gain access to the blood stream through the portal circulation or other tract and then it reaches the CNS or the heart depending on the tract.
- hepatitis A, hepatitis B, all cause primary viremia, one phase of viremia.

3) Neural spread: usually preceded by primary viremia but maybe direct.

- in the case of poliomyelitis the virus reaches blood stream then the CNS (primary viremia), whereas in rabies the virus gain access directly into nerve endings.
- there are cases of poliomyelitis where the virus reach directly not throw viremia:
  - in the cases of tonsillectomy: we have an outbreak of poliomyelitis and operations are made, tonsillectomy exposes the nerve endings and this can be associated of
invasion of the virus present in the oral pharynx directly to nerves causing what’s known “ Bulbar Paralysis “ which is very serious.

- can be introduced by injection of contaminated sites: enterovirus can be introduced by injection to nerve endings and they cause the invasion of CNS.

✔ Cells and tissue tropism is the major determent of spread

Why hepatitis A attacks the liver ? we don’t know , because there is a tissue tropism for the liver . Why coccacy B attacks the heart when they are in the blood stream when they can reach everywhere and can attack anywhere but they select to attack the heart? because of tissue tropism.

so tissue tropism is a major determent of spread of the virus , where to go, because it has that predilection for attacking .

so after transversing the epithelial and its basement membrane and body surfaces , invading viruses face multiple tissue and cellular defense( this will be covered in the second lecture “ Immunity to virus infection “ ) and they enter directly causing viremia ( like arbovirus ) or initially tacking by the lymphocyte system, then they reach the blood stream, and viruses may enter directly into the peripheral nerves like in the case of rabies, and invasion of few mucosal tissue subsequently to blood stream cause infection of certain type of target organs .

After viruses enter to the body they cause their replication in the target organ and they cause pathologic changes, and these pathologic changes will culminate in disease manifestations and the individual who is affected will start to suffer from signs and symptoms of disease.

✔ Incubation period

The time that elapses from point of entry until these manifestations are apparent is known as Incubation period .

- incubation period for viruses can range from few days , one day, two days for common cold. (localized infection)
• few weeks like chicken pox, hepatitis A. (systemic infection).
• few years like HIV or sometimes slow viral infection like rabies. Rabies usually have the incubation period in months (1 to 3 months), and weeks but Rabies acquired through corneal transplants may not be apparent before 3 years, so the incubation period is 3 years.

So there is significant variations with the respect to the incubation period. Now, calculation of incubation period is very useful in the epidemiologic studies and in predicting the spread of an epidemic disease.

Viruses shedding and transmission

someone asked a question about HIV and the doctor replied that HIV has 3 stages, there’s what’s called (the acute retroviral syndrome) which is apparent after few weeks, but HIV type “8” is defined as cellular immune deficiency leading to opportunistic infection with tumors like (Kaposi’s Sarcoma) and this requires years to take place but if we talked about the non-specific manifestation that are not specific for HIV infection then they take place after weeks.

1) Horizontal: From host to host of the same generation

• Direct: direct host to host contact like in the case of so there’s direct contact between an individual infected with the virus and a susceptible individual.
  - skin lesions (papillomaviruses).
  - saliva (rabies, mumps, CMV, EBV, HIV).
  - mechanical trauma (HIV, HSV: Herpes simplex virus).
  - aerosols (influenza, measles, rhinoviruses).

• Indirect: from host to fomites
an item is contaminated and this item is then utilized or act as a vector transmission of a virus. like if you contaminate your pen with rhinoviruses or influenza your colleague will be infected if he touches the pen. This is indirect because you didn’t infect him directly. Infection happened as a consequence of contamination of fomites then fomites are touched by the individual and finally the individual gets contamination.

2) Vertical: From host to progeny

it could be from mother to fetus and that’s congenital spread and it's can happen due to:

- Transplacental
- Perinatal: delivery, before or after delivery
- Breast milk.

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