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Virology

Doctor 2018 | Medicine | JU

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Note: This sheet was written based on section's 4 record.

Every virus has its own way of making a disease, and its own set of characteristics.

Some of the **varying characteristics of viruses** are:

a. The presence of an outer envelope (enveloped or naked).

b. The type of nucleic acid they have (ssRNA, dsRNA, ssDNA, dsDNA).

c. The type of tissue they target (e.g. CNS, GIT, skin).

d. The way they establish pathogenesis (make a disease).

-**Despite** these variations among viruses, there are some **common patterns** of **pathogenesis** shared by groups of these viruses, that'll make studying them easier.

Envelope creation: during replication, an 'enveloped virus' would use the cell to synthesize some virulence factors (in this case membrane proteins), send them to the plasma membrane of the cell, so that when the replicates leave the cell, they would take a proportion of the membrane with them -which has proteins important for the virus's infectious ability- thus creating an envelope for themselves.

Pathogenesis of viral diseases:

Overall, the outcome and the characteristics of viral infection are determined by the virus-host interaction, and the response of the host.

Factors affecting the susceptibility of an individual to the disease and the severity of the disease:

1) the mechanism of exposure and the site of infection.

2)the immune status of the, age and general health of the host.

3) the viral dose (inoculum size).

4) the genetics of the virus and the host.

	Host related	pathogen related (virulence factors)
definition	Anything related to the genetic makeup of the host's immune system, and how competent it is (The strength of the host's immune system).	Factors (components and activities) promoting viral replication, transmission, access, binding to target tissue and escaping the immune and the compliment systems.
Examples	- the presence of all types of immune cells and complement system molecules in adequate amounts. - the efficiency of the leukocytes which differs from one host to another. - the acquired immunity (due to previous infection), is the system immune or naïve, has it faced that virus before?	- some proteins acting as virulence factors meaning they would enhance the virus's ability to cause the disease. - complement inhibitory or regulatory proteins present in the virus's envelope helping it evade the complement system.
Flaws	- Immune deficiencies, individuals lacking some components of the immune system makes them more prone to infection.	- Enveloped viruses are more susceptible to heat and dryness, they would easily lose their envelope, the loss of the envelope makes them less infectious.

Disease-virus relationships (possible outcomes):

a) One disease caused by several viruses having a common target tissue.

e.g. hepatitis-liver, encephalitis-CNS.

b) Several diseases caused by same virus infecting different tissues.

e.g. HSV-1 can cause: gingivostomatitis, pharyngitis, herpes labialis (cold sores), genital herpes.

c) A certain virus could cause no symptoms/disease at all.

We now know that diseases and their presentation (their nature and severity) vary widely according to certain factors, but there are specific factors affecting the two of them, the factors affecting the

1) Nature of the Disease:

Nature of the Disease
Target tissue
Portal of entry of virus
Access of virus to target tissue
Tissue tropism of virus
Permissiveness of cells for viral replication
Pathogenic activity (strain)

For example, poliovirus causes movement disabilities, because its target tissue is the CNS.

Some viruses could cause diarrhea or vomitting because they first entered through the GIT, some would cause rhinorrhea because they were transmitted through the respiratory tract.

permissive cell: allows the virus to replicate by providing needed enzymes, proteins, etc.

nonpermissive: doesn't allow the virus to do what it desires (lacks needed machinery or enzymes)

The most prominent disease effects are not due to the pathogen's effect, but to the immune response. In fact, it's more devastating than the damage caused by the virus itself.

2) susceptibility of a person:

a) the mechanism of exposure (ingestion, inhalation, blood transfusion).

b) the site of infection (usually epithelial layers).

c) the genetics of the virus and the host.

d) the immune status of the patient (competent, weak, deficient).

E) the viral dose (inoculum size).

→ Inoculum size: amount of virus needed to have an infection.

For example: 10 particles of virus A are enough to cause the disease, from virus B, a thousand particles are needed to cause the disease (the doctor said commenting: so you need to eat a lot of the feces of the cafeteria worker to get the disease)

The lower the inoculum size → the stronger the virulence of the pathogen

(it needed fewer numbers to induce the pathogenic effect, so it's more capable of causing the disease because it required lower inoculum)

In common cold for example small droplets inhalation is enough to cause the disease.

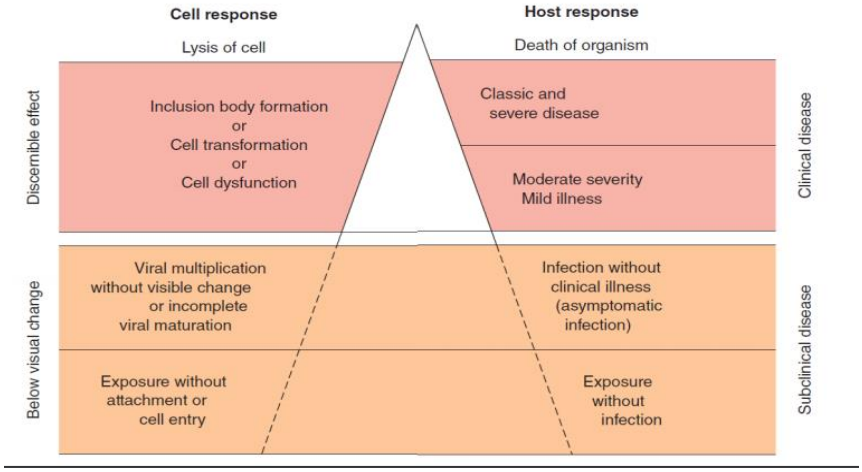
3) the severity of the disease:

Severity of Disease
Cytopathic ability of virus
Immune status (naïve or immunized)
Competence of the immune system
Prior immunity to the virus
Immunopathology
Virus inoculum size
Length of time before resolution of infection
General health of the person
Nutrition
Other diseases influencing immune status
Genetic makeup of the person
Age

You'll observe some over-lapping in the effective factors and the effected characteristic of the disease. It's normal.

Due to these variations (host or virus related), Diseases are on a spectrum when it comes to their presentation and severity, and the two extremities are

Either 1. **No** disease will show Or 2. a severe disease will take place.



You'll notice when studying virology that there's a period of time after infection, where no symptoms or signs would show on the host.

Progression of the disease shows in two scales:

1) macroscopic scale: changes in the host's overall state.

2) microscopic scale: changes observed in the infected cells.

Infection	Virus is present, not necessarily any symptoms or signs showing, might not be associated with a disease.
Disease	Virus is present, also signs and symptoms are present.

There's a period before the disease is showing where we are actually infected with the virus (aka prodromal phase), where viruses are replicating, attaching to cells, entering them, again replicating in them, not showing any distinct symptoms yet ,but the virus is preparing the army and the weapons.

This phase Could have (remember no disease shows in this phase anyway):

1. Caused some damage that's insignificant.

(infection is a subclinical disease)

2. caused some damage that didn't impair functions of the host.

3. caused no damage. (If you look at the cells, they will look fine, functions not disturbed even though the virus is going under replication)

Disease taking place (discernible effects) will show in:

1. Cells will start to be dysfunctional.

2. protein expression would be damaged (could cause the formation of **inclusion bodies**).

3. synthesis of some enzymes might have some problems.

4.The cell can transform into a cancer cell.

How does the cell turn into a cancerous cell by viral infection? some viruses would enter the cell and insert their genetic material next to sites related to cell growth and proliferation, cell would start replicating the virus and some growth factors along with it, thus the cell would get hooked up on growth factors and turn into a cancer cell.

In the case of inclusion bodies,

Which are aggregates of proteins that are basically pathogenic proteins, this is a normal case when a certain cell expresses the proteins of another type of organism, the accommodations of the cell may produce a protein that isn't in the right form, and that's due to the fact that the pathogenic proteins are foreign to the host cell, which will cause trouble and misfolding of proteins causing it's aggregation (inclusion body).

Inclusion bodies can affect cell function, since they are the result of aggregation of some proteins, we can see this effect in the cell. ON the clinical level as well, disease starts to show.

On a cellular level, severe infection will end up in cell lysis, and if it was severe enough, it'll cause the host's death. still though, lysis of cells doesn't always equal the death of the host

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Steps of infection and pathogenesis

1. **Acquisition** (entry into the body)
2. Initiation of infection at a primary site
3. Activation of innate protections
4. An **incubation period,** when the virus is amplified and may spread to a secondary site
5. Replication in the **target tissue,** which causes the characteristic disease signs
6. **Host responses** that limit and contribute (immunopathogenesis) to the disease
7. Virus production in a tissue that releases the virus to other people for **contagion**
8. **Resolution** or **persistent infection/chronic disease**

1. entry and primary replication:

a) Acquisition, happens by many ports of entry (skin by cuts, bites & infections, mucosal epithelial surfaces of the respiratory (**influenza**) and the gastrointestinal (**noroviruses cause gastroenteritis)** tracts, the urogenital tract and the eyes, even sometimes directly into the blood by blood transfusion (hepatitis B, HIV), or by insect vectors (arboviruses) Inhalation is the most common cause of viral infection.

b) primary replication, once the virus enters, it'll get in contact with the epithelial layer and the immune response will initiate and the virus will start replicating at the primary site of infection.

viruses normally would start replicating at **the primary site of infection,** and once they have replicated, they enter the blood stream or the lymph nodes and reach other types of cells.

2. viral spread and cell tropism:

viruses usually have a target organ, not always the same as the site of entry, they could initiate their action with other cell types (than those of target) but eventually they reach a target organ that is the most permissive, for example the **polio** virus is ingested **through mouth**, it replicates in **the intestinal epithelial** cells and then migrates through the blood vessels (viraemia) and reaches the CNS, once it's there we start viewing the disease markers of the virus.

-**aemia**: is a suffix showing that the substance is present in the blood. (viruses in the blood: viraemia)

Every virus has a target organ, sometimes the target organ is in fact the primary site of infection, e.g. viruses targeting the respiratory tract (e.g. Rhinoviruses → common cold) they enter the respiratory tract and they remain there. Virions may be free in the plasma (e.g. enteroviruses, togaviruses) or associated with particular cell types (e.g. measles virus)

<> The target organ depends on something called the Tissue Tropism, certain viruses will prefer certain tissues - hepatitis virus would prefer hepatocytes, influenza viruses would prefer the epithelium of the lung, herpes viruses prefer the skin.

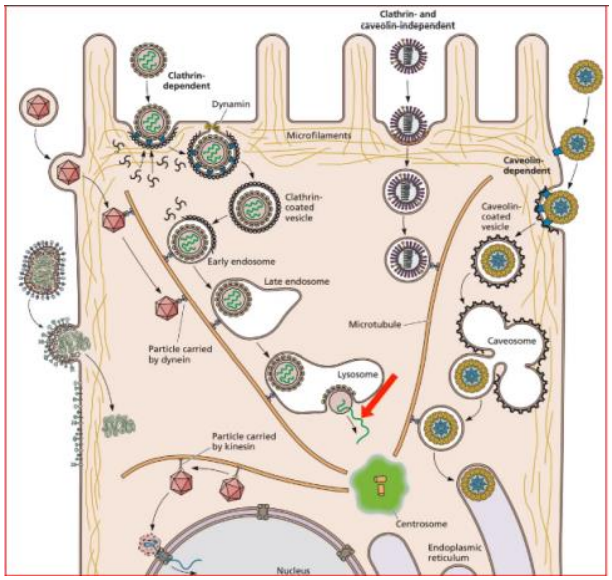
Tissue Tropism is the tissue's support of the viral growth, and tissues differ in their tropism towards certain viruses (e.g. hepatitis B virus has a tropism for liver hepatocytes).

→ tropism determines the pattern of systemic illness produced during a viral infection, because it determines where the virus will settle down (what type of cells).

Tissue Tropism depends on two factors:

a) Certain receptors on tissue cell surfaces that the virus recognizes. When it comes to receptors, viruses are so specific because their entire existence depends on recognition and attachment to these receptors, which'll further allow them to enter, infect and replicate in the cell. (more important factor)

b) the permissiveness of the cell. Does the cell have the required machinery for the viral replication? Some cells are more competent to accommodate the virus than others because of the proteins and enzymes that they have that support the replication of the virus, for example: he JC polyomavirus (human polyomavirus 2) **enhancer** is much more active in **glial cells** than in other cell types.



Here we can view viruses' dependence and independence on certain types of receptors, or cell surface components, which are main affectors of tropism and of entry of viruses to the cells.

there are several ways for how the virus could enter or exit the cell, some of them have a lipid membrane, some of them are .naked viruses (capsid+ nucleic acid)

The two types of viruses have different characteristics in the way they migrate or infect cells. They found that enveloped viruses are more susceptible to heating, drying and detergents, so they are weaker and easily demolished. Remember the lipid bilayer of the virus is taken from the cellular bilayer after some modification by the addition of some membrane proteins, a virus cannot synthesize its own envelope.

If the virus is normally enveloped, it'll be somewhat weaker, because the loss of its envelope will make it nearly noninfectious, since it needs some of those membrane proteins to infect cells.

→The transfer of this kind of viruses between people is harder, because they lose their integrity easily, or lose their infective ability by losing their envelope which makes it easier.

→The nonenveloped (naked) can stand most, if not all of the conditions the enveloped can't. They can move through the GIT without losing their infective abilities, they can stay in a dry food for a long time, so it's easy for them to transfer through eating.

The transfer pathways of enveloped viruses are usually wet, respiratory droplets for example. anything that disturbs the lipid bilayer, would kill the virus.

Box 36-4 Virion Structure: Naked Capsid

Component
Protein

Properties*
Is environmentally stable to the following:
- Temperature
- Acid
- Proteases
- Detergents
- Drying

Is released from cell by lysis

Consequences*
Can be spread easily (on fomites, from hand to hand, by dust, by small droplets)
Can dry out and retain infectivity
Can survive the adverse conditions of the gut
Can be resistant to detergents and poor sewage treatment
Antibody may be sufficient for immunoprotection

*Exceptions exist.

Box 36-5 Virion Structure: Envelope

Components
Membrane
Lipids
Proteins
Glycoproteins

Properties*
Is environmentally labile—disrupted by the following:
- Acid
- Detergents
- Drying
- Heat

Modifies cell membrane during replication
Is released by budding and cell lysis

Consequences*
Must stay wet
Cannot survive the gastrointestinal tract
Spreads in large droplets, secretions, organ transplants, and blood transfusions
Does not need to kill the cell to spread
May need antibody and cell-mediated immune response for protection and control
Elicits hypersensitivity and inflammation to cause immunopathogenesis

*Exceptions exist.

3) cell injury and clinical illness:

Cytopathic effects

Mechanism	Examples
Inhibition of cellular protein synthesis	Poliovirus, herpes simplex virus (HSV), togaviruses, poxviruses
Inhibition and degradation of cellular DNA	Herpesviruses
Alteration of cell membrane structure	Enveloped viruses
Viral glycoprotein insertion	All enveloped viruses
Syncytia formation	HSV, varicella-zoster virus, paramyxoviruses, human immunodeficiency virus
Disruption of cytoskeleton	Nonenveloped viruses (accumulation), HSV
Permeability	Togaviruses, herpesviruses
Toxicity of virion components	Adenovirus fibers, reovirus NSP4 protein

Uses the machinary of the cell to synthesize its own proteins.

Modifying (e.g. adding glycoproteins) the membrane because it needs to take parts of it with it, or to hide itself from the immune system (remember, they would cause some cells to decrease presentation of MHC 1)

Through the formation of inclusion bodies.

Sometimes once viral replication starts, cells would undergo apoptosis or necrosis.

Know the Effects not necessarily the viruses.

→There are many ways a virus can affect a cell, but the most damage we observe is caused by our body's response to this virus, not by the virus's mere presence.

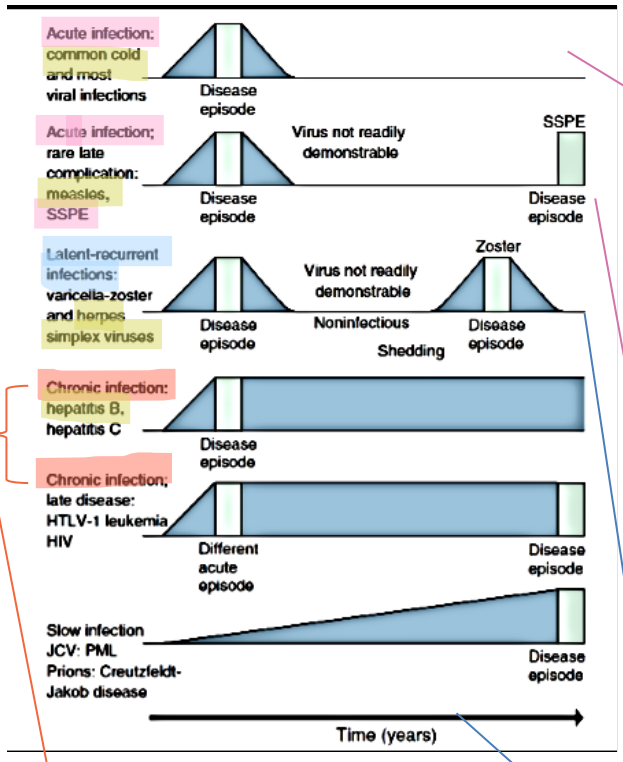
4) recovery from infection.

Now after the virus has arrived and an immune response was initiated, there are multiple possibilities of how it'll end:

a) the host can overtake the virus, recover from infection.

b) the body cannot take over (destroy) the virus so it persists chronically for life.

c) the virus overtakes the body and the host dies.



The time scale

Chronic, it **replicates**, shows a **disease episode** and persists life long, sometimes it causes damage by actively replicating for a long time enough to cause a new disease episode e.g. HIV, 1st episode causes flu like symptoms, then the virus keeps replicating, years later AIDS shows, after destroying so many leukocytes (WBCs).

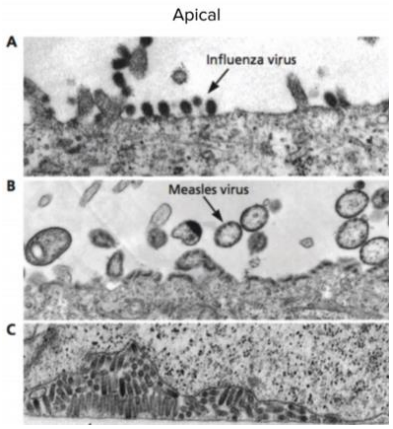
The blue colour means an active replication of virus (without symptoms, infection but no disease), then we have a disease episode with symptoms, after the episode, the virus is still present but it's not injurious enough to cause **symptoms** and the immune system will gradually contain it. In Acute infection cases, it comes then goes, but in some cases it could relapse.

Virus can persist in a latent form (after disease episode) not actively replicating, but suddenly a disease episode would show caused by the damage it made while hiding e.g. measles then SSPE.

Acute episode, system controls it, and then the virus goes and hides somewhere, but after a while it starts to replicate again, causing another disease episode, 2nd episode manifestations could be different or similar to the 1st and it continues in this manner life long. e.g. (HSV1, 2nd presentation in the form of cold sores that fade then reappear, although the 1st form of infection is mild pharyngitis or stomatitis).

It hides by going to a differnet type of cells (spinal neurons where it causes no symptoms), but once the immune status decreases, it relapses.

SHEDDING:

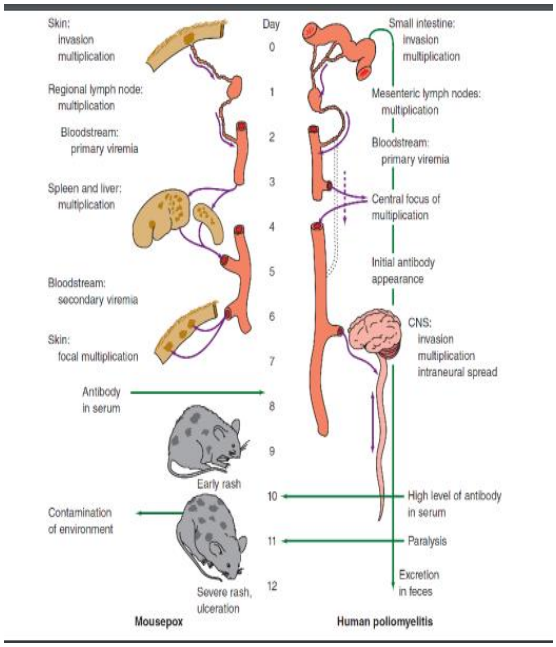


'' It represents the time at which an infected individual is infectious to contacts''

There's another stage called **shedding**. It could happen all throughout the disease. the virus damages the tissue and some of the replicants get out. These viral particles could be infectious to other people.

For example: a virus could damage the respiratory epithelium, so the respiratory droplets that got out will contain viral particles, because the virus starts shedding from cells. And these are infectious to other people.

• Shedding is important to maintain a viral infection in populations of hosts. In some viral infections, such as rabies, humans represent dead-end infections, and shedding does not occur



This picture **illustrates the steps of viral infection** as studied on mousepox, which has similarity to human polio virus,

First step is: the primary infection , where the virus gets introduced into the host to the primary site of infection (here it's the small intestines by ingestion) and replication.

Then , it moves from the primary site of infection through lymph nodes to the blood stream **(viremia).**

Critical point here: in the viremia step, if you are immunized to the virus (by vaccination for example) the virus will be neutralized by the pre-existing ABs in the blood stream and it won't cause further infection.

if not, it'll spread with the blood, reaches other organs, replicates more sending more viruses for a secondary viremia, they reach their target tissue, causing cytopathic effects that with the aid of the immune response would damage tissues even more and show more symptoms.

Good luck