**Sheet no.: Last year slides, Medical Virology
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\*Not all viruses replicate with the same mechanism, it depends on the virus whether it is double or single stranded DNA/RNA, and if it's positive or negative strands, etc. (This lecture and the previous one gives you general information about all types of viruses).

-Viruses cannot easily establish infection in our tissues, whether in the respiratory tract or GIT or skin, we are exposed in fact always for many types of viruses, but only small number of viruses can be established in our body and do the infection.
-Not like bacteria, which some of them can be as part of the normal flora, viruses rarely can be part of what we call normal virus flora in relation to our body, for example there are no viruses in the respiratory tract that are considered as part of the normal flora. We have in the respiratory tract or genital tract or intestinal tract certain types of viruses which can be present for a short period of time, but they are not necessarily present with infection. In addition we have certain types of viruses which produce latent infection in our body, such as herpes viruses and HIV and cytomegalovirus and other viruses like hepatitis B,Cwhich might establish a chronic infection in our body.
But in general, the number of viruses which resides in our body is very few in contrast to bacteria.

\*Why viruses cannot easily establish infection in our body?
-Because we have physical barrier (skin) and immunity in general (innate immunity). Viruses can only multiply in a living tissue (not in a dead tissue), therefore it's not easy for a virus to attach to our skin and produce infection without the presence of abrasions (skin integrity must be destructed for infection to occur), but in fact we are always exposed to many minor injuries/damage to the skin which might allow certain viruses to attach and later developing infection if the virus reached the subcutaneous tissue. For example we have the human pappilomaviruses which are associated with variety of diseases which we will mention later. Also we have herpes virus which mainly establish infection in the mucosa (oral cavity mucosa, and genital tract, etc.), but it might start the infection in the skin if the infected person got in contact with another susceptible person (the virus can be transmitted to the hand of the susceptible person), this is well known in dentists with minor cut or abrasions in their fingers, which they might acquire the infection from the oral cavity of their patient during dental manipulation.

The other aspect of infection of the skin is related to insects "mosquitoes" which might carry very dangerous viruses especially from tropical countries such as arboviruses which are associated with the CNS, and there are dengue viruses which is also related to tropical countries which can produce a thousand to a million case of infections only by the inoculation of the virus to the skin by the insect bite.
Don’t forget that viruses are not only transmitted from virus aerosols to the respiratory tract by inhalation, but there are some animals that have viruses in their oral cavity and can transmit them to people by biting, for example rabies virus which is associated with dogs and cats and some other animals. There are 5-6 cases of people that are infected with rabies virus each year.
\*\***Nevertheless, the respiratory tract infections are considered the main source of infection for the majority of the human pathogenic viruses.
\*\* 70-80% of viral infections are associated with the respiratory tract of humans.**The group of respiratory viruses includes: influenza viruses, rhinoviruses, adenoviruses, respiratory syncytial viruses and many other viruses.
-In order for the virus to establish infection in the respiratory tract, you have to return back to what we have mentioned before in the mechanism of infection of intact living tissue and mucosal and epididymal cells.
-Any type of virus cannot establish infection in the respiratory tract without the presence of specific surface antigen epitopes attached to surface antigen receptors on the mucosal cells (the virus must carry specific antigens and the mucosal cells must have specific receptors for these specific antigens in order to have an interaction between them), and later the virus will start slowly invading the epithelial mucosal cells developing the infection.

But this doesn’t happen easily, for example it's not necessarily if you got exposed to influenza virus to establish infection. Only few percentages (about 3-4%) of people who are exposed to the virus develop what is called over clinical disease (clinical disease of influenza), why?
Due to the fact that our mucosa usually resists the infection, how?
There is an immune-defense mechanism that is divided into specific and non-specific defense mechanisms, especially the IgA antibodies in the mucosa are highly important in the defense mechanism. In addition to the cell mediated immunity (T-cell immunity)which might also resist the infection to some extent. Resistance is much better in people that got infected again with the same specific serotype of a virus than people infected for the first time with a new serotype of a virus, like in children infected with mumps or rubella or measles, which once they are infected they develop humoral antibodies and specific T-cell mediated immunity and this will suppress the infection and you are protected!
IgA antibodies are more specific than IgM and IgG antibodies. Many viruses before they reach the blood stream, they must be first attached to the mucosal surfaces and must replicate and produce inner virus particles to produce damage to the infected cells and then might be carried to the bloodstream or might spread via the lymphatic system.
Certain viruses like influenza viruses cannot easily spread to the blood, the infection will remain in the infected mucosal cells, and therefore **rarely** you recognize the presence of the virus in the blood.

-In relation to the **GIT**, we are lucky to have high acidity in the stomach, because this high acidity will filter the majority of viruses that can be swallowed by eating or drinking, except the latent viruses, these viruses can tolerate a pH from 1.5-2 and might escape and reach large and small intestines and establish the infection.
In addition to stomach acidity, we have another important fluid secreted in the small intestines called bile solutions which are secreted in the bile duct and only affects the enveloped viruses. Why it affects the enveloped viruses and not the non-enveloped (non-capsulated) viruses?
Because the envelope is composed of large amount of lipoproteins, and lipoproteins can be dissolved by bile salts, whereas the non-capsulated or non-enveloped viruses can escape the acidity of the stomach as well as bile secretions and might reach the small and large intestines developing specific types of diseases, for example poliovirus which belongs to enteroviruses that might produce latent infection in our bodies (a very serious disease), and there is another virus that is related to enteroviruses which is hepatitis A.

-In relation to the **genitourinary tract**, not all viruses can attach and can produce infection within the genitourinary tract. There are some viruses that can be disseminated in the GUT and goes to other part of the body, such as cytomegaloviruses, and that’s in relation to the antigenic part of the virus. Also herpes virus grows in the oral cavity and in the genital tract cavity, but not in the intestinal cavity, because the virus cannot establish infection in the mucosa of the intestines and the virus usually will be filtered before reaching the intestines.

-In relation to the **conjunctiva**, the conjunctiva is the MOST common site which might acquire a variety of viruses, more than the respiratory tract and the GIT and the GUT. Conjunctiva viral infections might result in systemic infections. Examples on viruses that can be acquired via the conjunctiva are adenoviruses and herpes viruses and enteroviruses, even the influenza virus.

-In relation to **blood**, it's not easily for viruses attached to the respiratory tract or GIT to reach bloodstream, there are certain viruses that reach bloodstream. Viruses that are inoculated directly into the bloodstream (not reaching the bloodstream through GIT or respiratory tract, etc.), those viruses are transmitted by a special arthropod vectors especially mosquitoes like dengue viruses and arboviruses and others.
Unfortunately we have some viruses that are transmitted through blood transfusions which can be associated with certain types of fatal viral infections such as hepatitis B and C as well as HIV and cytomegaloviruses, that was a problem in the past but now it's under control. And we as dentists must be aware of those types of infections during oral manipulation, especially if we have cuts in our fingers.

Again, the spread of viruses in community (and among the population) is such a tricky topic due to the presence of susceptible and non-susceptible people, people that can respond by the production of specific cell-mediated immunity which results (to some extent) in stopping the spread of viruses.

Generally, the genes plus the basic immunity in each individual contributes in the susceptibility and the resistance of that individual to the infection by the virus, which means that it's not necessary that a group of brothers would have the same recognition to a pattern of infection by the virus, one brother might be susceptible and the other not. So, there are a lot of factors that contribute.

-Keep in mind that, once a virus reaches the blood stream, we have to expect (just like in the case of bacteria) the presence of VIRAEMIA; living virus particles circulating in the blood stream, they could be thousands, millions. And often, the primary viraemia might extend for a short period of time in the blood of the infected person, why?

Because the human body usually responds by the production of specific antibodies and those specific antibodies enhance the opsonizing and the killing effect during the phagocytosis, etc. and by that we will get rid of a large number of viruses. But, primary viraemia might be only for a short period of time, for example, measles, mumps, and rubella. And later, it might disappear and manifest in the form of other body infections, in the skin, or other organ tissues, but notice that the secondary viraemia is very rare (few).

-Now, what actually happens is this:

The infection is established first in the blood stream for a short period (few days to few weeks) and later, it disappears from the blood and manages to spread to the CNS or to the mucosal system,…etc. or to the skin, and return back through the lymphatic channels to the blood stream and produces a secondary viraemia, such type of viruses are the most dangerous ones, because the secondary viraemia is usually associated with severe damage in various parts of the body, for eg: the rabies virus which will specially affect the CNS, causes severe damage and fatal outcome sometimes.

Now, the immune-response of the viruses;

 as we know from the bacteria, that usually all types of bacteria which produce inflammation in any part of the body( because our body's usual response is by means of inflammation)increase in the inflammatory cells, and this can be manifested and recognized by the presence of wounds on the skin for example, abscesses and so on. But in the case of viruses you might not recognize these features, even, the fever might not be associated in our immuno-defense, not any major clinical sign or symptom is associated with the immune response, for that reason, generally, viral infection might produce very mild asymptomatic infections without being recognized.

NOTE: Humans are exposed to a variety of viruses and only a few numbers might manifest to a clinical disease and this is due to specific (antibodies) and non-specific defenses.

Our body's response by the production of specific antibodies protects us (to some extent) from the infection by viruses, the SPECIFIC and the NON-SPECIFIC defense mechanisms are important.

Now, viruses in the respiratory tract (for example: influenza virus), can establish the infection, but if we already have memory cells that can know this type of virus, this means that a specific antibody would be available and that specific antibody would inhibit the replication of the virus with the help of the T-cell immunity of course. And by this the virus will not result in a clinical infection.

And what we mentioned above is what usually happens in the case of respiratory viral infections (THE MAJORITY), only a few percentage develop clinical infections. Therefore the mucosa of our respiratory tract usually contains secreted IgA antibodies, IgG, complement and with certain enzymes. And it can easily enhance the production of T-killer cells with of course the general immuno-response to protect us against the establishment of infection. But, if the virus managed to establish infection in the mucosa of the respiratory tract (as an example), it might later spread in to the bloodstream and produce viraemia or it might spread to the lymph system and from the lymph system (producing inflammatory reactions) and might reach again the bloodstream and produce viraemia, here we might recognize the clinical features of the disease, but at the same time, our body will always (in immuno-competent people(healthy individuals)) enhance the production of T-cell mediated immunity as well as the specific antibodies.

NOTE: if we compared the viruses with the bacteria, the viruses enhance the production of specific antibodies within 1-2 weeks, whereas the bacteria; at least 2 weeks- 10 weeks in order to recognize a high titer (high level) of antibodies against the invading bacteria. This means that our body can easily produce more specific antibodies against viral infections than in the case of bacterial infections. Therefore, the general duration of infection with the viruses is shorter and often, there is no need to have a specific treatment, whereas in relation to bacteria, individuals may die when not treated with specific antimicrobial drugs and you cannot rely here on your immuno-response to produce sufficient amount of antibodies, phagocytosis, etc.

Generally, in the developing of immune response; the specific antibodies, they are directed against the specific viral epitopes (the surface antigen determinants (glycoproteins), like in specific viruses, we have specific spikes composed of glycoproteins, so, if our specific antibodies managed to interact with these, then the virus can't develop the mechanism of encoding and replication within the infected cell, it will be outside the cell, it will not manage to enter the cell and this is the most important, but, these surface antigens (glycoproteins) should be known in our memory cells, which means that we might have been exposed in the past with some sub-clinical doses of the virus which means that a few number of viruses might enhance the production of those specific antibodies and that will protect us later against more attacks from the virus particles, so, it depends on our history, if we were exposed or not by these viruses, and this is why we are (to some extent) immune against certain viruses specially the ones that are largely distributed in the nature, for example the rhinovirus.

NOTE: normally we have resistance against certain serotypes which are distributed in the community.

In addition, if the virus managed to reach our blood, the mechanism which we already mentioned happens (enhancing the opsonizing by the presence of the cytokines and the macrophages…etc) which can easily stop the replication of the virus, and even if the virus performed its action it'll be lysed by the help of the complement system eventually.

So, to sum it up, we have immunocompetent people which manage to stop the infection and to get rid of the side-effects. And we also have the host-immuno-deficient people which have a defect in the immunity system especially in the activation of the T-cell mediated immunity and also a defect in the production of specific antibodies and the enhancing of the opsonization. Those people can easily be affected by the virus and sometimes the end-result might be very severe (fatal outcomes). So it depends mainly on the basic immunity of each individual.

\*INTERFERONS:

They are the first non-specific defense mechanism in the response of viral infections, although they cannot directly affect the viruses, for example it cannot affect the presence of the specific antigen epitopes, rather they (the interferons) change the structure of the infected cells, so they actually prevent the infected cells from the completion of the process supporting the virus which means INHIBITING the virus, because the infected cells proteins and enzymes will be defected (to some extent) by the interferons and by this, the cycle of the living virus would not be completed, because those enzymes and proteins were necessary for the completion. (Make the infected cells resistant to the viral infection).

In addition, they (the interferons) activate immune system and therefore cells like the natural killing cells and macrophages.

NOTE: interferons are directed against any microorganism (bacteria, parasites, fungi) not that specific to viruses. They are general.

Not all people produce the same amount of interferons and this is important especially in relation to viruses.

The interferons might also attack the glycoproteins (which are found on the viruses) INDIRECTLY and it also may help to produce certain specific antiviral proteins (in addition to the already existing proteins in the cell that are antiviral) which help in inhibiting and stopping the replication of the virus in the infected cells, because of that, the interferons might play a role in certain malignancies, it may help in the control the development of certain malignancies.

\*we have THREE types of interferons:

1- ALPHA-IFN: produced by blood mononuclear cells; neutrophils, lymphocytes. And here we have many subtypes; it is also the MOST IMPORTANT TYPE in the infected cells with viruses.

2-BETA-IFN: produced by the fibroblasts cells. It works along with the alpha.

3- GAMMA-IFN: produced by the T-lymphocytes as natural killer cells in response to specific antigenic signal.

These are not that important in the defense against the viral antigens; it will indirectly activate killer cells. In short, the interferons will not directly interact with the viruses, it will rather be directed against the infected cells, and once the infected cells stop producing the specific proteins and enzymes that help the viruses replicate, the viruses cannot survive and it will be diminished.

Please refer to the slides for more understanding.