Immunology
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Lecture No -57
Active and Passive Immunity and Vaccination (Contd.,)

So, welcome back for the continuation of active and passive immunity and vaccination. You are going to continue what we are discussing in the last lecture.

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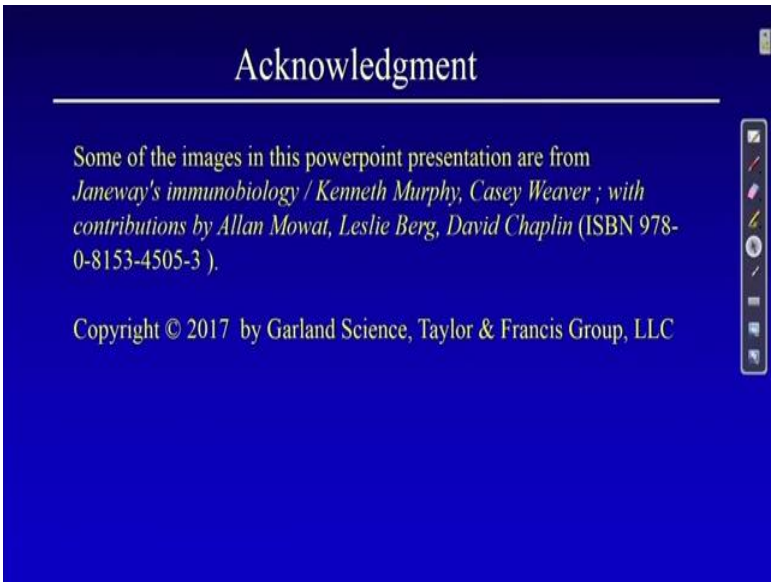

So this is the routine acknowledgment like, definitely I am very much using many images and slides from Janeway's Immunobiology books.

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And in continuation like what we are already discussing, vaccines can be based on attenuated pathogens where material from killed organisms. Whichever is possible, whichever is available depending on that and advantage disadvantage that will come right both of them has a problem.

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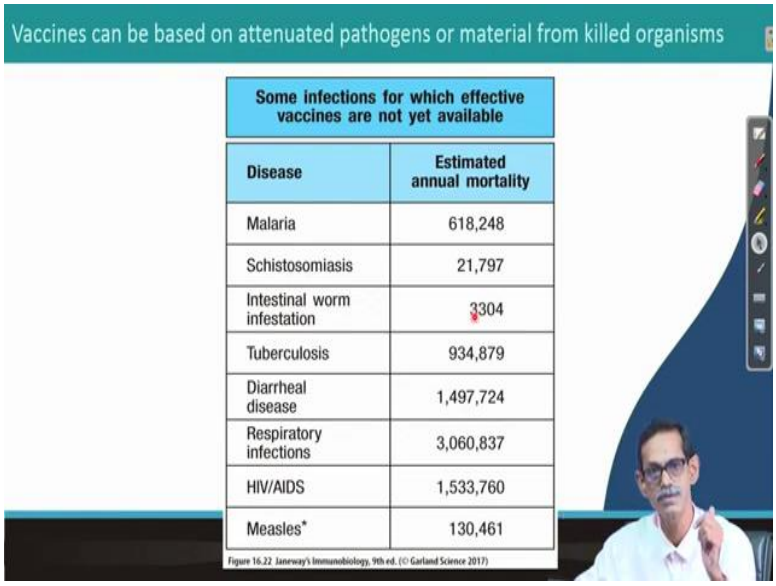

But before going to that what I would like to say is that even if we know there are so much vaccines and it is so simple to discuss like you kill the virus or make attenuated or whole organism or subunit vaccine make it do the primary injection, so the body will give the protection. No, it is not that simple because the organisms are even smarter than that. So they can somehow bypass the immune system in such a way the vaccine does not work.

Everybody is particularly this year when I am taking this course, this your whole world is under a pandemic of Covid-19, all over the world is trying to develop vaccines, not only that Covid-19 is a very recent outbreak. But before that old disease like malaria, you see the right hand side what we are showing here in this table, this is the name of the disease and this is the estimated annual mortality rate.

You see the Malaria, there are almost 618,000, Schistosomiasis is not much but it is a very painful disease. Intestinal worms, very little but child are suffering for that. Tuberculosis 934,000, diarrheal disease, it is 149700 almost 15 lakhs, Diarrheal disease many times kill individual, it is a lot of casualty happens but most of the time Diarrheal disease like where there is some vaccine infection, viral infection or a parasitic infection like amoebas Giardia, protozoan parasite infection.

It is not killing the individual but it is killing lot of man-hours. So a lot of people are suffering from this diarrheal problem all over the world and you can see the number. So we need a vaccine, a real vaccine, not only to save the people from death or casualty but also a lot of individuals are losing man-hours because of the stomach upset. Respiratory infection is a huge number; Corona is one of them, HIV, AIDS.

Measles, so these measles have vaccines are there but not 100% protective. So what happened these diseases still people are trying to develop vaccines. So it is not that theoretically production or making vaccines is very simple and easy and straightforward but it is not a real case, scientists are trying all over the world for many such diseases, so that vaccines can be developed. We are not as lucky as smallpox and we are going to be lucky for another disease very soon.

I am sure that the World Health Organization is going to say that polio is eradicated from the earth. Just like the smallpox was declared long time back 1979. Polio is going to come back in the same way, we are going to see there is no polio, I mean there number of polio patients are very rare now but it is not zero. So until unless it is next ten years there will be no infection we cannot say that it is eradicated, so you are waiting to hear the good news from the World Health Organization.

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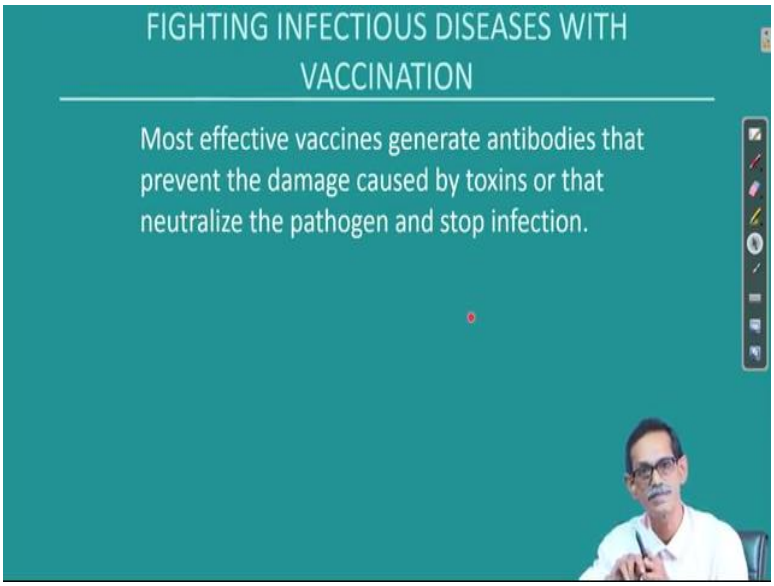

So most effective vaccine generated antibodies and what the antibodies are doing, you know the effect of function of antibodies what? The effect of function of antibodies is neutralization of the toxins because if there is any toxin they will bind a neutralized so the toxin cannot find opsonization separation or kill the bacteria from the system and complement activation. So somehow it stopped pathogenicity and infection, it will remove the existing one, it will clear the toxin.

Our goal will be to produce a vaccine candidate so that it can induce the humoral immunity much more so that in normal bacterial infection cases, humoral immunity much more so that it can effectively work against bacteria. But if it is in case of the virus, definitely humoral immunity is very important because antibodies can neutralize the virus particle also, but at the same time we have to induce the T cell immunity so that cytotoxic T cells can kill the virus infect itself.

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So this is one, another or few more points of the good vaccine candidates or it should be long lasting protection, it is not the one vaccine, I mean many vaccines you will see particularly the tetanus vaccine. Every time there is a cut we go to the doctor they ask when did you take the last time. It is definitely improving but their memory or their effectiveness is not that long.

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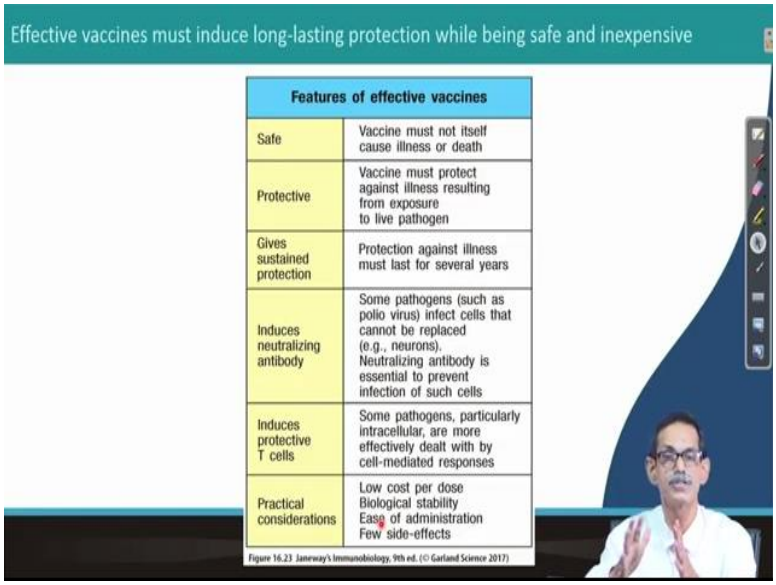

There are few things we have to remember during production or synthesis or discovery of the vaccine. One it should be definitely safe, vaccine must not itself cause illness or death. So initially at the very beginning what happened before 1900 or very early 1900, the regulation or the act was not that strong, I mean when all this Pastor and Jenner when discovered and many

others when discovered the different vaccines the regulation actors not that strong but now it is very strong.

I mean we cannot have a single casualty if possible we definitely should, so it should be safe, it should be protective like a vaccine must protect against the illness resulting from the exposure of the light touch and that is the purpose gives us stain protection that just I told, it should protect for several years. Many vaccines you have to take every year for different reasons, some are not good vaccines or some infectious agents are changing like the influenza virus.

Every year there is a new outpost of a new variety, so the old one is not working, we have to take it. Nothing doing; but some vaccines does not work properly or not sustainable so that we have to take again. Induces neutralizing antibodies that I just told it should induce more antibodies so that it can neutralize a toxin or the pathogens that will give better immunity. Induce protective T-cells that I just told in case of virus it should give the protective T cell immunity.

So that not only virus if there is a intracellular pathogen, you know (())(08:18)) Mycobacterium tuberculosis, Mycobacterium leprae which is grow inside the macrophage. Then we need Th1 response, so in that case if you would like to develop the vaccine so we have to manipulate in such a way that particular vaccine should induce the Th1 response as soon as new infection comes.

It is not the T-cell is not the only virus infection we need cytotoxic T-cell, Th1 is also important and definitely T helper cell is important everywhere. And practical considerations that are very important, it should be low cost, it should be biologically stable. It should be easier ministration and may have zero or minimum side-effects, few vaccines have certain side effects, these are also important.

It is a management problem, we may not think at this moment we may not consider that but this is a serious problem, in fact I will not continue it again. Suppose developing a vaccine or discovering a vaccine inside the lab testing 5-10 animals or a thousand individuals is one thing.

Thousand individuals is also a big scale but when you see the total population like in this moment, at the present time like the whole world is affected with corona virus or the Covid-19.

So if we develop a vaccine it is not like one two thousand people, everybody needs to have it, so first thing is identification development the research part, then you have to produce that much amount of the product so that you can distribute it. Not only that from the production side to the extreme corner of the country like where there is no maybe good electricity or may not have a good roads to reach there.

So their stability here and most of the time vaccine as a protein or the organism it should be in the cold, many parts of the country or many parts of the world there is no electricity and even electricity is there, no guarantee like how long it will stay. So the maintenance is very very important and if the vaccine is not maintained throughout their life properly it loses its activity, even immunization you may think the vaccine is administered but it will not do its own job.

So that production, supply chain management, huge everything else is important. Second, ease of administration is a very very important thing. Why it is important, because many times we see that vaccines are administered by injection, even if simple injection is also not cost-effective. You need a syringe, you need a needle, you need some alcohol and in the expert hand, if it is oral or a nasal, you take just one or two drops anyone can do that.

You can train how to do this in 5 minutes. But training or giving the training to someone how to inject if it is muscular is fine, many ways you can do it administer the vaccine candidate, it may be intramuscular, intravenous, subcutaneous, peritoneal, oral or nasal. So best is definitely oral and nasal, intravenous is more critical. It takes a lot of time and the person who is going to give the intravenous injection needs to have real good training.

Development of vaccines, this route of administration is also important, and route of administration is important for another reason.

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Let me talk this one, I will continue this. Live attenuated viral vaccines are more potent than kill vaccines. Why? Because killed vaccines and how does the virus immunity grows? You remember again I am repeating and that is how come the knowledge of immunologists little bit required. Viruses go inside the cell; viral antigen is presented by MHC1 which is recognized by the T cell. So now if you inject the dead cells or dead virus what will happen?

That will be recognized by a B-cell. It is fine but the T-cell, how the T-cell will recognize because that virus is not going to grow inside, they are not going to grow in any antigen. So there will be no MHC1 presentation, no cytotoxic T-cell activation, so half of the immunity is closed. Am I clear? So heat killed viruses is not going to produce any or synthesize any protein if they do not synthesize any protein, no more antigen presentation by MHC1.

If MHC1 is not doing that cytotoxic t-cell activation is not happening, the antibody production is fine right. So half of the immune system is not working against that. So any cytotoxic T-cell memory is not going to be there, but in just in other cases like the live attenuated virus what will happen? The live attenuated virus, in that case they cannot make the disease but they can activate the immune system.

Because they will go inside, they will grow and produce the protein do the MHC1 presentation and rest of the thing will be only difference they are not causing the pathogenicity or the

manifestation of the disease. So that way heat killed is more safe, definitely more safe than the attenuated because there is always a chance to come back if there is a natural mutation. But it is not that effective.

Same way the route of administration is also important. I am giving the example, similarly. Suppose one particular virus is infected through nasal infection, now this time again I am taking the current situation like the corona virus whether it is a not necessarily Covid-19, SARS, MERS, Influenza virus what are they doing? They are infected to the nose. So the immune system is going to see them in the lung and other respiratory regions first.

But if you make a corona virus or the SARS or the Influenza virus surface protein purify, make a subunit protein and inject into muscle, so the natural path is disturbed. So whatever the immune system is supposed to do in case of a virus which infect the lung and if the protein is seen in muscle that will not give the real or cannot mimic the real situation, so that way the administration route is important.

Some bacteria say Salmonella or there in the throat and some bacteria cause disease in the alimentary canal, so if you inject that protein into muscle, the protection of the alimentary canal which we need the IGA mostly because that is the only one secrete, that response is not going to happen, if the immune system the real basic what we are doing actually we are trying to mimicking the whole system as if some natural infection happen.

Natural infection will not happen by injection and needle in the muscle most of them right, so live attenuated virus and the natural path of administration is always better. But this is not always possible, it is definitely the oral administration that is easier that we just discussed I am not talking about that but biologically or in immunological point of view live attenuated virus and real root of infection if that can be done is best.

If anything in elementary canal; either the fecal or the oral route will be the best way to administer the antigen because that is the place where it is a natural habitat in an individual. So live attenuated virus what we use actually in today's date is the polio measles mumps rubella and

varicella, so all the childhood immunization after birth most of the immunization, this polio measles mumps rubella and varicella are very slow we do not do it here in our country, but this is the childhood vaccination.

In adults also we do in some special cases not always, other attenuated live viral vaccines that are licensed for special circumstances for the use of a high risk population that pox virus, yellow fever virus, in some cases. Because when you are using vaccines we are assuming that the individual whom I am going to be vaccinate is immunologically perfect. So that is not always true there are a lot of people which are immuno compromised.

They do not have an immune system working for many reasons such as those who are under immunosuppressive drugs and in case of any disease mutation of disease or other disease HIV infection their immune system is already down. So their T-cell, B-cell is not working properly, so vaccine is not always going to work for them, vaccine is only for individuals who have good immune system or at least moderate immune system

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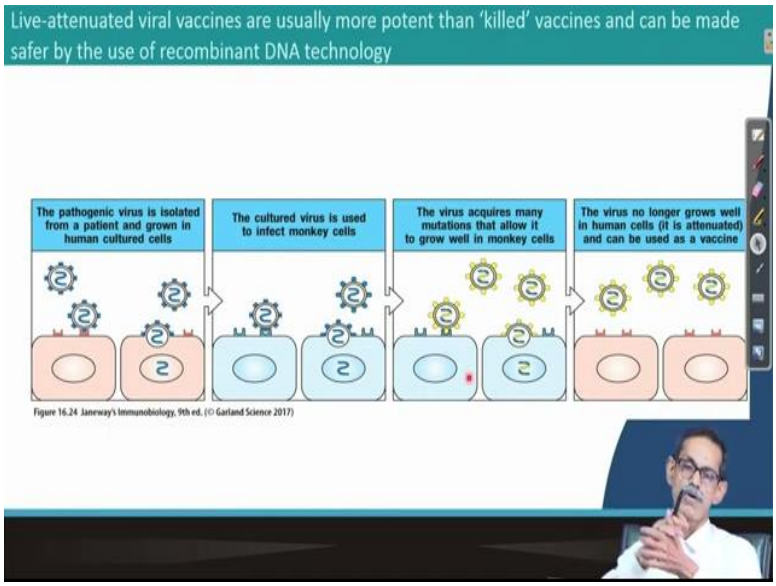

So how do we make the live attenuated virus? Major practice or the best way to do that is a common practice I should say, the common practice is say this is the human pathogenic virus. So what we do is we cannot use a human as a reservoir or the farming organism. So we grow animal cell in culture or laboratory, we incubate the virus along with the animal cell so it infects grow

and normal cycle, what you have we have to grow the cell and supply the virus, so more virus will come.

After culturing the virus in human cells you take this it does not always happen in this case everywhere, in sometimes some virus grows in egg cells also. That is how I put in may contaminate particularly in case of the poliovirus, so if you take these viruses initially grown in animal cell transfer it to monkey cell, human cell line and monkey cell line are not the same, they will also infect. When they are growing monkey cells for a long time what will happen, the change or they will have some mutation so that they can better fit in the monkey cell.

While growing in monkey cells what will happen is that they will change itself so that it will grow better in the monkey cell during that process it loses the pathogenicity to infect humans. So these viruses no longer grow well in human cells that is called attenuation, clear? So human viruses were initially cultured in human cells, they were happy, suddenly the target or hostile change, so they grow slowly and after that they change themselves so that they can grow better.

But while doing while acclimatizing them or adjusting or adapting them in the monkey cell they lost that pathogenicity or the effectiveness against the human cell or human. So that virus we can use, this is called attenuation we can reach that by recombinant way also.

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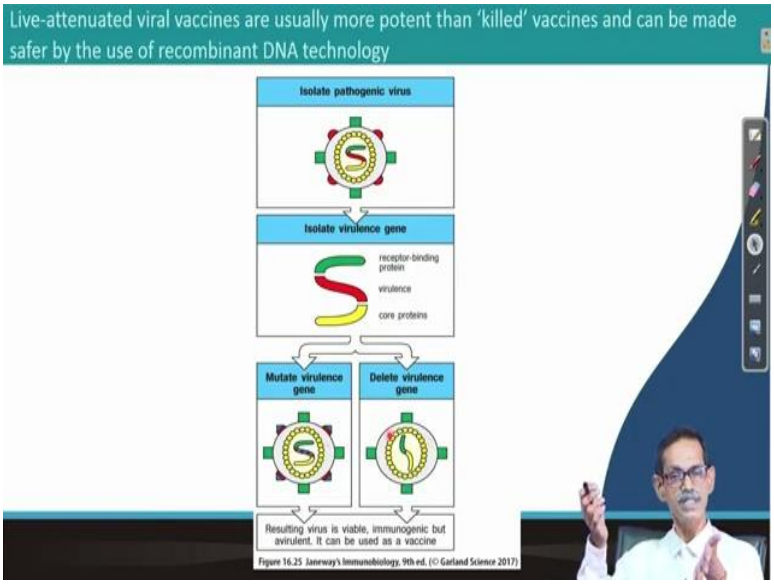

So suppose this is the virus and you see there are three genes say, for example one is green another is red, another is yellow, so just to simplify the whole thing, three color three genes are there. So in a recombinant way RDNA technology what we can do is, we can modify the red part you see red is one of the surface antigen. Say suppose by which it infects or attaches to the human cells. If we change this red part mutated in some way, you see here also that it was like a circular half circle and here it is a triangle.

So it changes the mutation or the protein structure in such a way so it will not express this red one as such it will change its shape and size, what you delete completely, the red gene completely deleted. So the virus become a different kind of virus that surface protein is not here, now these virus we will be newly generated virus coming in technology either this one modified on or deleted one, what will happen they cannot attack or infect the human cells by the or in one word I can say they will lost their virulencing, so they cannot cause a disease.

If this one is very unlikely that the mutation will revert back to its original form because it is not a single mutation but this both the virus will maintain its immunogenicity but lose its virulence, this way also we can make the attenuated virus.

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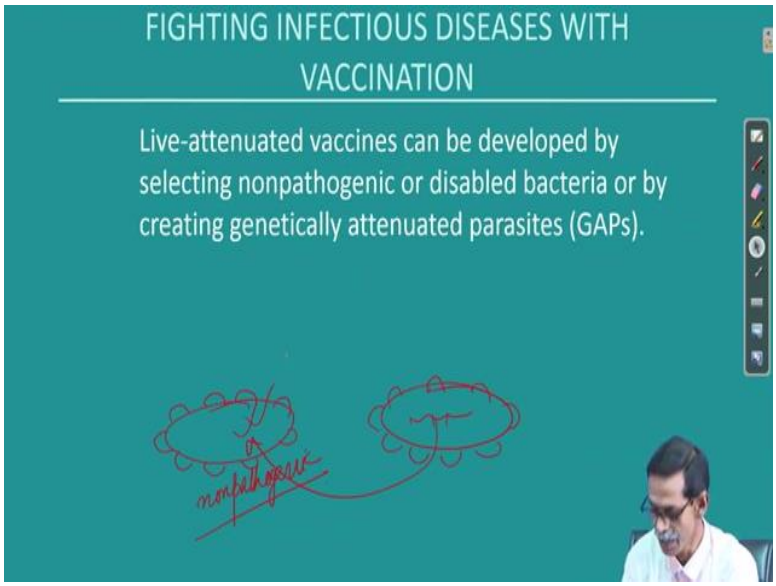

So live attenuated vaccine can be developed by selecting non-pathogenic or disabled bacteria or by creating genetically attenuated parasite, so attenuation this is one culture differently or you

can say that non-pathogenic bacteria you take a non-pathogenic bacteria or disable bacteria and make or express, so one variety which has a similar property but non-pathogenic, for example if we go quickly.

Suppose this is one bacteria, this bacteria or the set of bacteria is non-pathogenic this is non-pathogenic. But another bacteria which is pathogenic has some protein on the surface. So somehow I can say this is a natural mutant that we developed by recombinant technology possible. So naturally it lose its virulence but it does not have that particular protein, so what we can do we can take some DNA part from here put here.

So that nonviolent but it will express some immunogenic protein which can be similar to that, so these particular bacteria will have the immunogenic property like the virulence one, but it will not have any pathogenicity, that can also be used as a live and attenuated person.

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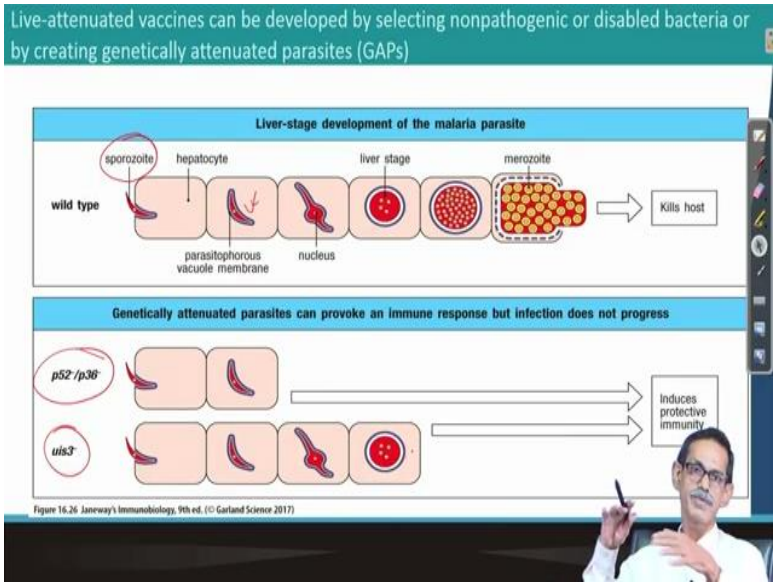

Another thing is safe parasites, what happened to malaria parasites? One of their lifecycle they grow in the saliva of the mosquito, from there the saliva of the mosquito when the mosquito bite there is a form called sporozoite that sporozoite come the wild-type person what happened, first they go to liver, it is a very interesting life cycle so any of you are interested further go and read the malaria parasite life cycle, it is very interesting but here is very brief.

So hepatocytes to liver and liver stage and then it makes the monocytes and that monocyte come out to the blood and start infecting the RBC. So now what happened by genetically an attenuated virus, it can be induced by mutations single mutation and double mutation, what happened? This mutation is given as a single mutation; this is a double mutation that happened, by this mutation in two different genes the sporozoite uses its effectivity to grow inside the hepatocyte.

So they enter but they cannot continue their life cycle. What will happen? So the sporozoite will remain the same and this particular cannot grow and proceed further, so no disease the same way as a single one it will go little more it will go out to the liver stage but cannot proceed further. So this is also a process by which we can make that innovation, so that the organism is exactly the same but one or two genes change their life cycle or the cell cycle here because it is a single cell so that they cannot cause the disease but can be used as vaccinations or immunizations.

And this is people are trying what the scientists trying to develop this way, there are many other problem in parasite that is why there is so far today then till to death, there is no vaccine available cover silly or approved vaccine against any parasitic disease not only malaria, no parasitic disease vaccine like malaria's, trypanosome, agre, amoeba, Kiko Moniz whatever Toxoplasma any protozoan parasite you name no vaccine is developed, so that means they are even much smarter than us or our immune system.

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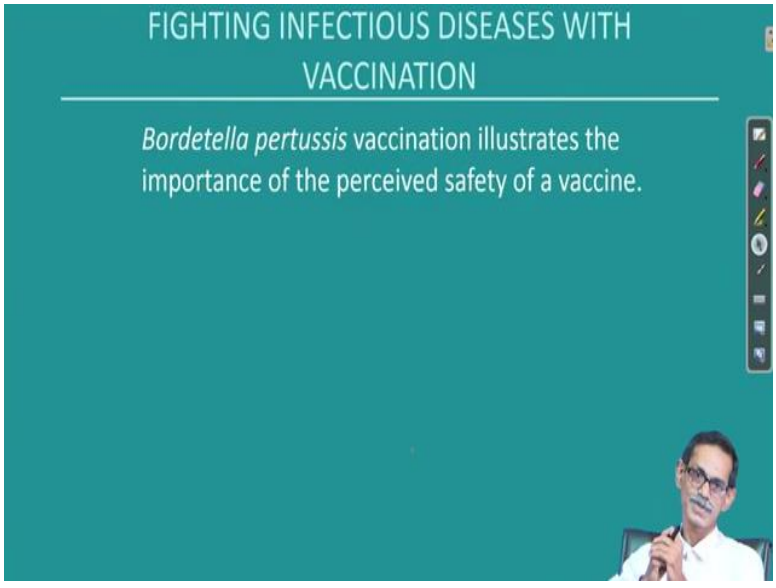

The route of vaccination is an important determinant of success that I already told discuss like why it is because original route of infection if we can follow that is the best, otherwise definitely there is some time we cannot do that, we have to take because something is always better than nothing, so without any alternative we do some other alternative route but best is the natural path by which it infects. This bordetella pertussis vaccination illustrates the importance of the perceived safety of vaccine.

This is what this is: the organism is a bacteria that causes whooping cough. Why is this line there? People realize, people understand that vaccine is very important, what we can understand now when I am giving the lecture in 2020, we know a lot about the immunology, we know a lot about the medical science, vaccination immunization but if you go back only 50, 60, 70, years people who are not aware of immune system much.

Antibody development was discovered, MHC discovered in 1958 only the first MHC reported people had an idea something is there, but what is that nobody knows in 98 or 99 I do not remember correctly, they may see one structure was determined first. So immunology is that way in still in infancy, immune system or immunology and even vaccination neither the scientist nor the general people were very much aware.

So people who are scared about whether they should get the vaccine because that time the subunit vaccine or all the modern generation vaccine system or technique was not there, most of the time the live vaccine or attenuated by chance. So the first one is the polio in that history, so people did not trust them, everybody was skeptical about what would happen if I took what would happen? But something if disease happens normally that nothing is doing but I cannot help but knowingly or purposefully.

I am injecting the pathogenic organism in my body and people are very cautious about it. But these discovery of this whooping cough before this vaccination a lot of people or children used to die, but when these vaccinations start in the childhood, it not every country accepted at the very beginning. Particularly in the case of Japan what happened it started in 1972, just 60 not 50 years back and in China the age of three months.

What happened, in 1975 one child died and as it is a Japan government stopped this vaccination, they said no it should not give them that early, it should be an adult age, so they started again and there is a five years of age of the kid. As soon as they stop this in childhood the mortality rate increase again, so then they realize no maybe one or two sporadic cases may happen, this may be for something else, they bring it back.

So this particular vaccine, the whooping cough vaccine or the bordetella pertussis vaccine actually tells the whole world that vaccination is very very important until unless you immunize your child, wait for the natural infection and get them immunity, it is not a wise decision. So, now I will stop here, I will continue the same topic and same storytelling episode in next class.