Medicinal Chemistry
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Lecture No 44
Tutorial -11 Drug Administration Routes and Finding a Lead

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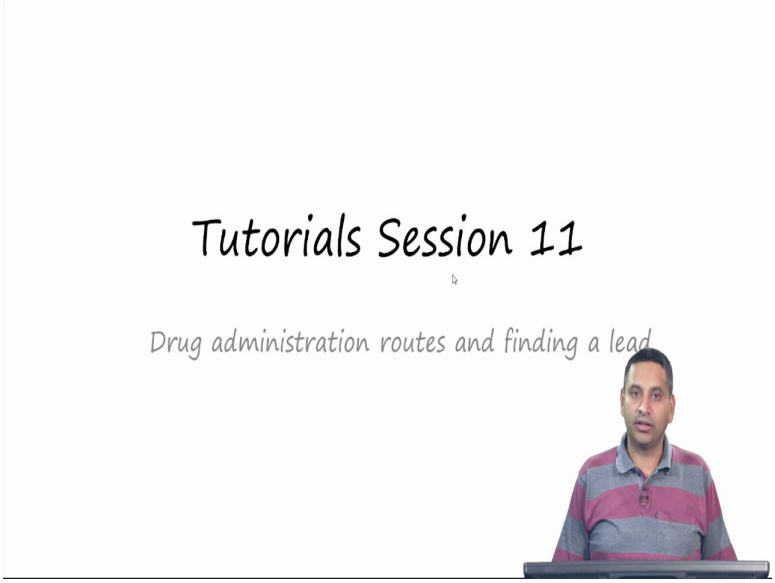

So in today's tutorial session we will be solving some problems related to drug administration routes in finding a lead.

So the first question here is

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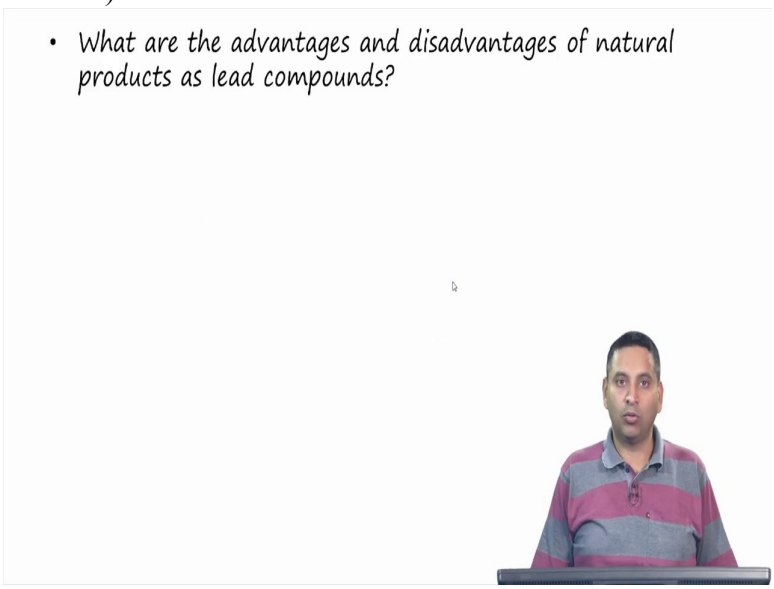

what are the advantages and disadvantages of natural products as lead compounds?

So in order to address this question let us go back to the topic that we discussed in the previous lectures.

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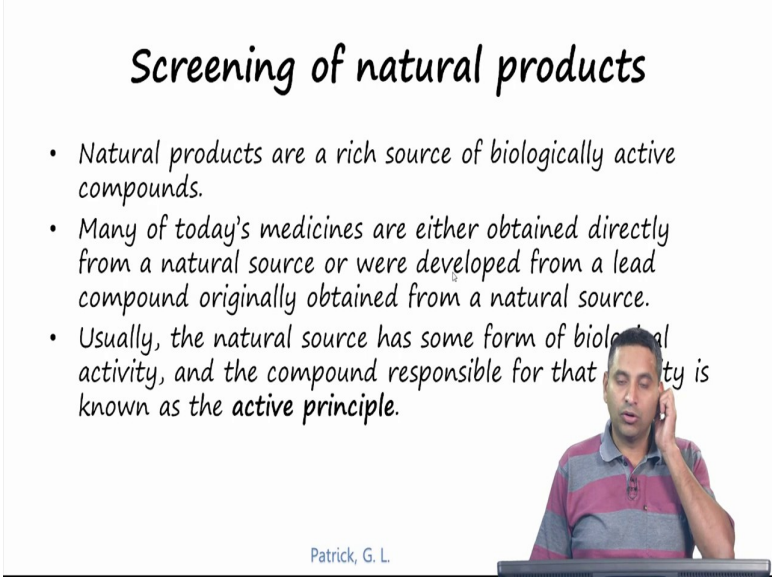

So screening of natural products is a very good way to identify biologically active compounds. And as we have come to realize a number of today's medicines are actually either obtained directly from natural source or were developed from a lead compound that is originally obtained from a natural source.

So the main component of the natural source that is active is called the active principle. So it is this active principle that we are really interested in because that is a single molecule that is going to have the desired biological properties.

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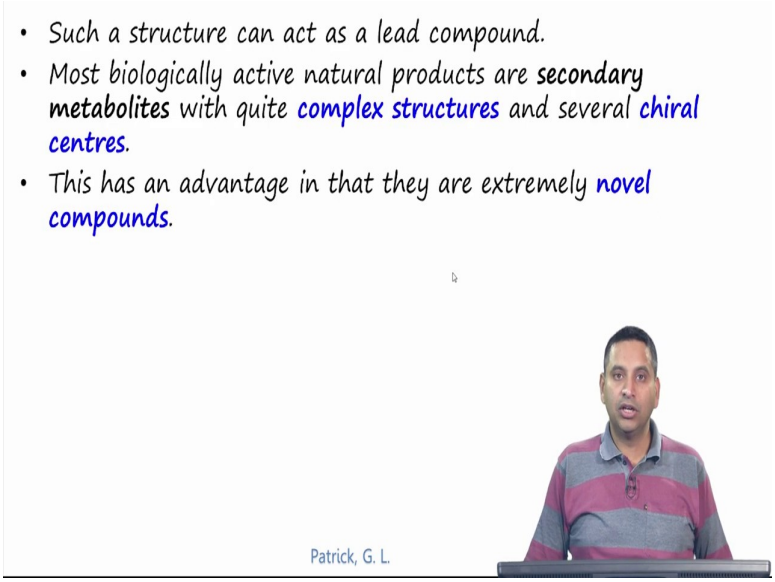

So this structure which is the active principle can act as a lead compound.

So the number of these natural products are actually what are known as secondary metabolites. And they have quite complex structures. And we have looked at several examples where they have a number of chiral centers.

So we have already discussed that chiral centers are not very desirable to have in a drug because you will have to isolate and you have to synthesize the other isomer and test that as well.

So when you have a complex natural product which has a chiral centre then it makes it difficult to synthesize. So this has an advantage because these compounds are typically very novel.

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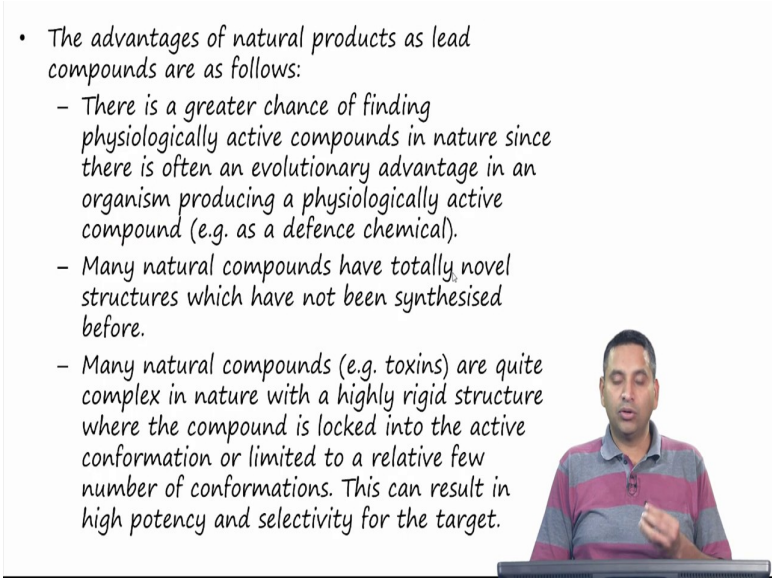

So to summarize the advantage of natural products are there is a greater chance of finding physiological relevant compound in nature

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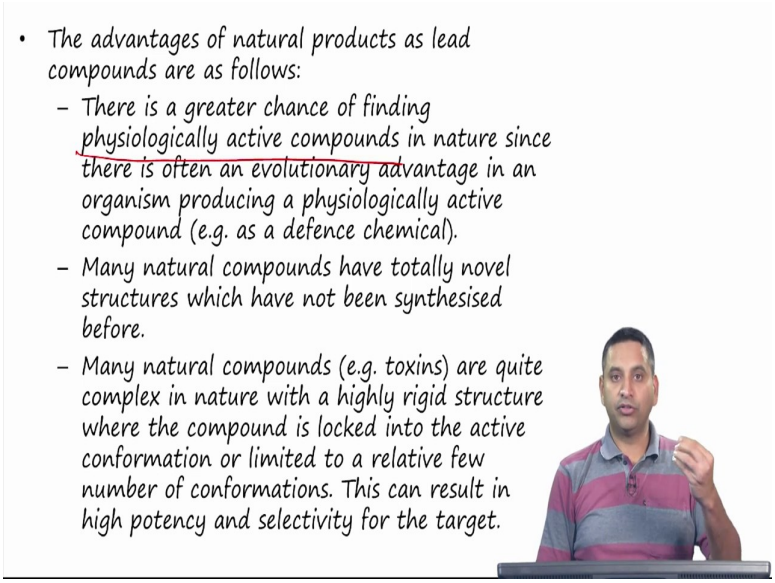

because this is an evolutionary advantage for the organism.

So imagine that there is a biological warfare going on between one set of organisms and another set of organisms, typically microbes. And one of those microbes is going to win.

That means that one of the microbes is going to do something to get rid of the other one. So these are typically physiologically active compounds that are isolated. And they are used in self-defense.

So the other advantage is that they have totally novel structures

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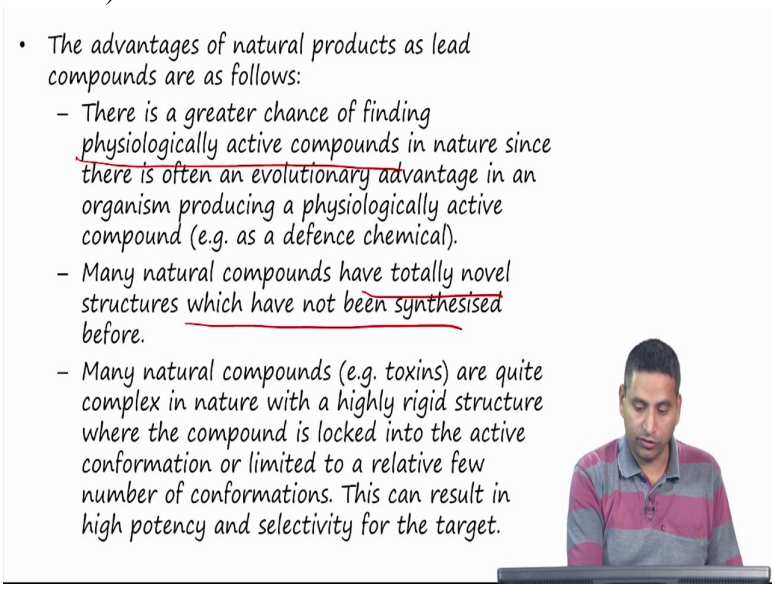

which have not been synthesized before. So that makes it very attractive. And there are also toxins for example which are secreted by organisms sometimes and they are also quite complex in nature with a highly rigid structure.

And now when the compound is locked into the active conformation or they are limited to a relatively few number of conformations, so this

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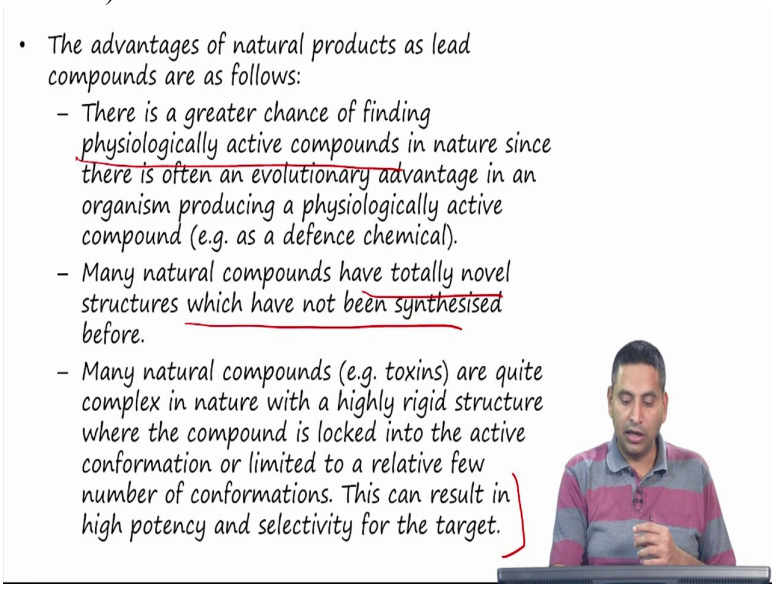

can result in very high potency and selectivity for the target.

So these are some of the advantages. So by using a natural product there is a high chance that you can have totally novel compounds and they have also evolved in self-defense and so it is possible that some of these compounds may be active.

And there are toxins which have been deliberately synthesized and they are quite complex in nature. And sometimes they are highly rigid. And they are designed; they are synthesized to be present in the active conformation to hit a particular target.

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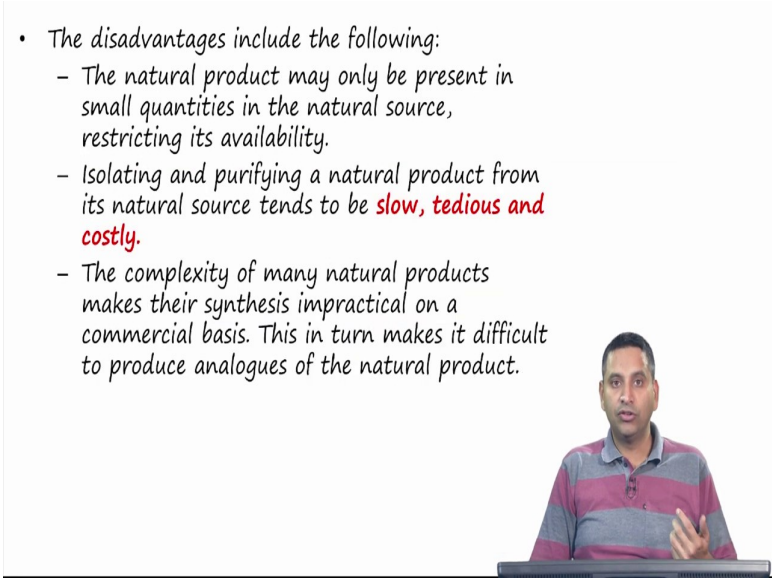

So these are some of the advantages. Now the disadvantage is that the natural product is typically isolated in very small quantities. So they are present in very small quantities. And typically from kilograms of the natural source if you are lucky you will isolate a few milligram.

So this is also a very slow and tedious process and it can prove to be quite expensive depending on the source of the compound. Also because they are so complex, natural product synthesis make is very challenging, especially if you have 6, 7, 8, 9 chiral centers you need to make a natural product as a single enantiomer which is very challenging.

So therefore making this on a commercial basis is nearly impractical. Also because it is impractical to make it, making analogs of the natural product is also difficult. So these are some of the advantages and disadvantages of using natural products.

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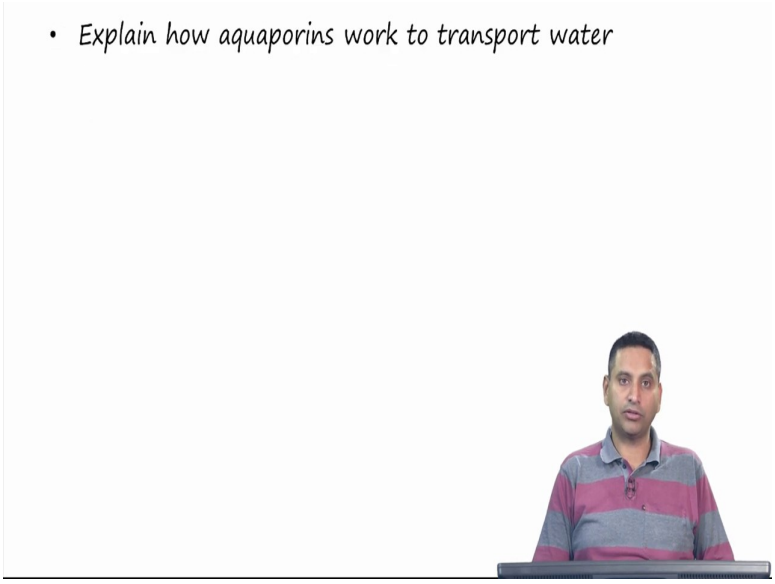

Next question is; explain how aquaporins work to transport water.

So we have discussed this

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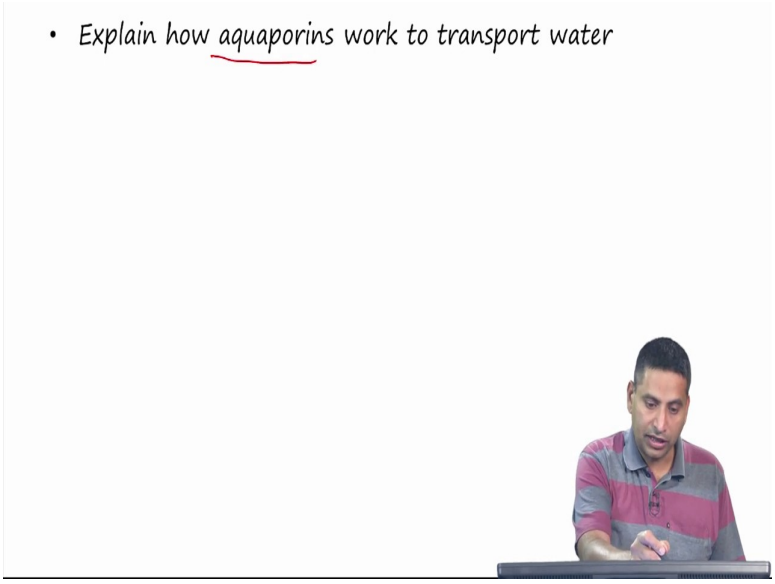

in class. Aquaporins are a class of proteins which help with transporting water. Now in order to understand or to address this question let us go back and look at how kidneys function.

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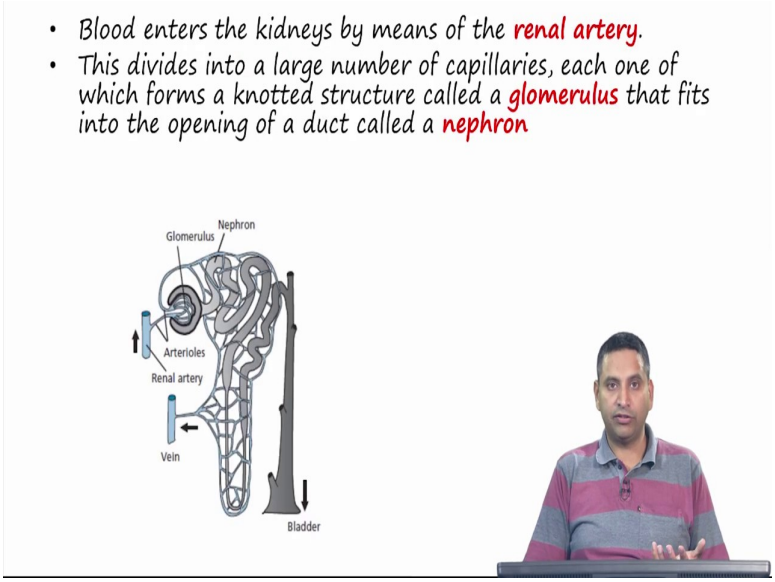

So when the blood enters the kidneys by the means of the renal artery, then what happens is that they divide into larger number of capillaries and this in turn goes and forms a knotted structure called the glomerulus.

So the glomerulus

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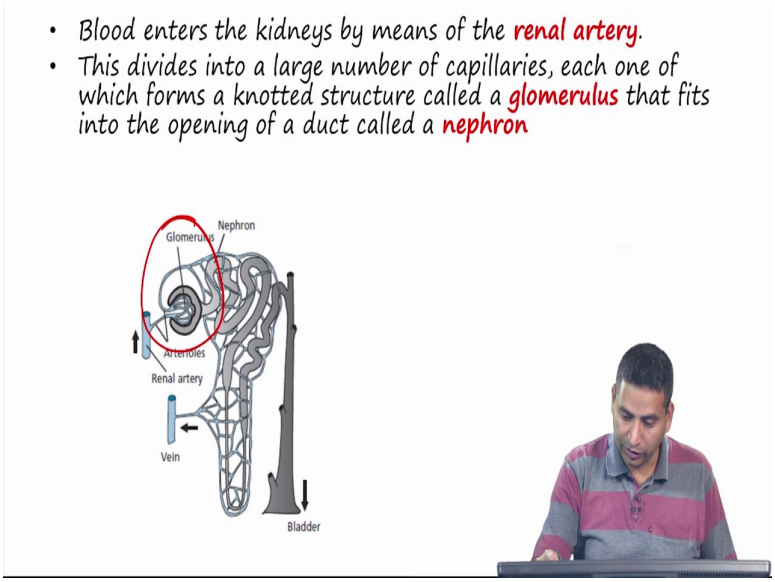

is shown here, Ok and this glomerulus then sits in the duct which is called a nephron. So this is the nephron

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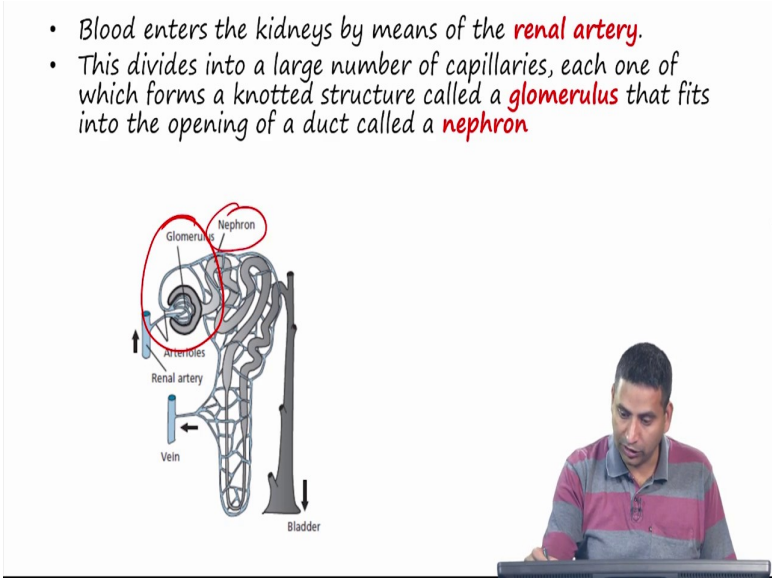

as shown here. So therefore the blood that enters the kidneys is going to form this kind of a structure.

Now

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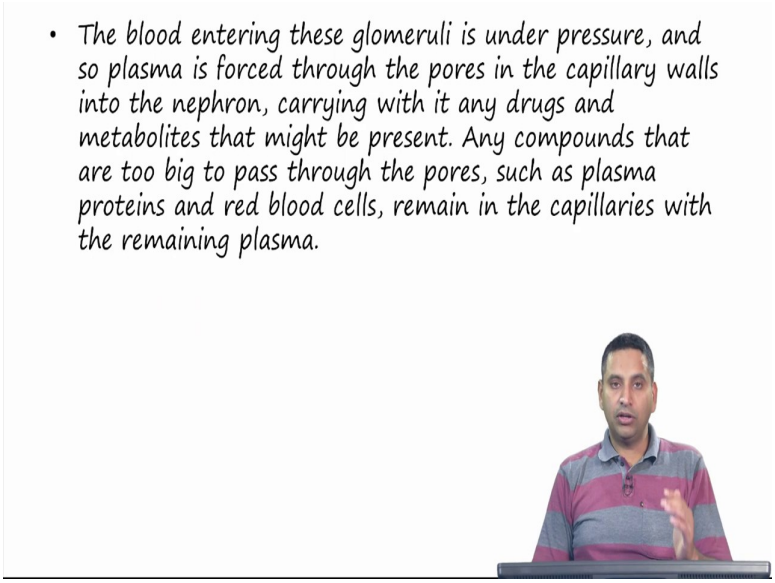

since it is entering under pressure then what happens is that because there are small pores on the capillary wall, the plasma is forced through these pores. So along with the plasma, any drug that is present in the plasma is also carried along with it, or other metabolites.

And so any compound that is too big to pass through these pores such as plasma proteins and red blood cells remain in the capillaries while all others are expelled.

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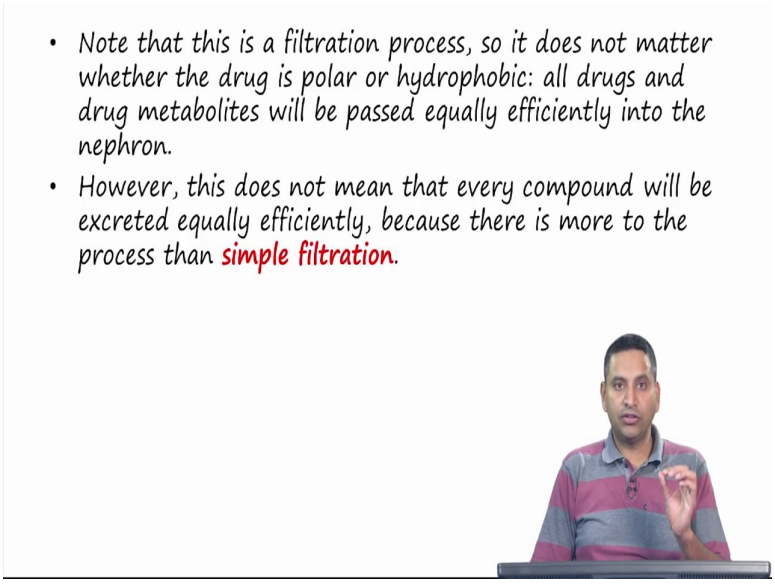

So this is a filtration process.

So here it really does not matter whether the drug is polar or hydrophobic. And all drugs and drug metabolites will be passed equally efficiently into the nephron.

However this does not mean that every compound will be excreted with equal efficiency because there is more than a simple filtration process that is involved.

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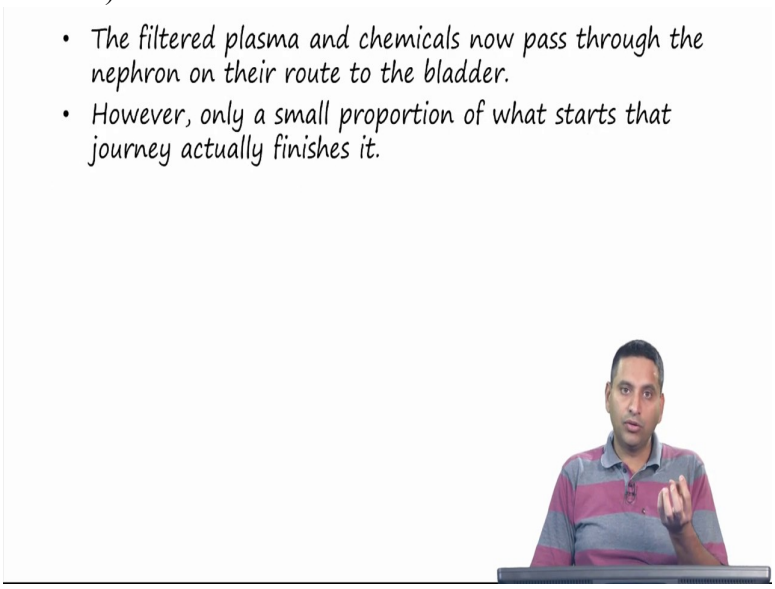

So the filtered plasma and chemicals now pass through the nephron on to their route to the bladder. However only a small portion of what starts the journey finishes it.

This is because

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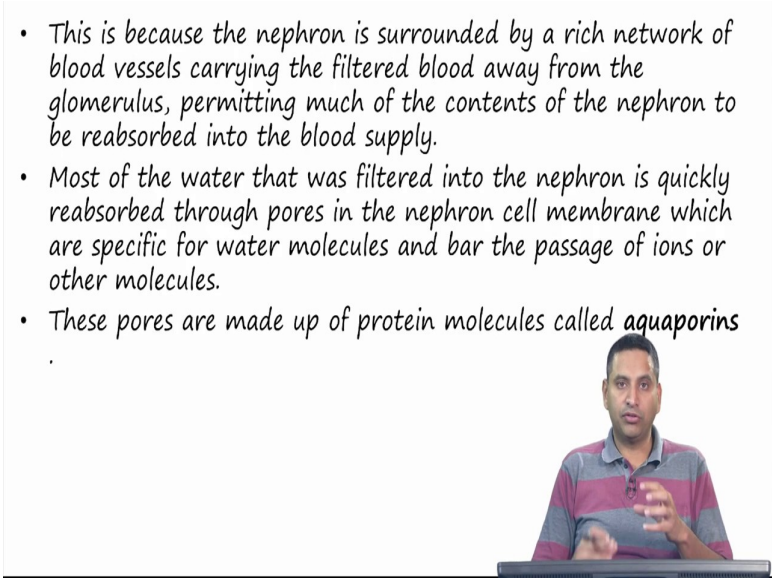

the nephron is surrounded by a rich network of blood vessels carrying the filtered blood away from the glomerulus. So therefore the contents of the nephron can be reabsorbed into the blood supply.

So, most of the water that was filtered into the nephron is quickly reabsorbed through the pores on the cell membrane which are very specific for water molecules.

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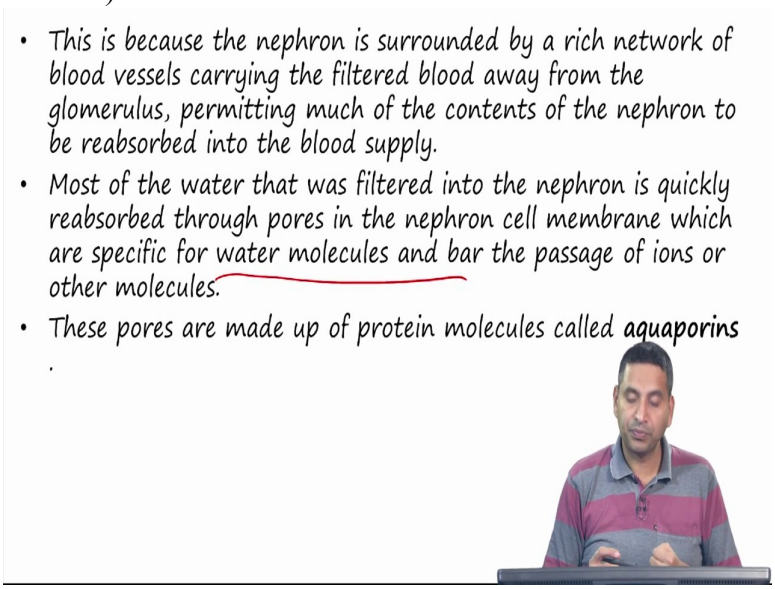

And these do not allow passage of ions or other molecules. And these are the pores that we are interested in and these are called as aquaporins.

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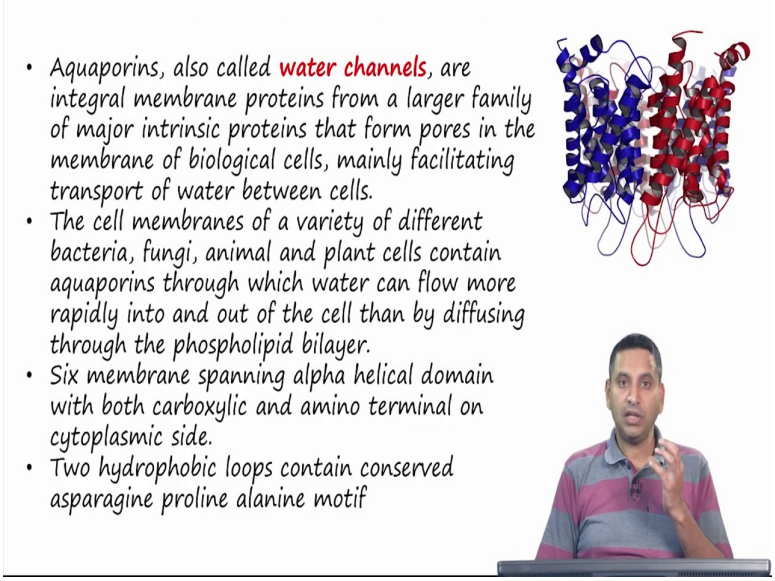

Aquaporins also known as water channels are integral membrane components and they form a larger family of major intrinsic proteins that form pores in the membrane of biological cells.

So the main function of these aquaporins is to facilitate transport of water between cells. Cell membranes of a variety of different bacteria, fungi, animal and plant cells contain aquaporins through which water can flow.

So 6 membrane spanning alpha-helical domain which both contain carboxylic and amino terminal on the cytoplasmic side is present. And then there are two hydrophobic loops which contain conserved aspargine, proline, alanine motif.

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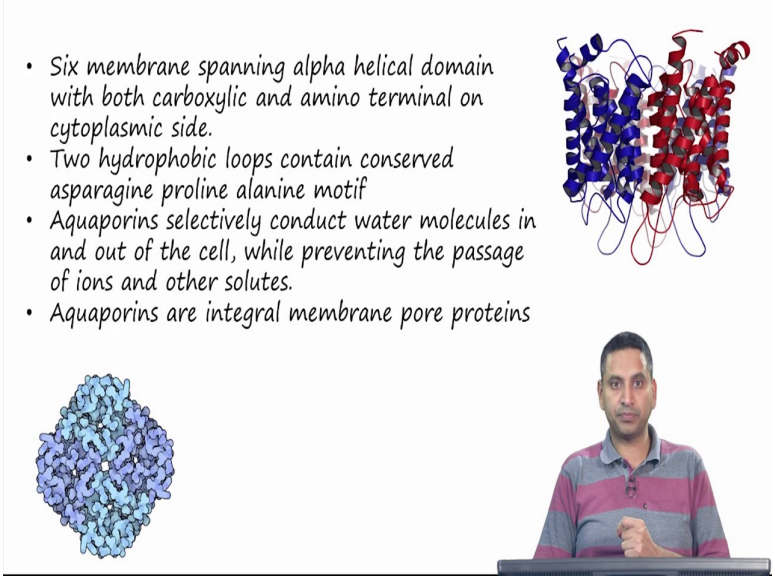

So these aquaporins help in selectively conducting water in and out of the cell while preventing the passage of ions or other solutes. Therefore aquaporins are important components in this process.

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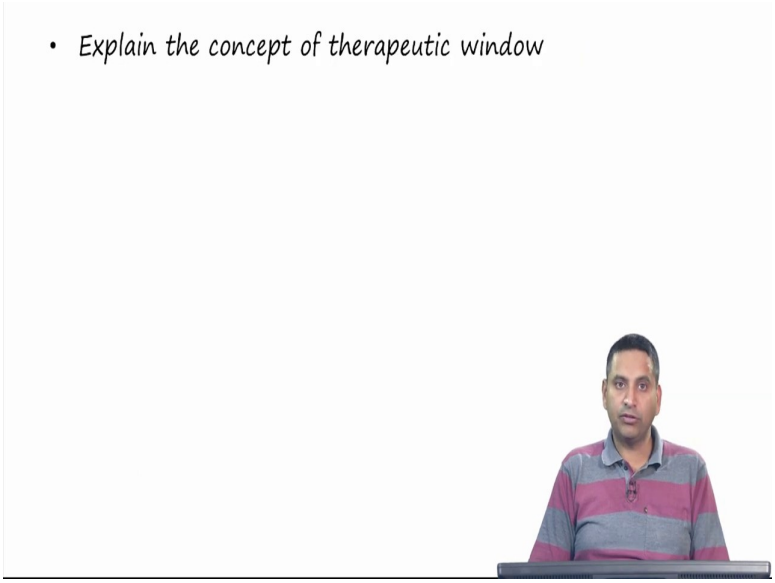

The next question is, explain the concept of therapeutic window.

So in order to address this question let us draw a plot.

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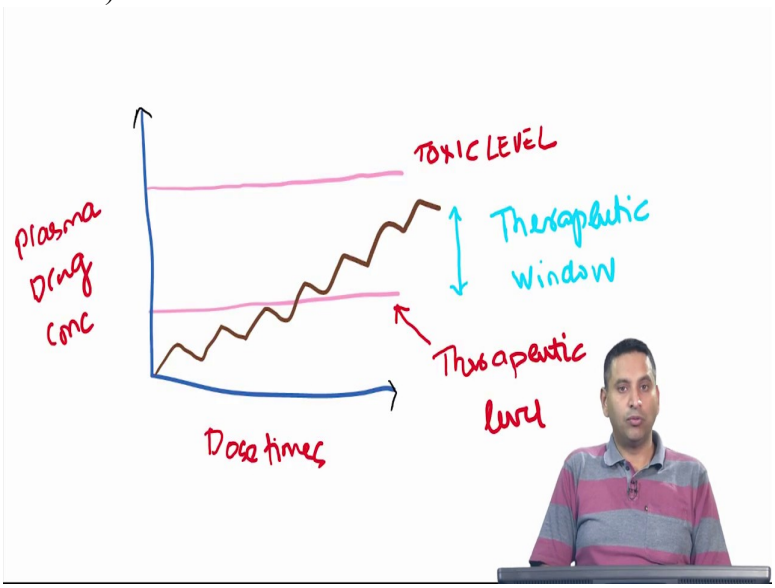

So when a drug is administered on the x-axis here

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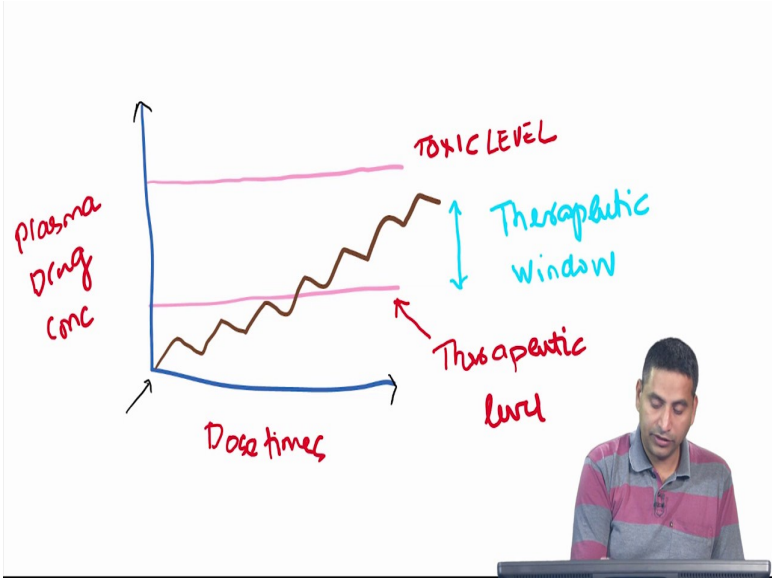

is the number of doses.

So here basically you give a dose

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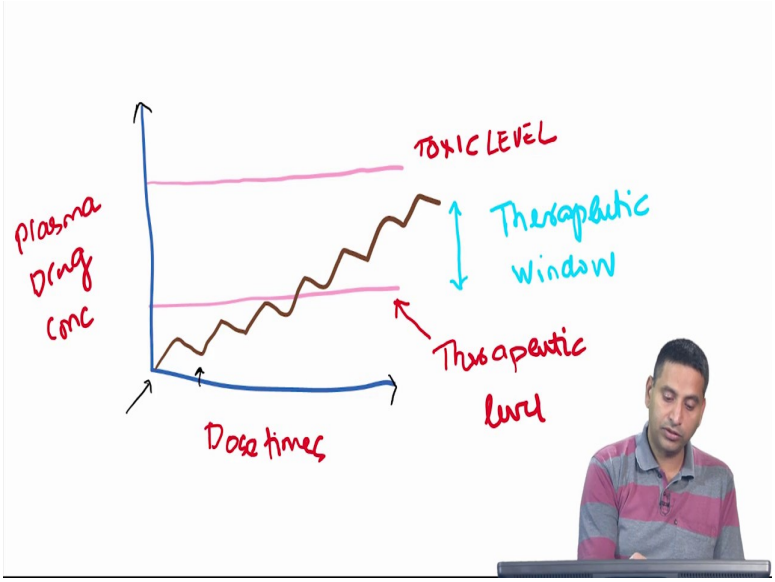

and then there is another

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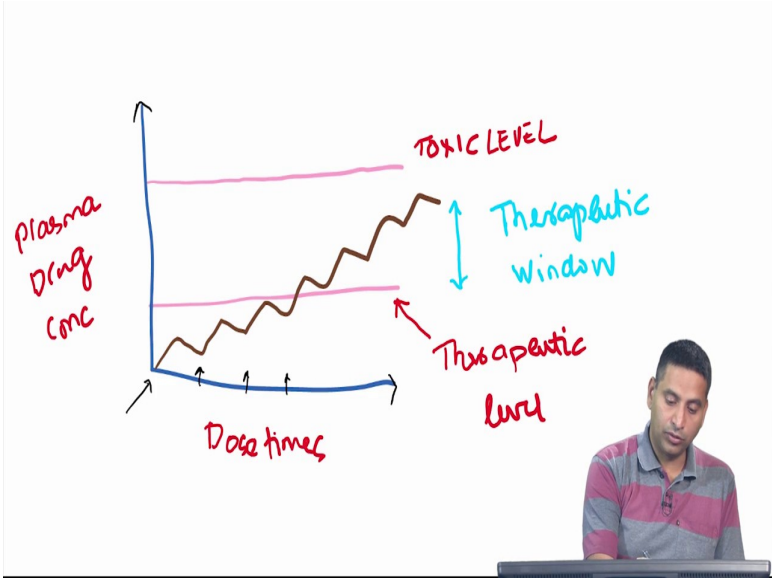

dose that is given here, another dose that is given here and so on, Ok.

And then what we do is we measure the plasma drug concentration on the y axis.

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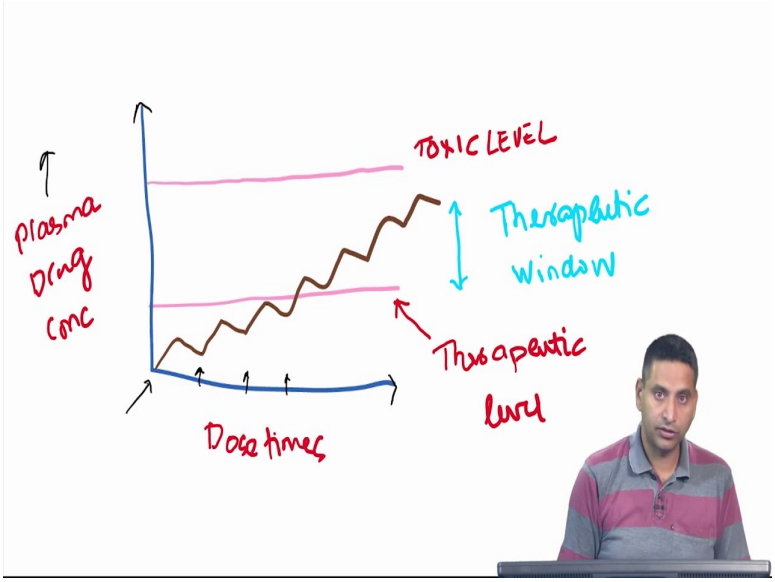

So now there is a concentration of the drug in plasma wherein there is a therapeutic effect,

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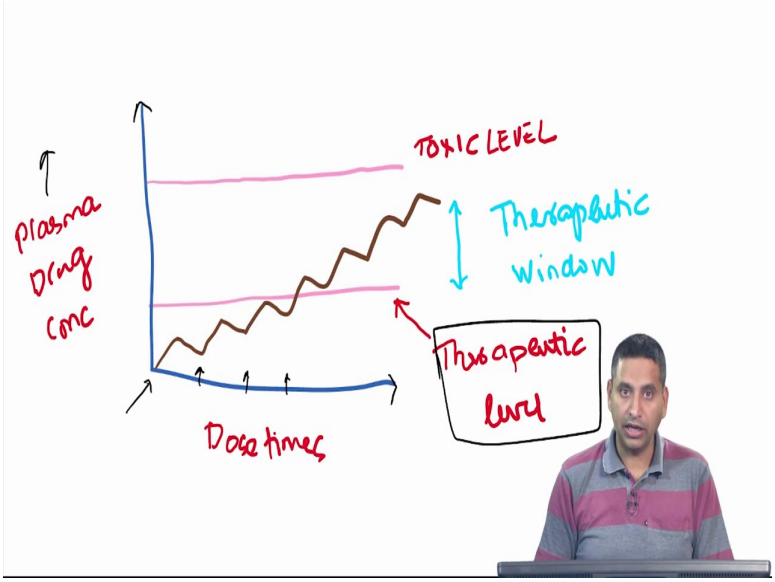

Ok. So any concentration above this therapeutic effect that is anything that is above

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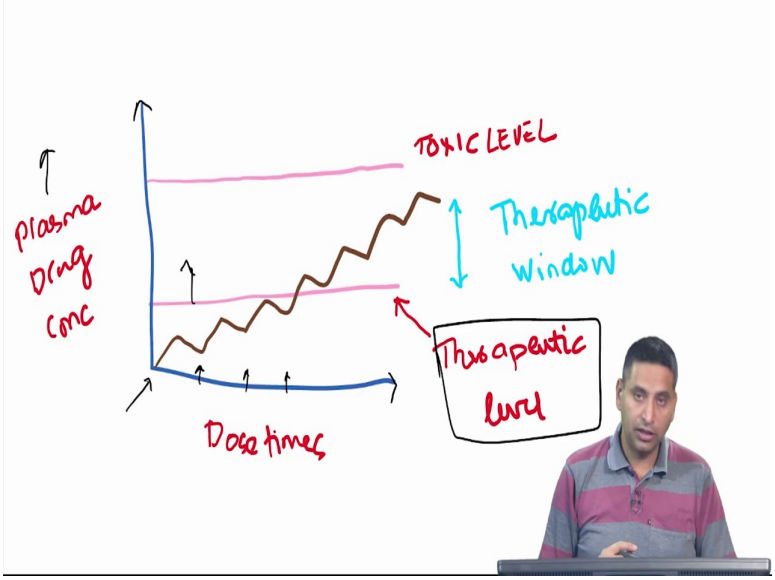

this level, there is going to be therapeutic effect.

So for example if you are taking a drug to address a headache, so there is a dosage at which the headache is going to go down. Any concentration above that is called the therapeutic level.

By the same measure there is also a dose wherein it can achieve toxic levels.

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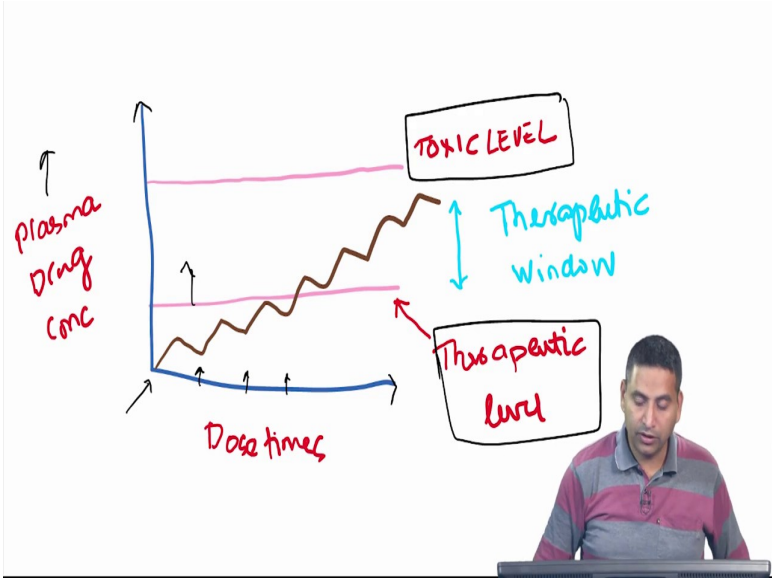

So most drugs that we take are going to be toxic at high concentrations.

So this top line here is called the toxic level. So the window that is formed between these two levels, that is the therapeutic level and the toxic level is called the therapeutic window.

The larger the therapeutic window, the better it is in terms of how you want to administer a drug. The smaller the therapeutic window the higher the chances that the drug would be toxic and therefore one needs to establish a fairly good therapeutic window if we wish to administer the drug to humans.

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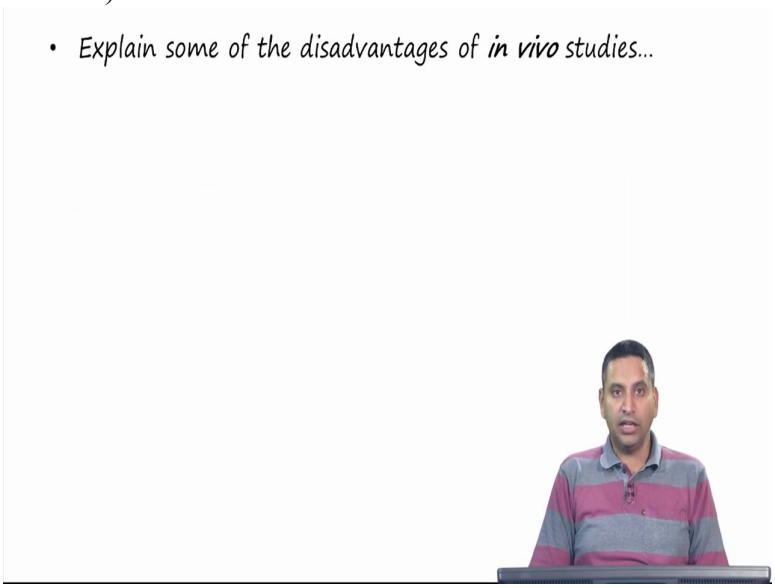

The next question is, explain some of the disadvantages of *in vivo* studies.

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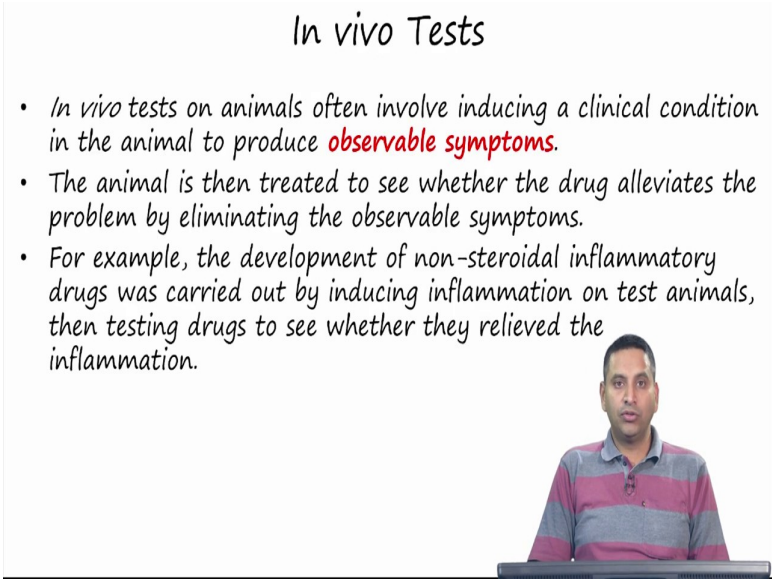

So *in vivo* tests are nothing but tests that are conducted on animals. And these animals typically are used

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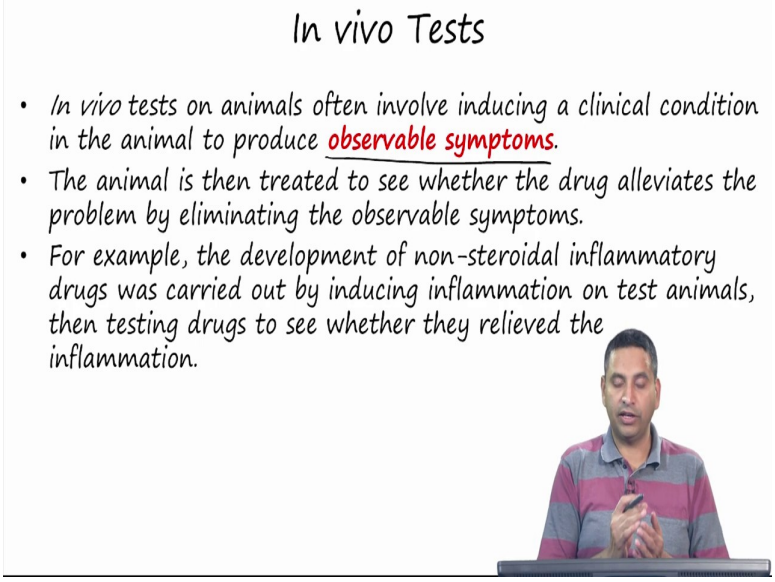

in such a way that they have observable symptoms. So for example let us say we have an animal which has been induced with cancer.

So now one can use this model to study whether the drug is going to work or not. So if the drug is an anticancer drug and if the size of the tumour goes down then we can study in this animal model whether our molecule is active or not.

In another example if you want to study inflammation and if our non-steroidal anti-inflammatory

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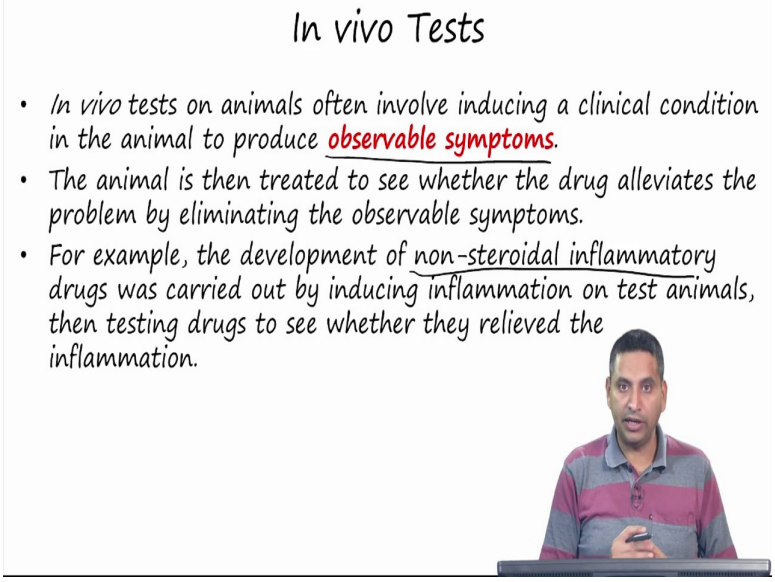

drug is going to be, this is anti,

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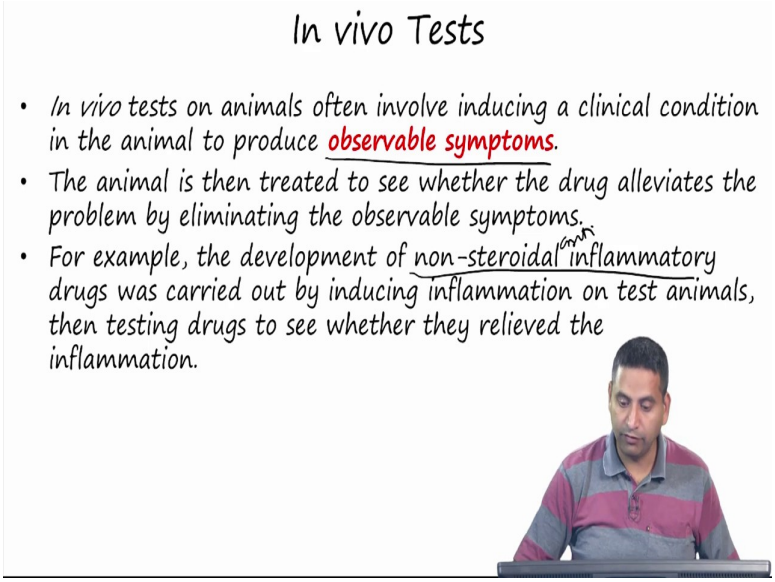

anti-inflammatory drug is going to be useful then we would need to develop a model wherein we induce inflammation on the test animal and then find out whether this molecule has any anti-inflammatory effect.

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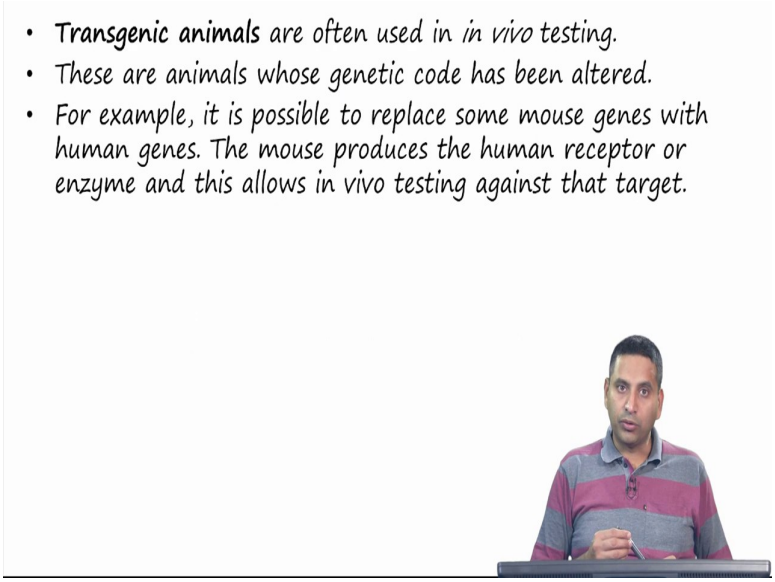

Also in *in vivo* studies very frequently transgenic animals are used. These are animals whose genetic code has been altered so that you can use them for better testing.

So for example we can express the human receptor in a mouse. Or you can express the human enzyme in the mouse by altering the genetic code.

Now when we administer a drug we can find out whether the drug acts on the human receptor as it would act on humans or on the human enzyme for example. And it will allow us to test in an animal model before we take it into humans.

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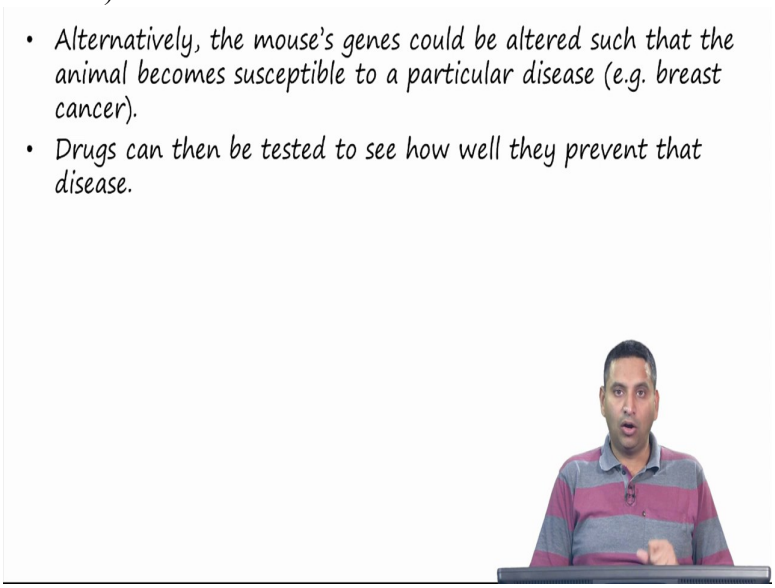

Alternatively the mouse genes can also be altered such that the animal becomes more susceptible to a particular disease, for example breast cancer. So then we could test whether the drug will help in preventing that disease.

So here we get a direct readout as to whether the drug can be efficacious in prevention.

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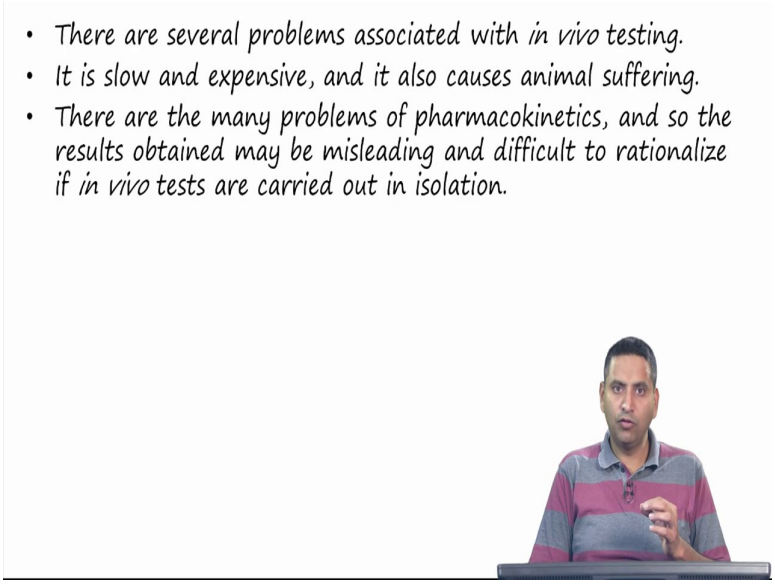

Of course one needs to understand that there are several problems associated with in vivo testing. A, it is slow, B it is expensive, and it also causes a lot of animal suffering which if we can avoid it would be better.

There are also many problems associated pharmacokinetics. Sometimes the results that we obtain from animal studies can be misleading.

Also if we just do animal studies or *in vivo* tests in isolation, the results that we get may be difficult to rationalize. Because, sometimes the metabolism in animals can be very different from metabolism in humans.

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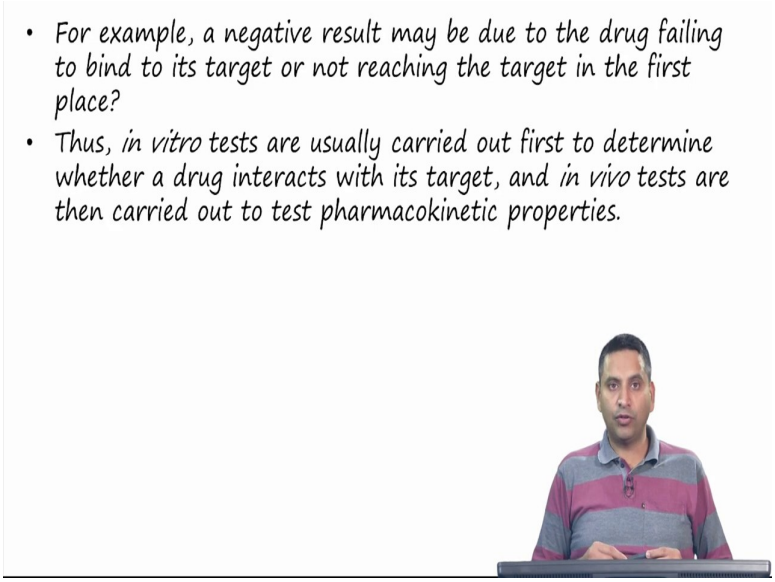

So for example, a negative result may be due to the drug failing to bind to its target or not reaching the target in the first place. So *in vitro* tests are also carried out to determine whether the drug interacts with its target and then *in vivo* tests are carried out to test the pharmacokinetic properties.

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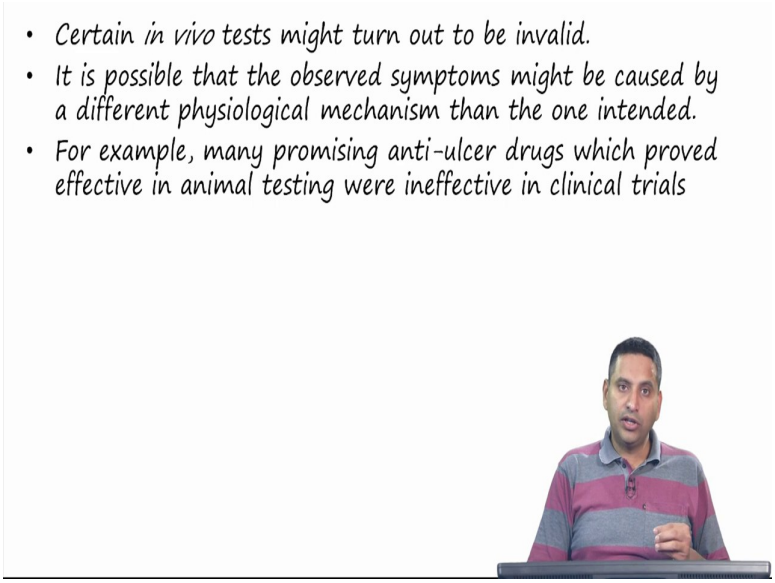

Certain *in vivo* tests also turn out to be invalid. So if for example the observed symptoms might be caused by a different physiological mechanism than the one intended.

So there are many promising anti-ulcer drugs which have proved very effective in animals but completely ineffective in clinical trials on humans.

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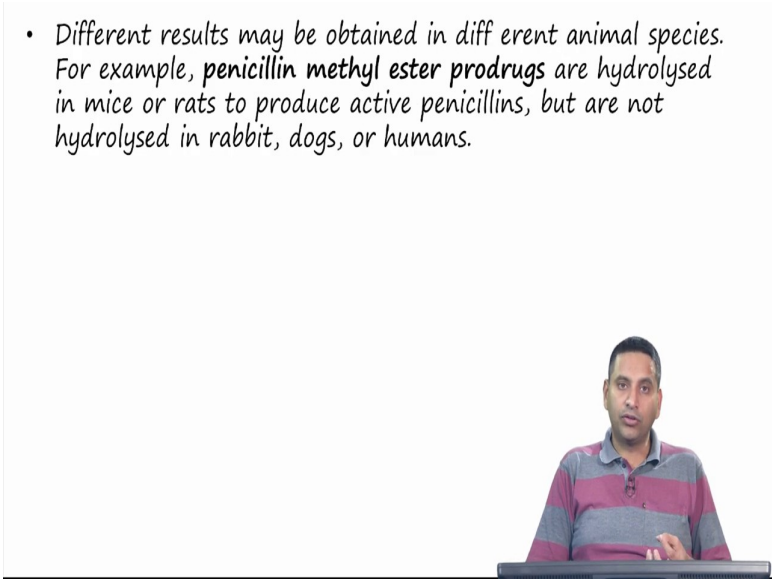

Also there could be different animal species that have different sets of enzymes or drugs. So for example penicillin methyl ester is hydrolyzed in mice or rats to provide active penicillin, but are not hydrolysed in rabbits, dogs or humans.

So here we would be carrying out an experiment in the in vivo model on mice for example and we would find that the active form of penicillin is produced but in reality in humans this may not be effective.

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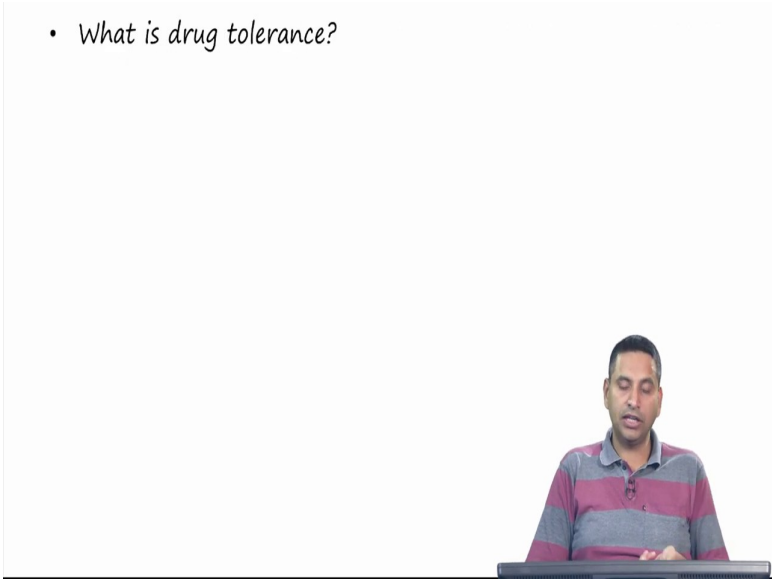

Next question is what is drug tolerance?

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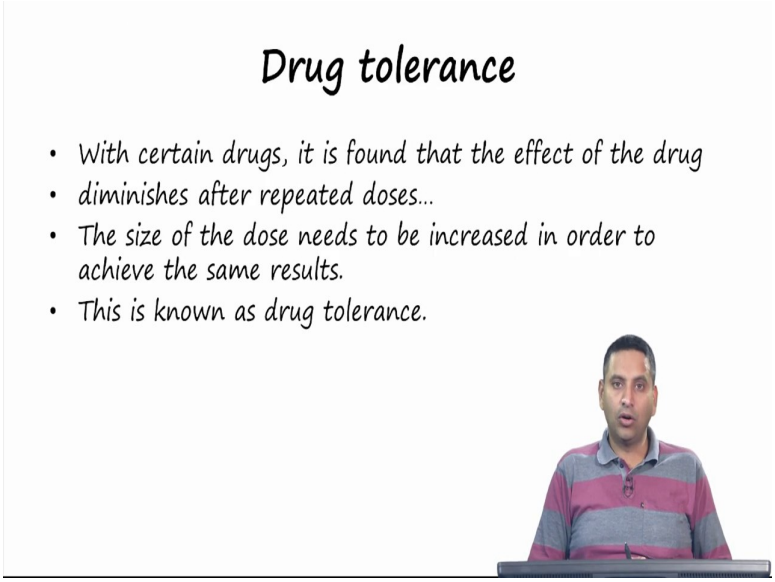

Drug tolerance happens with certain drugs when the effect of the drug diminishes as the number of doses increases. So then to achieve the same effect one needs to take a larger dose of the drug. So this is known as drug tolerance.

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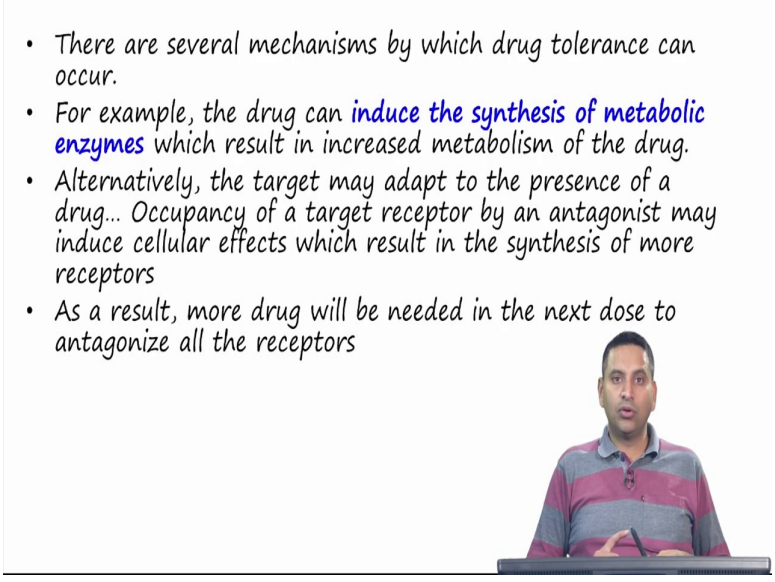

So there are several mechanisms by which drug tolerance can occur and some of them are not very well understood. But one of the ways in which the drug tolerance can happen is if the drug can induce the synthesis of a metabolic enzyme.

So what happens is that once this metabolic enzyme is increased then the drug is going to be metabolized before it gets to its target.

So you need a larger amount of the drug for the same effect. Alternatively the target may adapt. So for example if there is a receptor, the receptor may actually mutate and the binding may not be as effective.

The occupancy of the target receptor by an antagonist may induce cellular effects which result in the synthesis of more receptors.

So now what happens is that instead of having n number of receptors you have 2n or 3n. Therefore you would need a larger amount of the drug to antagonize all the receptor.

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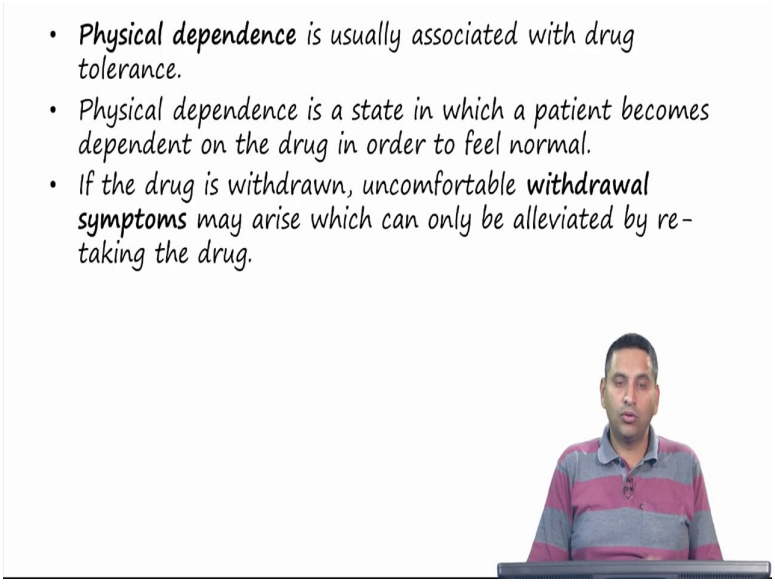

So drug tolerance is very closely associated with physical dependence. Physical dependence is the state where a patient becomes dependent on the drug in order to feel normal.

And these lead to what are known as withdrawal symptoms.

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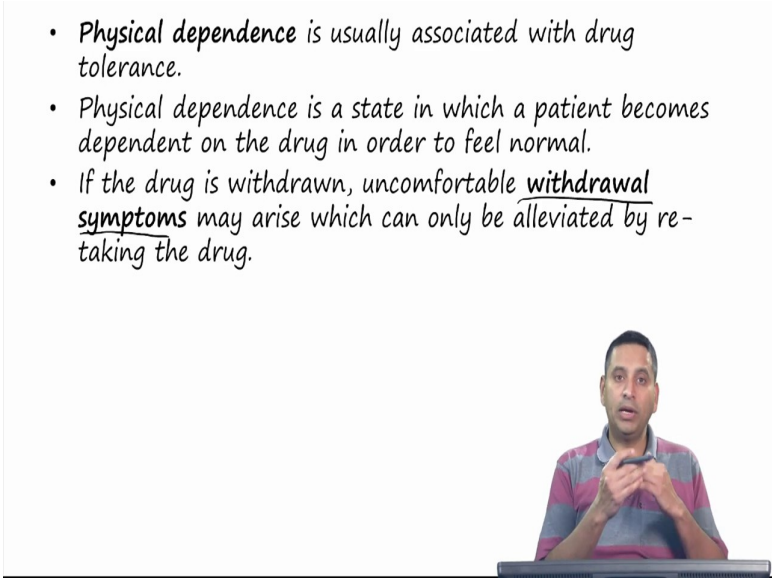

So you may have observed a lot of people who smoke have withdrawal symptoms if they do not smoke for a long time.

This is because of the physical dependence that is associated with nicotine.

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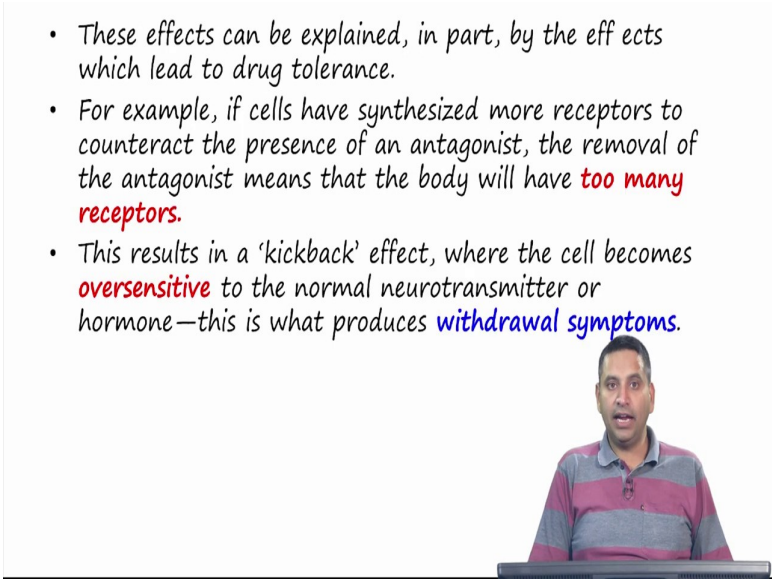

And the effects can also be explained by the effects which lead to drug tolerance.

So what happens is that if the cells have synthesized more receptors to counteract the presence of an antagonist then the removal of the antagonist means that the body will have too many receptors.

This results in what is known as a kickback effect where the cells become oversensitive to the normal neurotransmitter. And this is what produces withdrawal symptoms.

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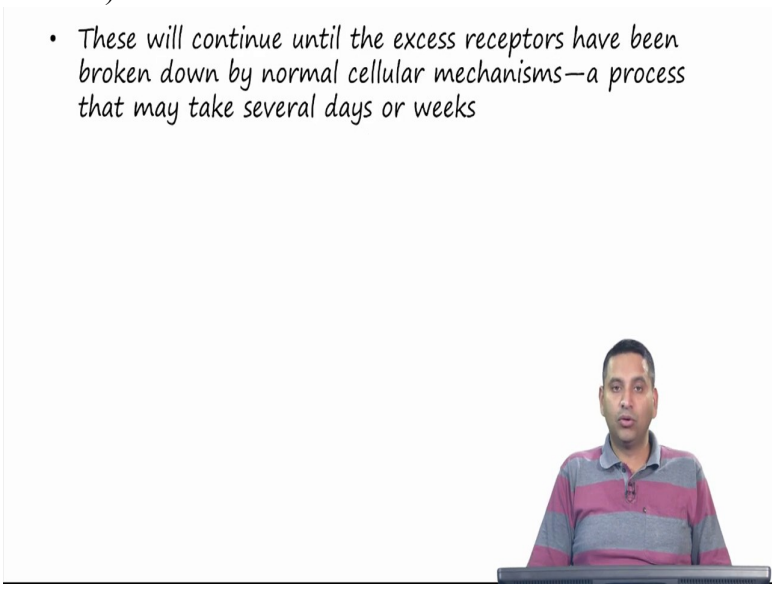

So these will continue until the excess receptors have been broken down by normal cellular mechanisms, a process that may take several days or weeks.

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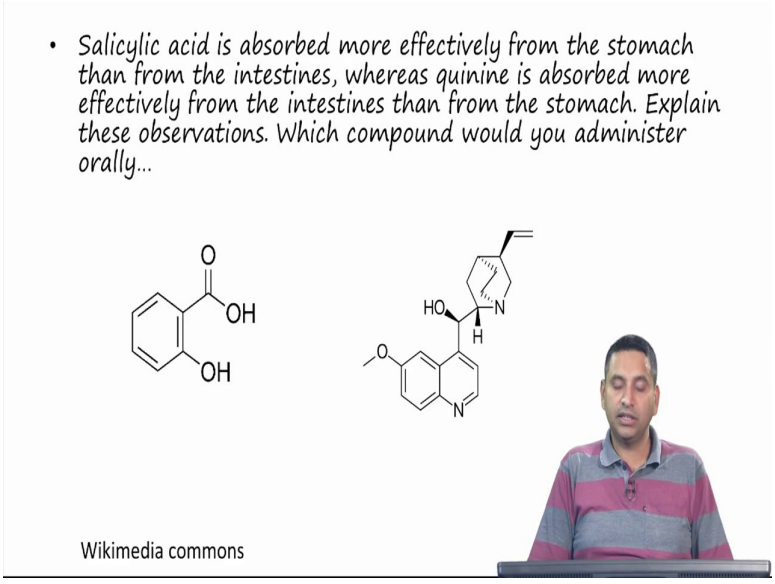

The next question, salicylic acid is absorbed more effectively from the stomach than from the intestines whereas quinine which is shown here

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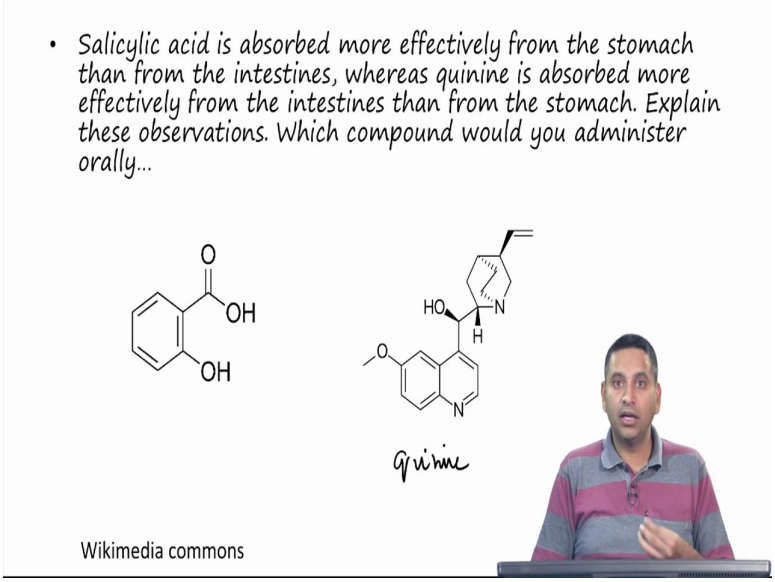

is absorbed more effectively in the intestines. So explain these observations and which compound would you administer orally?

So here is salicylic acid. So

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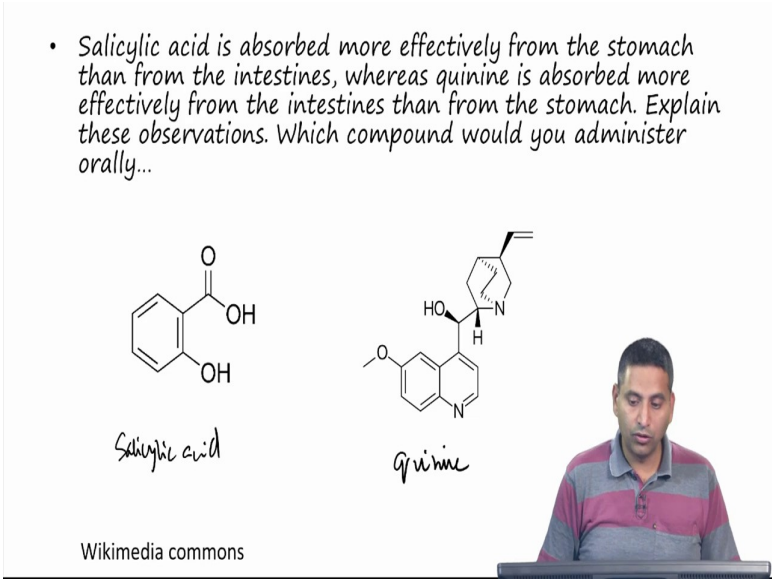

in order to address this question let us now look at some acid based effects.

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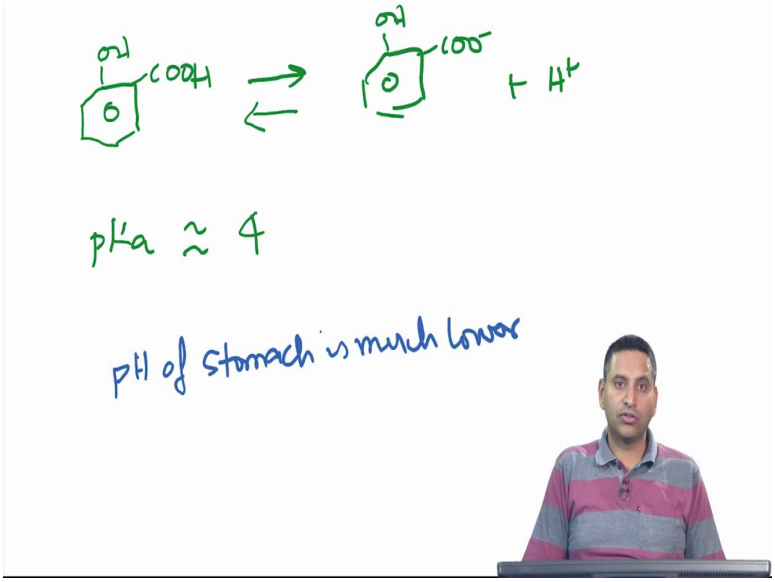

So salicylic acid one would expect that the carboxylic acid would have pKa of around

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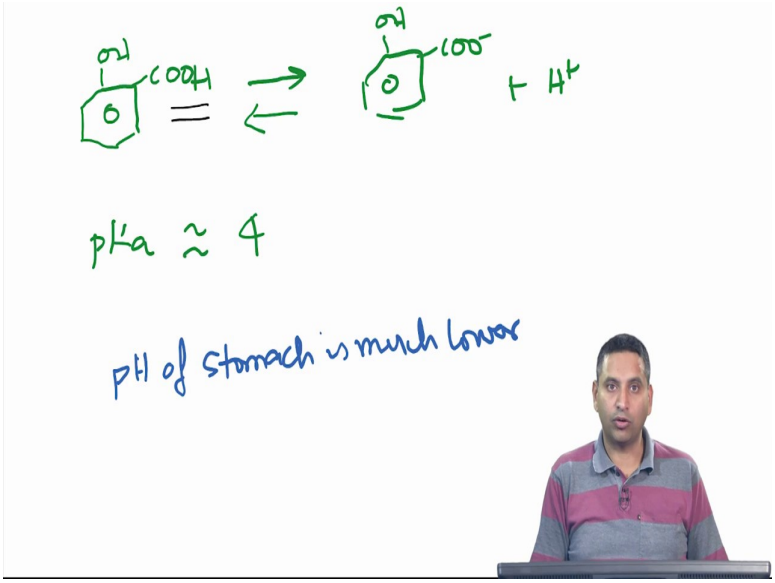

4. And it can ionize and form COO minus and H plus.

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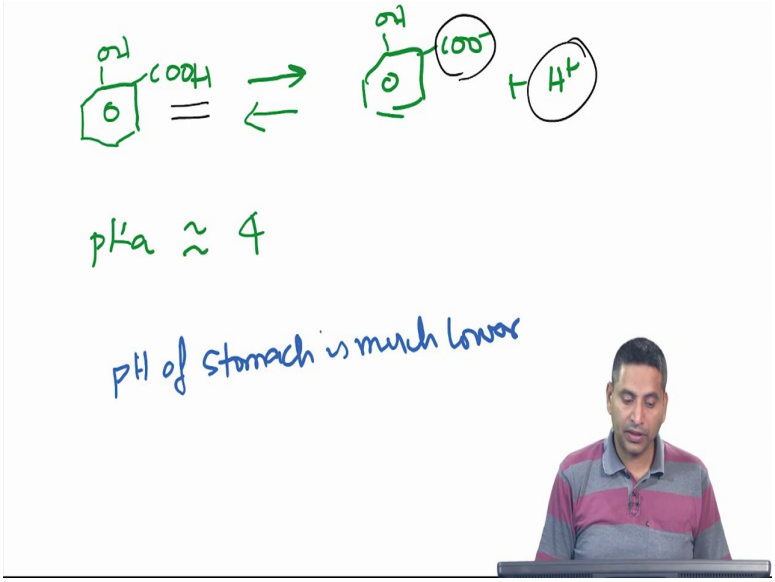

Now the pH of the stomach is significantly lower than this number. So therefore you would expect that this equilibrium would be largely in favor of

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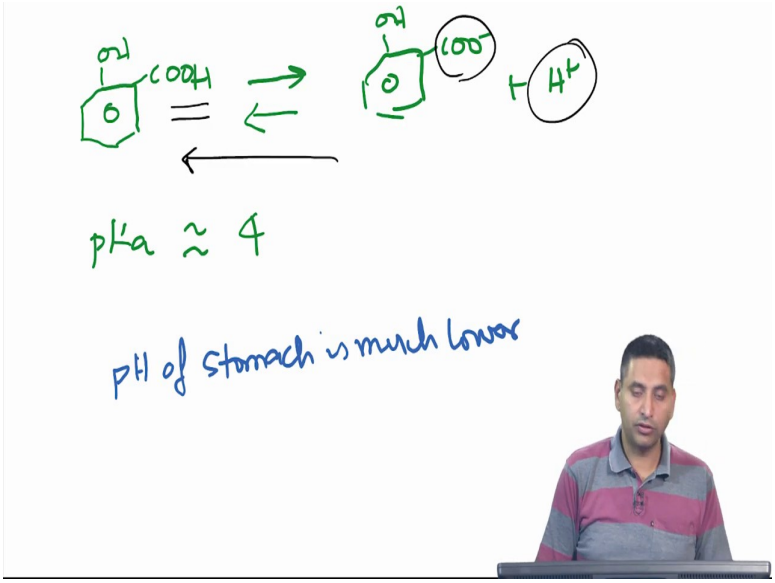

the salicylic acid.

So since salicylic acid is a neutral molecule one would expect that it would be absorbed in the stomach because it can get across the membranes better.

In the second

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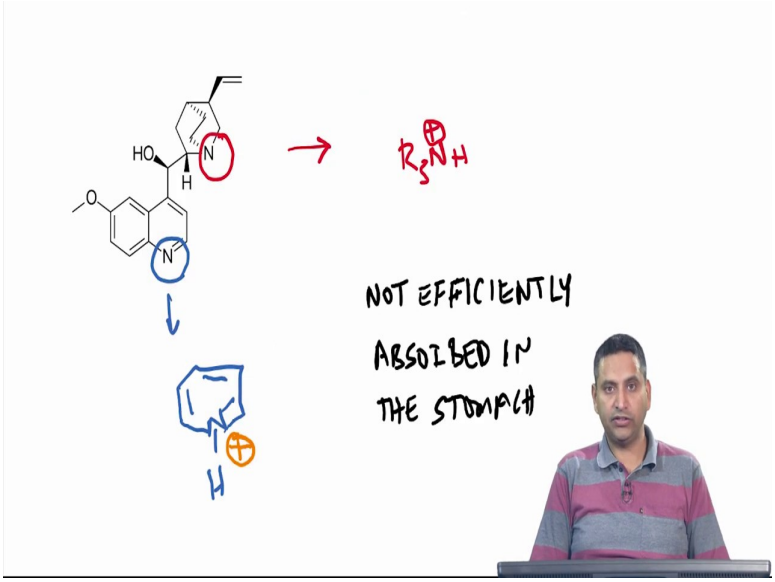

case you have two potential centers which can be protonated in low pH. Here is the amine which is here and the pyridine.

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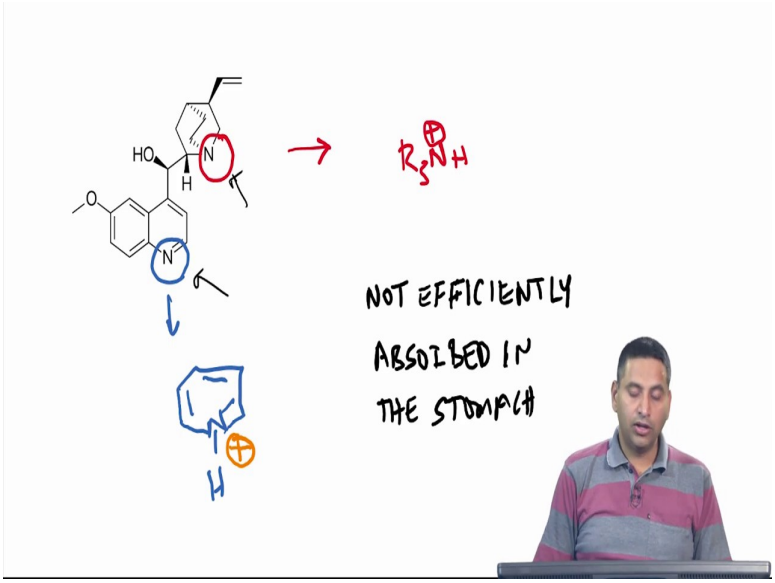

So if the amine gets protonated or the pyridine gets protonated it forms a quaternary ammonium salt.

Now once this salt is formed then it is not efficiently absorbed in the stomach because it does not get across the membrane. Therefore one would expect that it would be efficiently absorbed in the intestine where the pH is substantially higher.

So now one would expect that if salicylic acid is administered it would be better absorbed in the stomach while this quinine would be better absorbed in the intestine.

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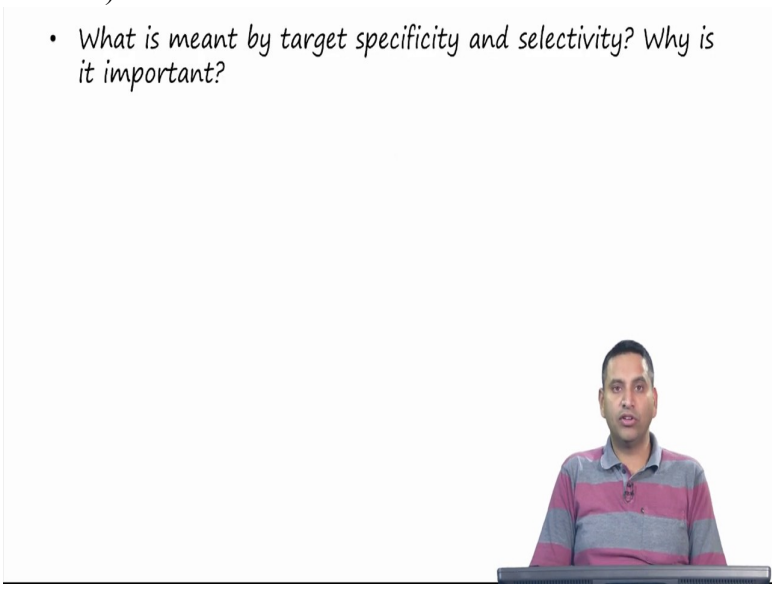

What is meant by target specificity and selectivity and why is it important?

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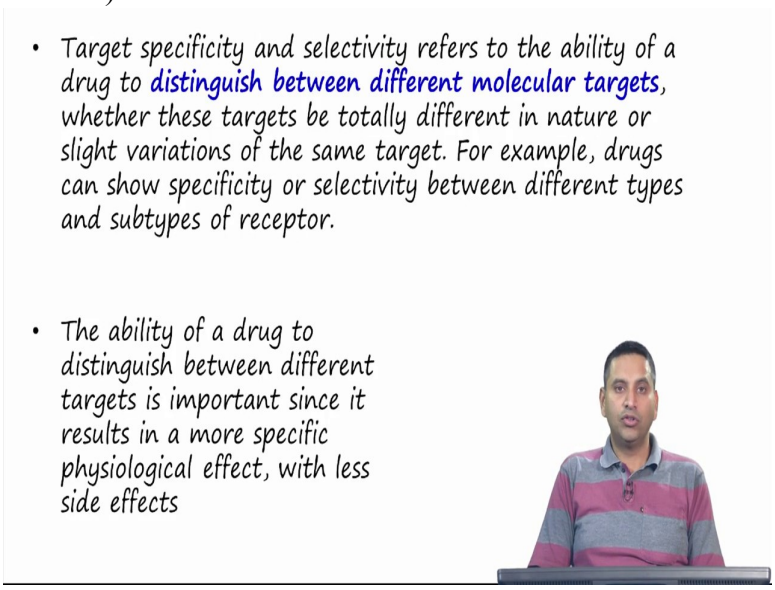

So this is again something that we did in class. So we will repeat it here. Target specificity and selectivity refer to the ability of a drug to distinguish between different molecular targets.

And whether these targets can be totally different in nature or they can be slight variations of the same target. For example drugs can show specificity or selectivity between different types

and subtypes of a receptor. The ability of a drug to distinguish between different targets is very important because it results in a more specific physiological effect with less side effects.

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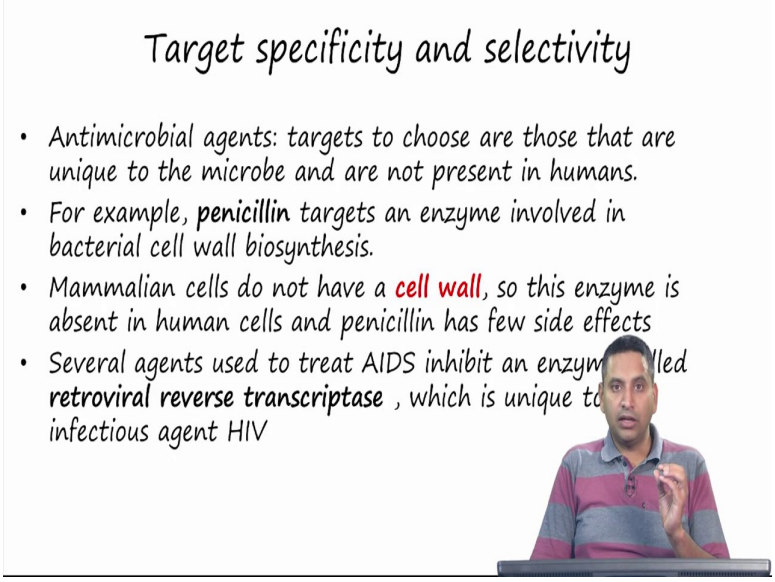

Let us look at the case of antimicrobial agents. So antimicrobial agents are, one would want to choose the target that is unique to the microbe but it is not present in the humans.

For example penicillin targets an enzyme which is involved in the bacterial cell wall synthesis. Mammalian cells do not have a cell wall. And so this enzyme is absent in human cells. And penicillin has few side effects.

There are also other agents which are used to treat AIDS which is Acquired Immuno Deficiency Syndrome. And these inhibit an enzyme called as retroviral reverse transcriptase.

This enzyme is unique to the infectious agent HIV.

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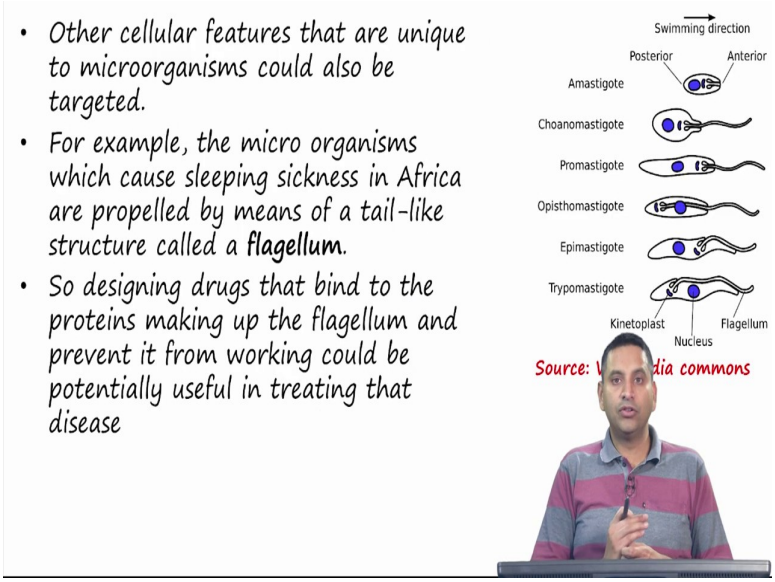

So there are other cellular features that are unique to microorganisms that could also be targeted.

So for example the microbe which causes the sleeping sickness in Africa is propelled by means of a flagellum, Ok.

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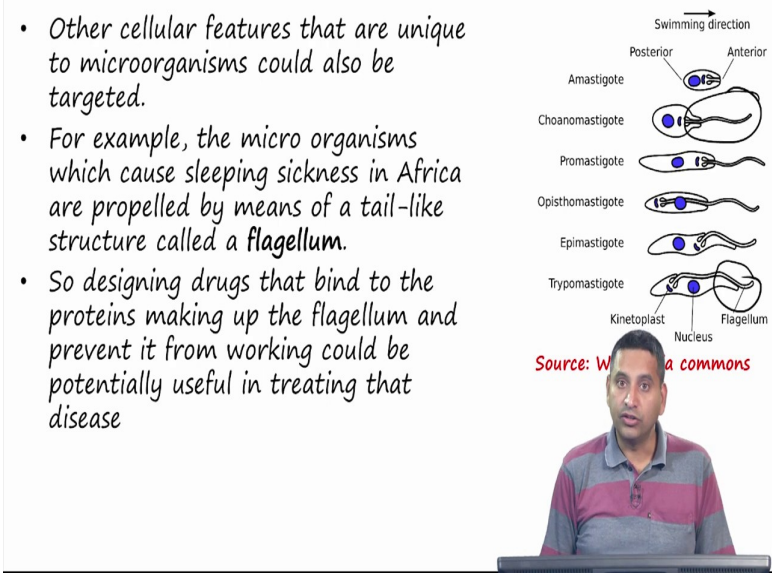

So this flagellum is very unique structure and so we can design drugs that binds specifically to proteins making up the flagellum and prevent it from working. And that might be useful in treating the disease.

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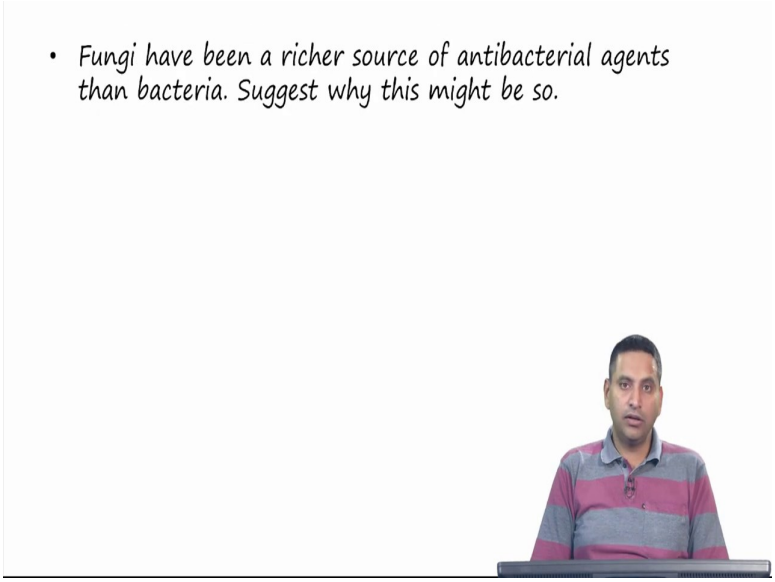

Fungi have been a richer source of antibacterial agents than bacteria. Suggest why this might be so?

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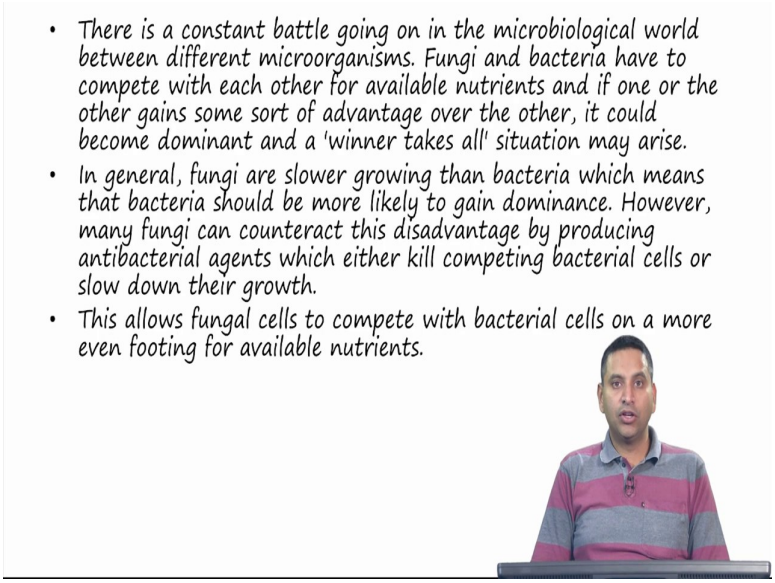

So as we described earlier there is a constant battle going on in the microbial world. So there are different microorganisms and these compete for the same space and same resources.

So fungi and bacteria have to compete with each other for available nutrients. And if one gains some sort of advantage then it could result in a dominance and then it could also result in the winner-takes-all situation

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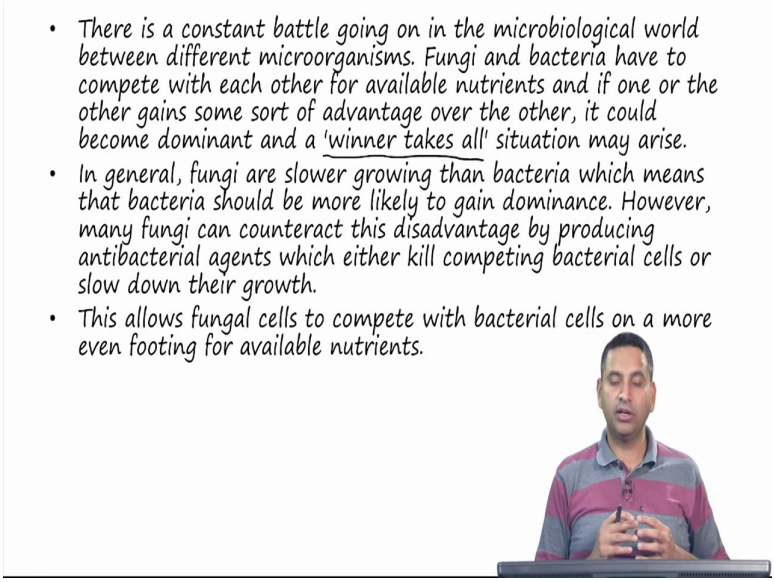

wherein there is only organism that survives.

In general fungi are slower growing than bacteria, which means that bacteria should be more likely to gain dominance because they grow much faster. However many fungi can counteract this disadvantage by producing antibacterial agents which either kill competing bacteria or slowdown their growth.

These compounds allow the fungal cells to compete with bacterial cells on a more even footing for available nutrients.

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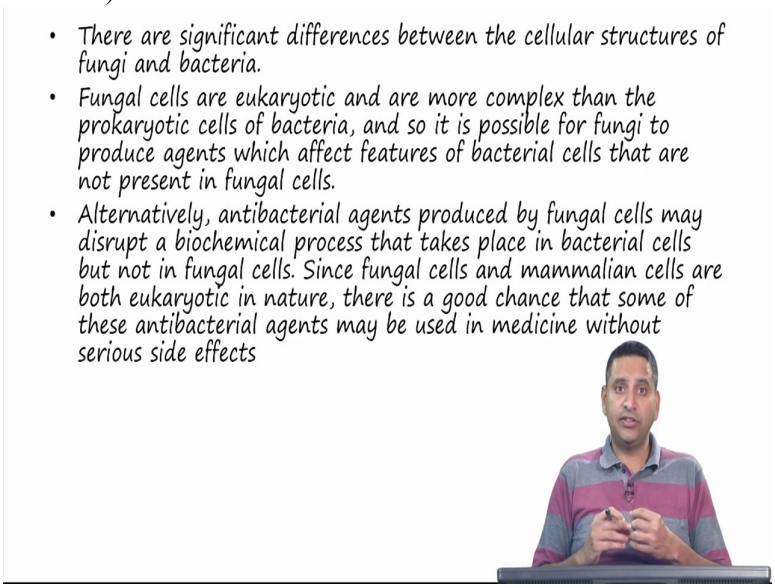

And since there are significant differences between the cellular structure of fungi and bacteria which need attention.

So fungal cells are eukaryotic and more complex than prokaryotic cells or bacteria. So it is possible for fungi to produce agents which affect features of bacterial cells but that are not present in fungal cells. Alternatively antibacterial agents produced by fungal cells may disrupt a biochemical process that takes place specifically in bacteria but not in fungi.

Since fungal cells and mammalian cells are both eukaryotic in nature there is a good chance that some of these antibacterial agents may be used in medicine without serious side effects.

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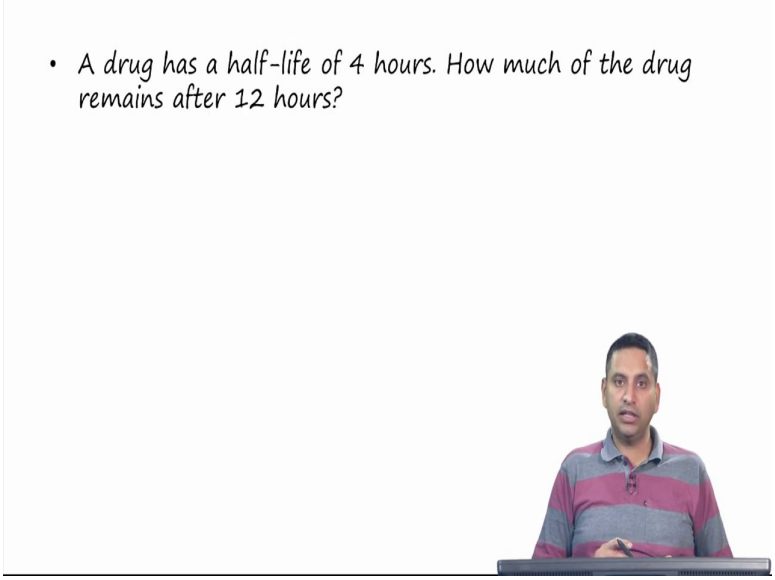

The next question is a drug has a half life of 4 hours. How much of the drug remains after 12 hours?

So in order to answer this question let us start with 100 percent of the drug.

In 4 hours it becomes 50 percent. In

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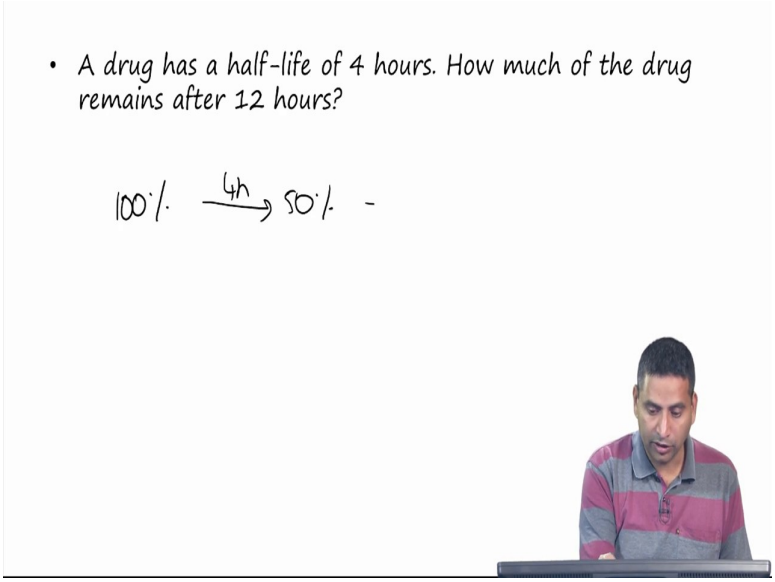

another 4 hours it becomes 50 percent of 50

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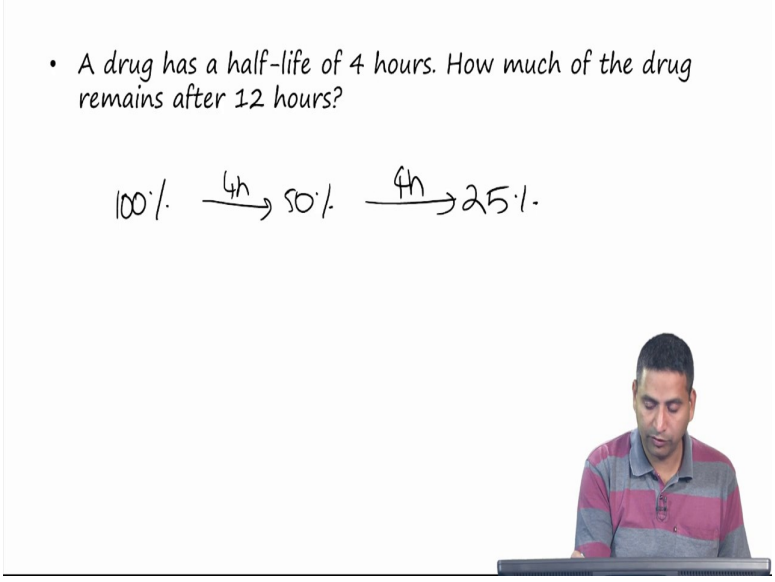

which is 25 percent. In another 4 hours it becomes 12 point 5 percent.

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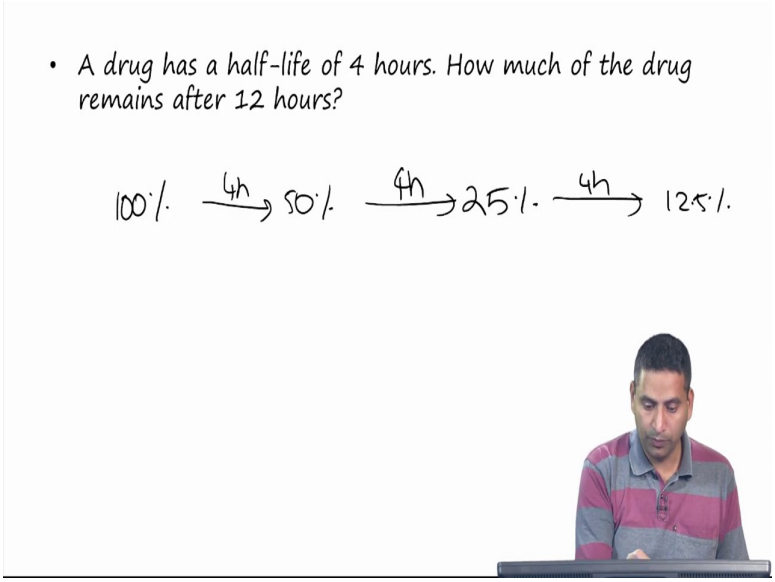

So 4 plus 4 plus 4 equals to 12 hours, so in 12 hours we would expect 12 point 5

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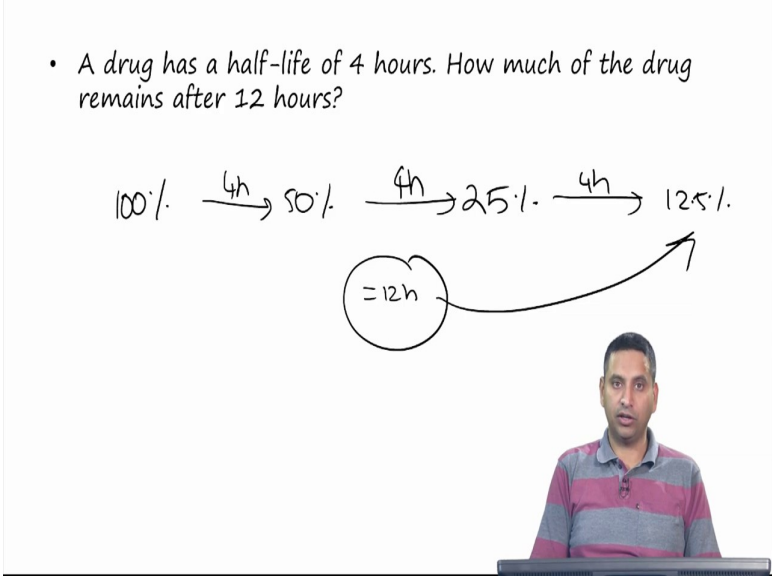

percent of the drug to remain.

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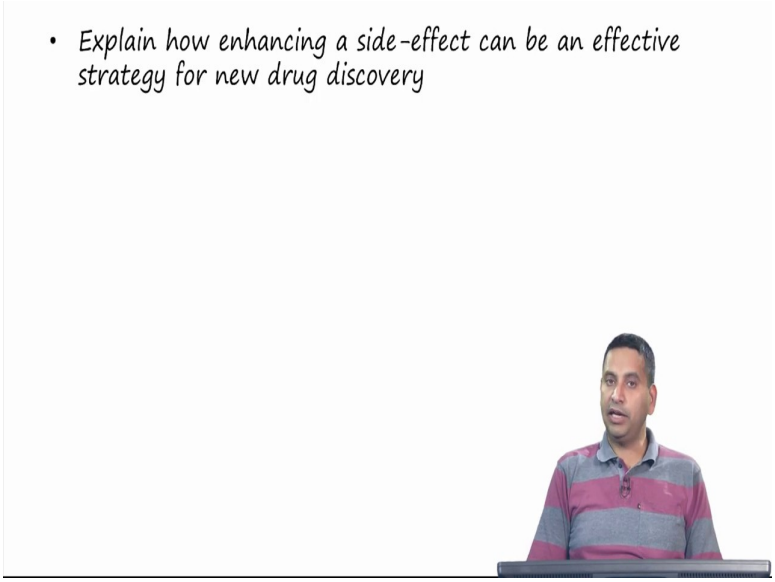

Explain how enhancing a side effect may be an effective strategy for new drug discovery.

So we have looked at several times about how we want to avoid side effects. So here is a very interesting strategy where we want to enhance the side effect.

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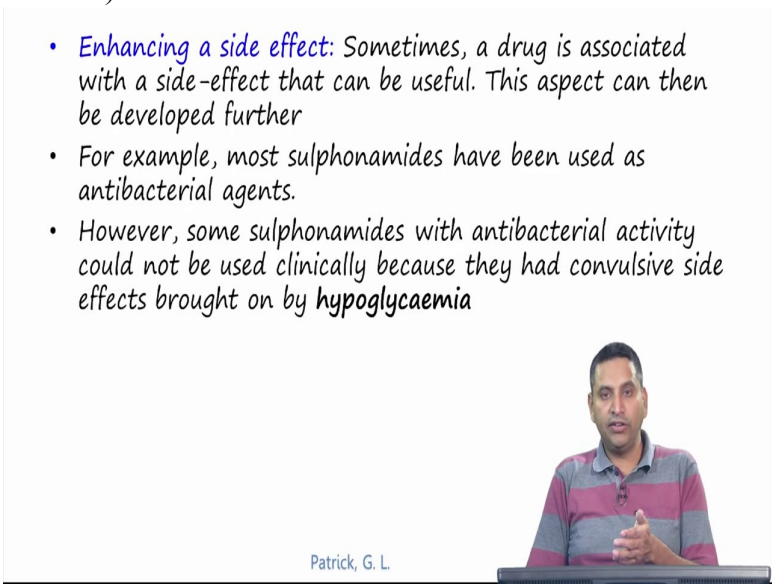

So enhancing the side effect is usually a strategy that we adopt during clinical trials. So when a drug is found to have a particular side effect then one can use that, or exploit that to develop a new drug. So for example sulphonamides have been used extensively as antibacterial agents.

But there are some sulphonamides which have antibacterial activity but they could not be used because they are associated with convulsive side effects

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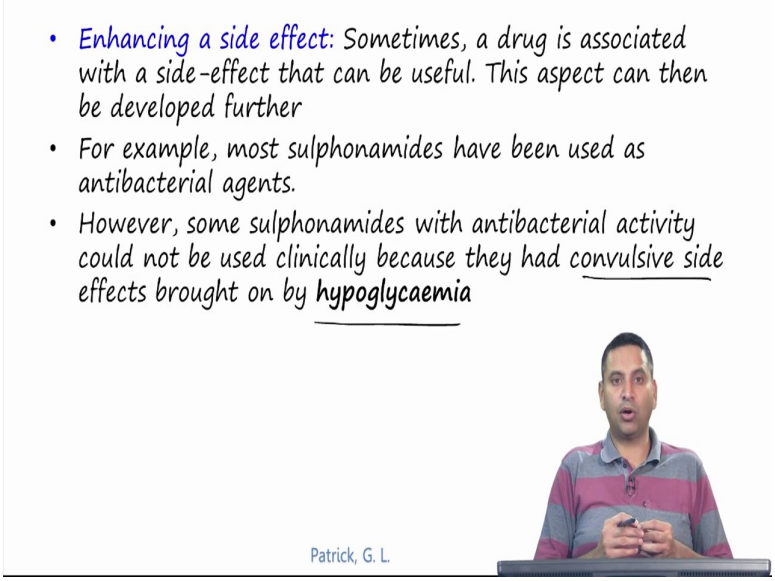

brought out by hypoglycaemia. Hypoglycaemia is nothing but lowering of blood sugar.

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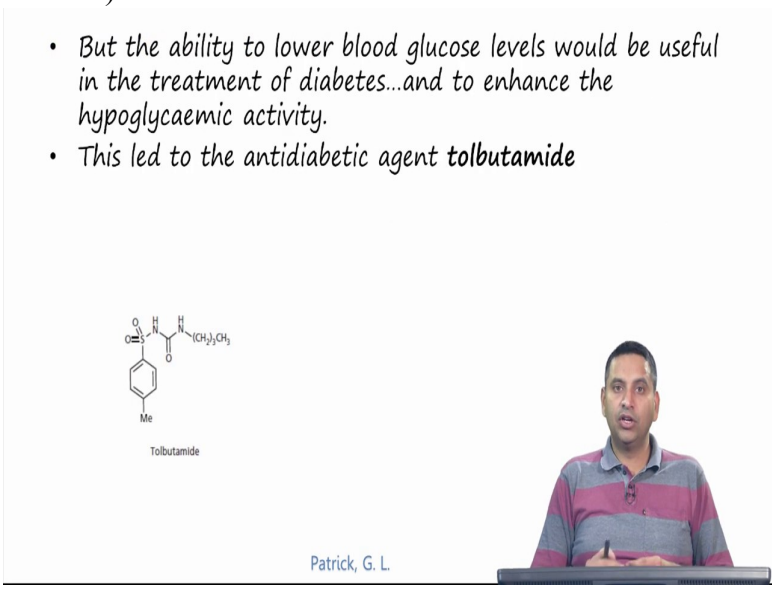

So the ability to lower blood sugar or blood glucose levels is useful in the treatment of an entirely different disease which is diabetes. So one can now use this method to enhance the hypoglycaemic effect and this strategy led to the development

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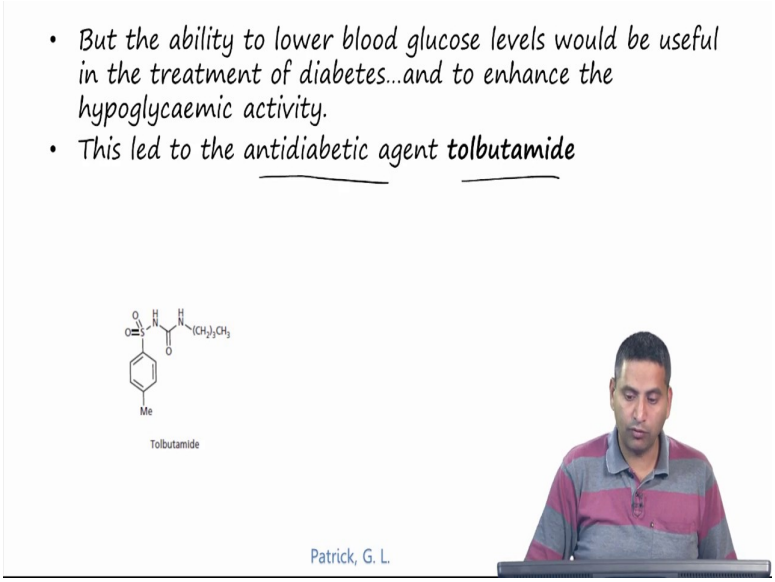

of tolbutamide which is a antidiabetic drug.

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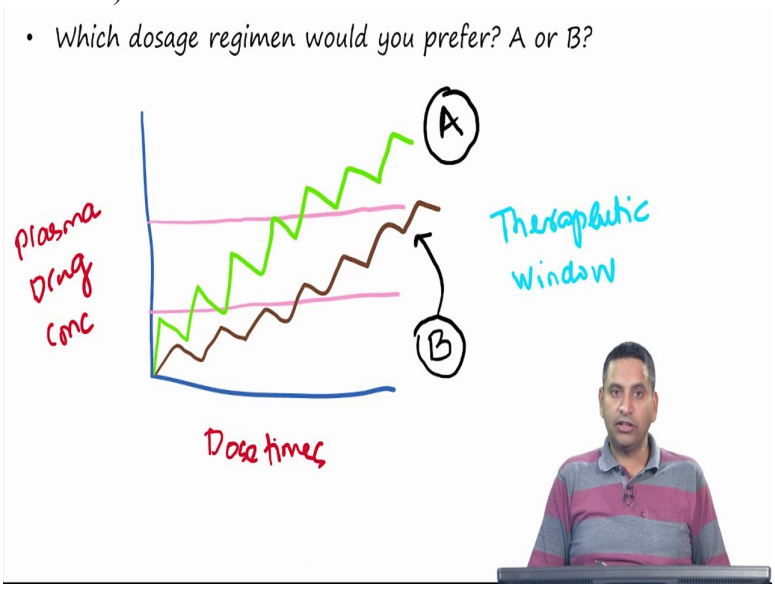

Next question is which dosage regimen would you prefer, A or B?

So this is an interesting question because we have a well-defined therapeutic window which is here.

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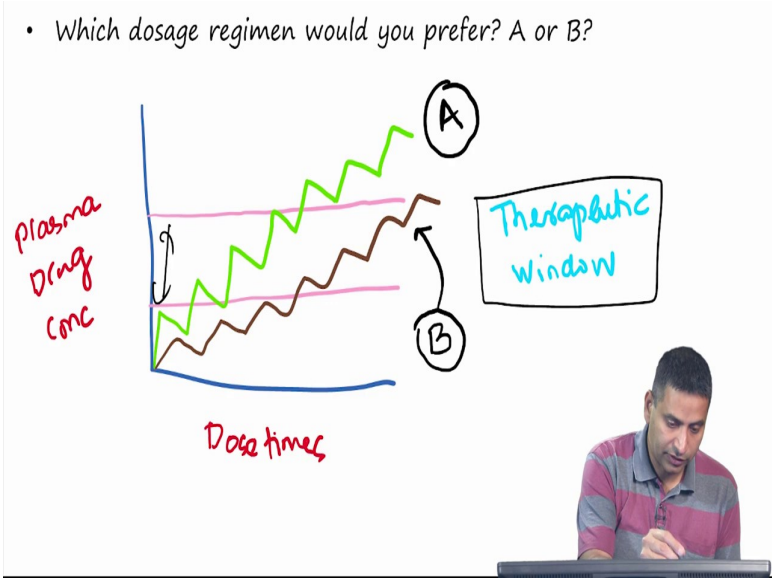

On the y axis is the plasma drug concentration. In the x axis it is dose times.

So here the dose is given, as you can see here is the second dose, here is the

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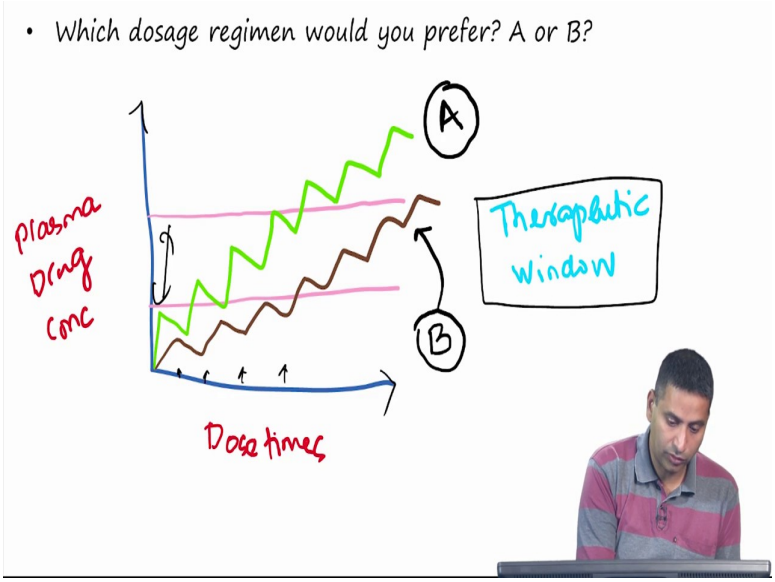

third dose, here is the fourth dose, fifth dose and so on. So if we want to have a rapid effect, that means within the third

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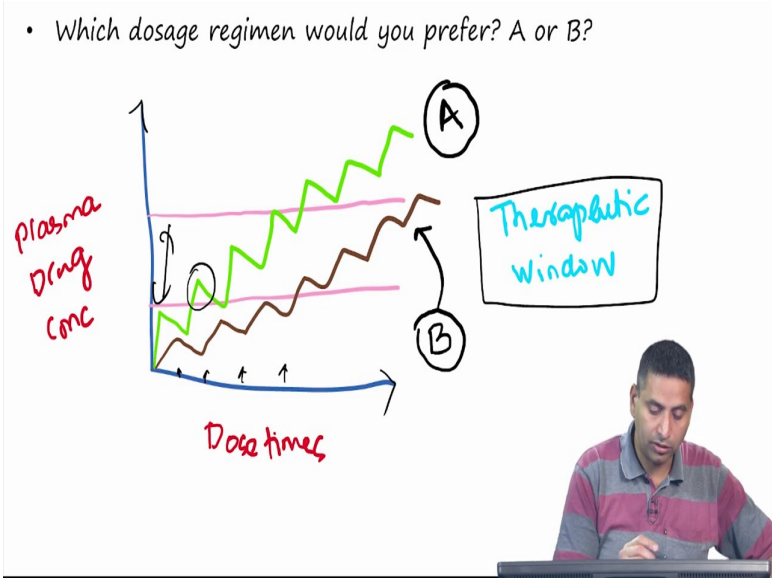

or fourth dose you have efficacy then we would prefer A.

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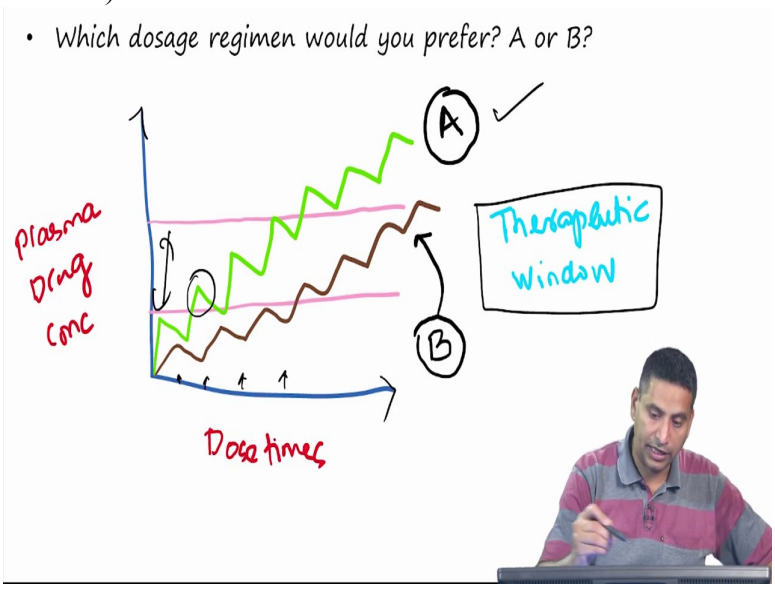

But we need to make sure that we do not go

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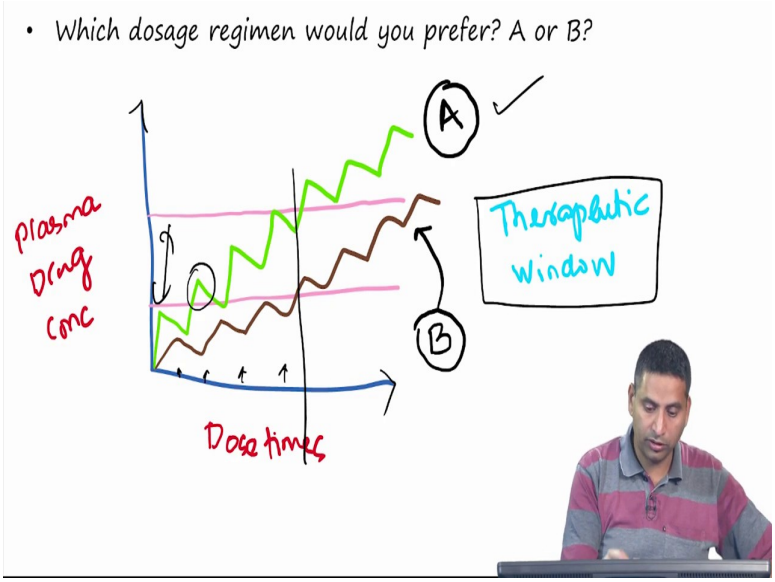

beyond this dosage regimen. If we prefer a longer duration of treatment and better efficacy for longer time then we would prefer B

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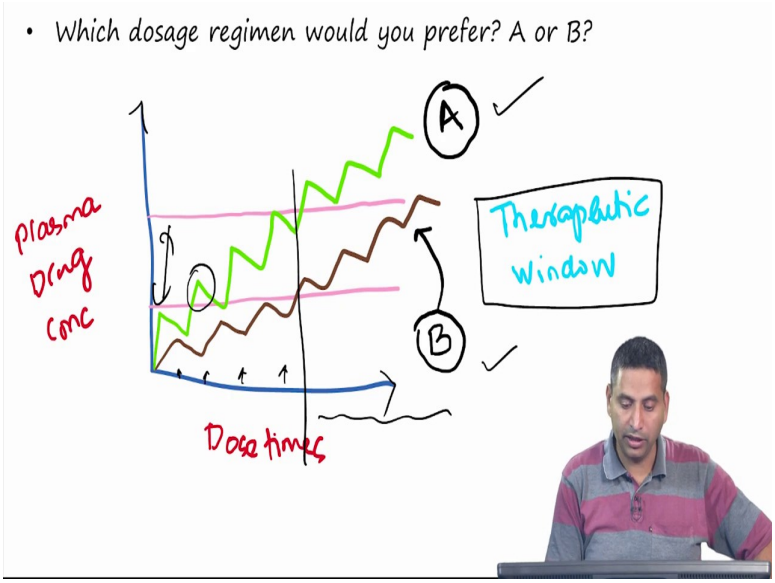

because this has a longer therapeutic window, or a broader therapeutic window under which the drug is still efficacious. However the number of doses needed for us to achieve the therapeutic window

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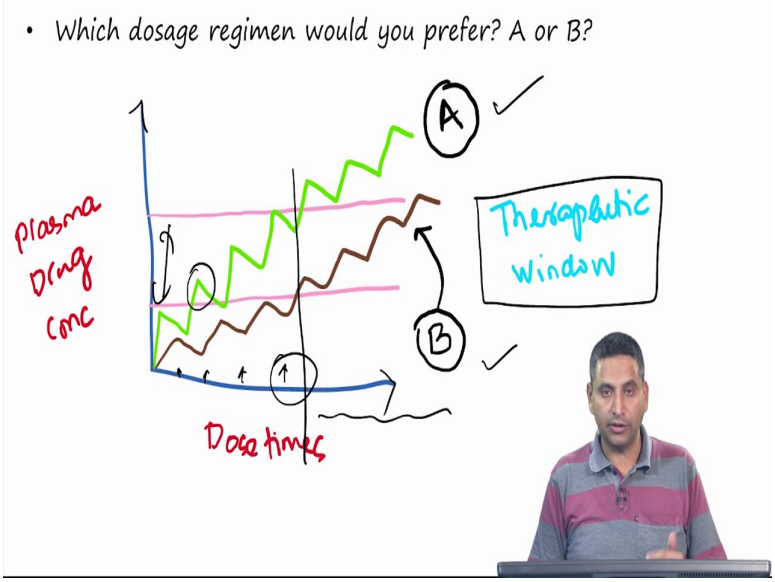

is still higher.