Medicinal Chemistry
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Lecture No 32
Pharmacokinetics Part I

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In today's lecture we are going to look at pharmacokinetics. So just

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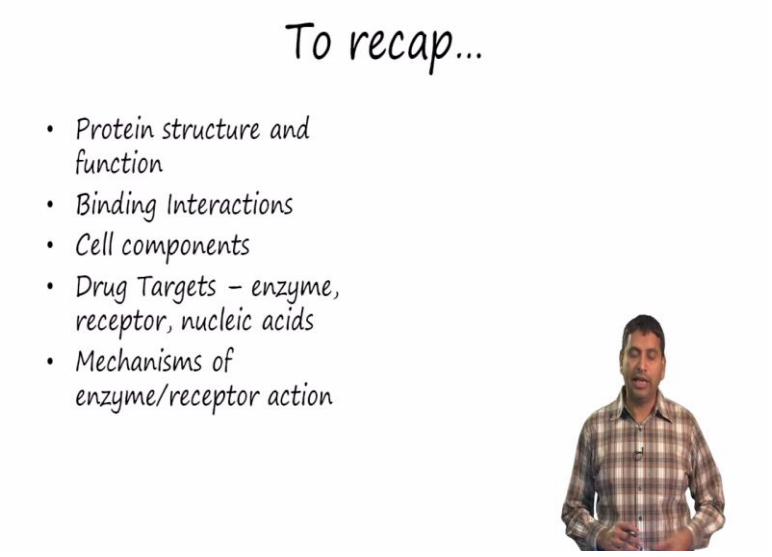

to recap what we have done so far. So what we have done is basically we have started from, you know some of the ways in which drugs were discovered in the past and we figured out that, you know most of those methods were not really rational in nature and they are, so they happened purely by accident and also to one observant person.

So the discovery of penicillin for example. If the person, Fleming had not observed the phenomenon it would have been difficult for us to discover the drug.

And then we decided or we sort of agreed that we would like to design drugs in a rational manner. And so in order to design drugs in a rational manner, we need to understand how cell functions. And so for that we looked at various components of a cell.

So if you look at, you know any cell it has a nucleus which is shown here, right.

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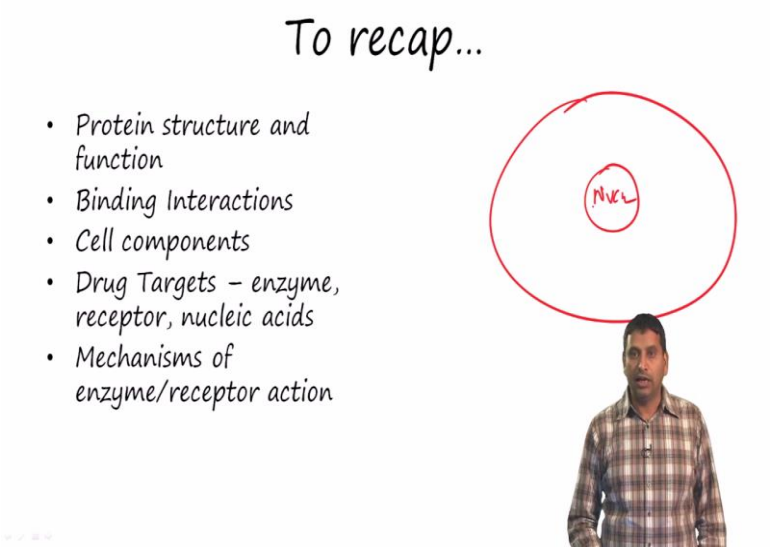

And, you know then you have mitochondria which is considered the

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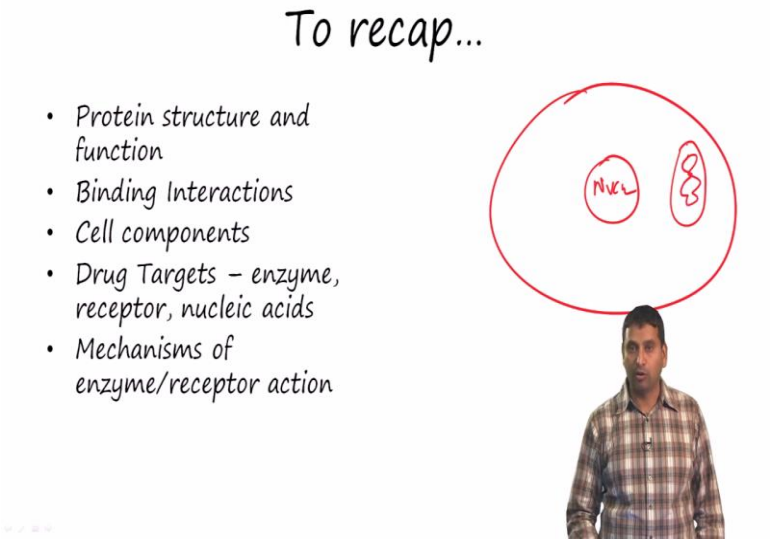

power house of the cell. And then you have, you know endoplasmic reticulum,

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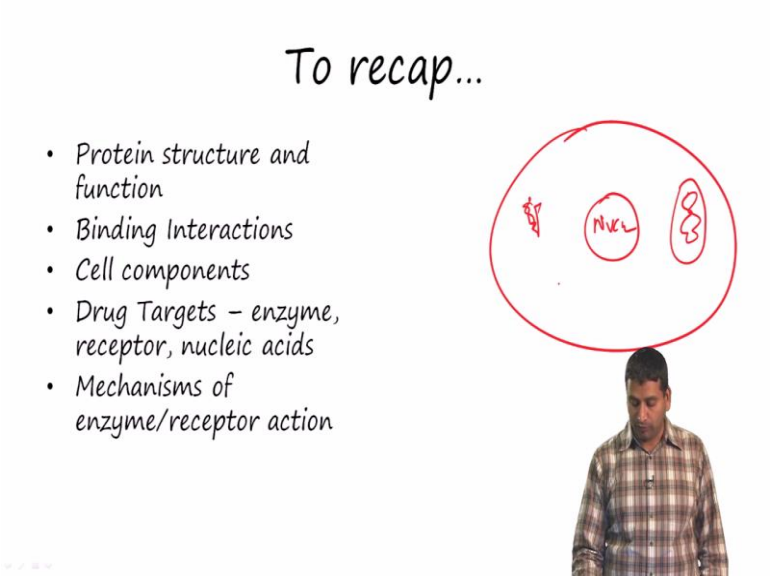

you have Golgi apparatus

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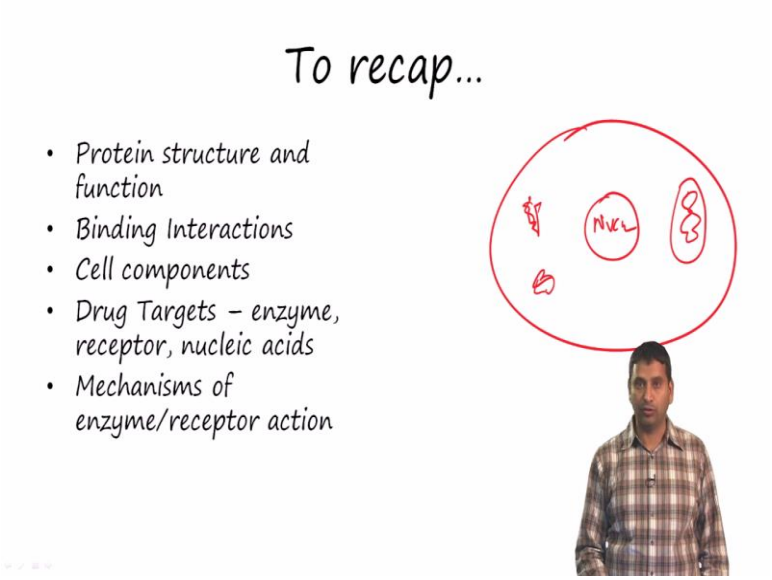

and so on and so forth, right.

And we also looked at, there is a, like there is a membrane

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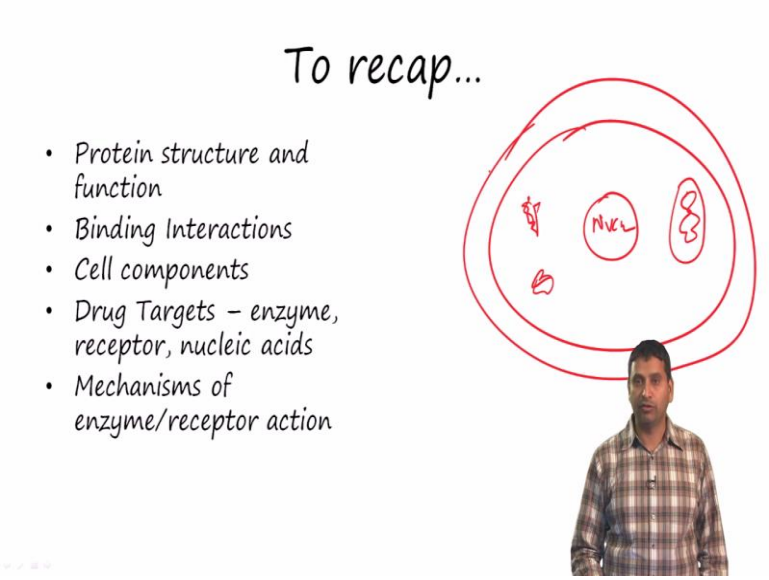

which is lipid rich membrane which has a bilayer, lipid bilayer and so on,

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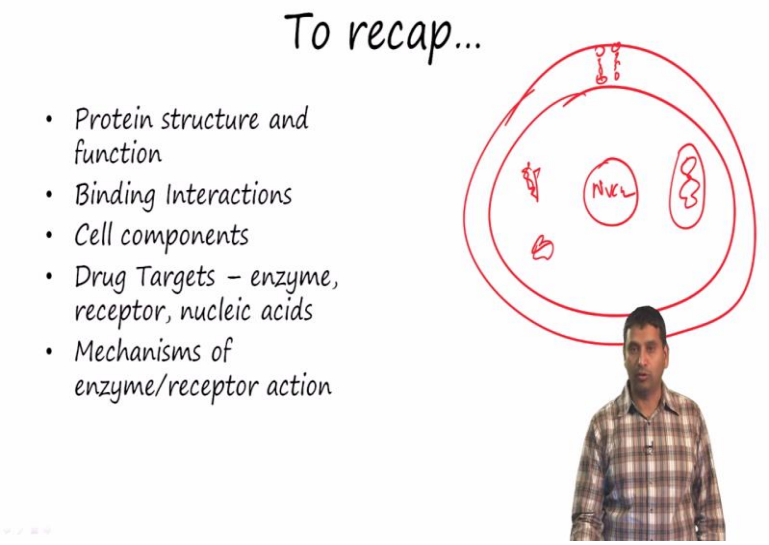

right. And so an important component of this, of the cell is a, is a protein

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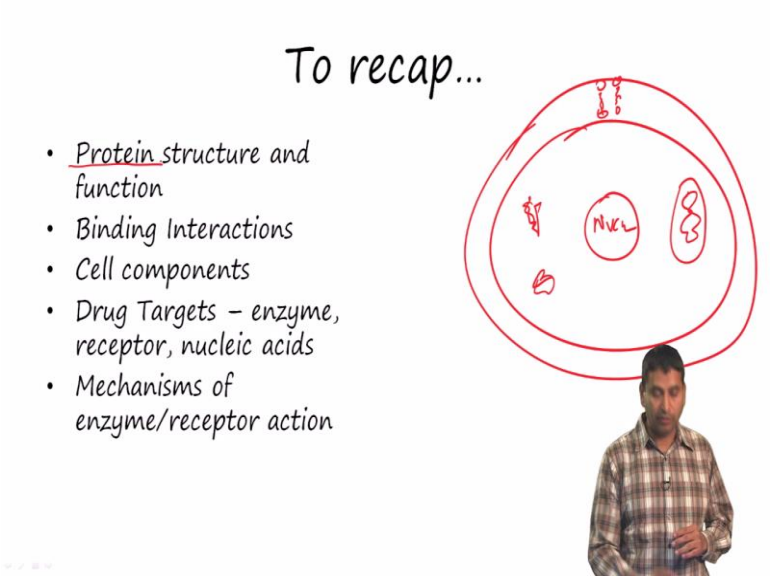

Ok.

So proteins are made of amino acids, so they are polymers of amino acids. So we looked at how the protein structure - primary, secondary and tertiary structures are available and we looked at how the function of a protein is determined by the, by the structure and what kind of amino acid residues are, are present on the surface.

So for example, a protein that is anchoring itself on the membrane, this part of it has to be,

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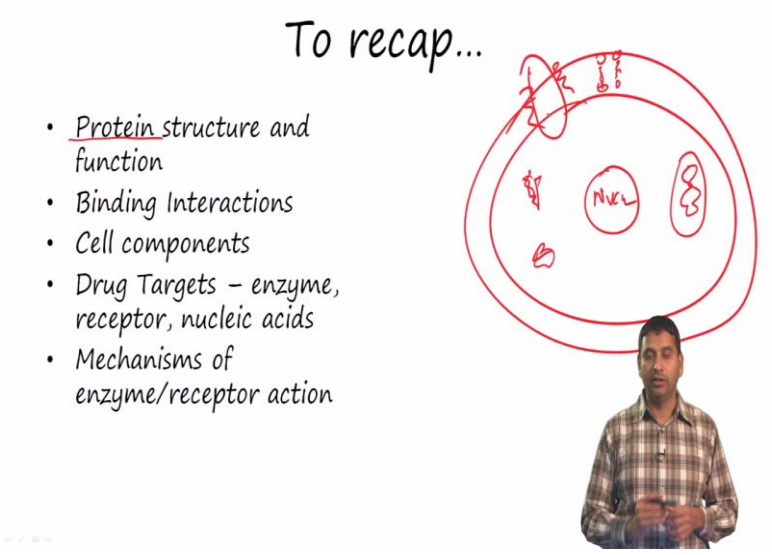

or would be expected to have lipid-rich region. So it would have amino acids which are hydrophobic in nature whereas the, the central part of it might be

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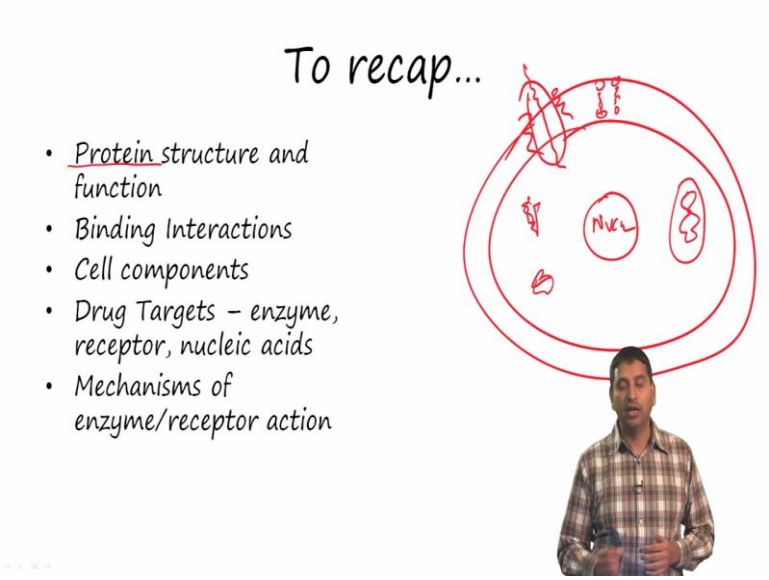

hydrophilic and so on.

So these are some of the important characteristics of, of the way in which a protein structure is organized and all this organization happens because of interactions among these various amino acids and across several amino acids as well which, which seem to be, you know in a coordinated manner they seem to be functioning and that is what, you know we understood from protein structure and function.

So these binding interactions that we looked at is,

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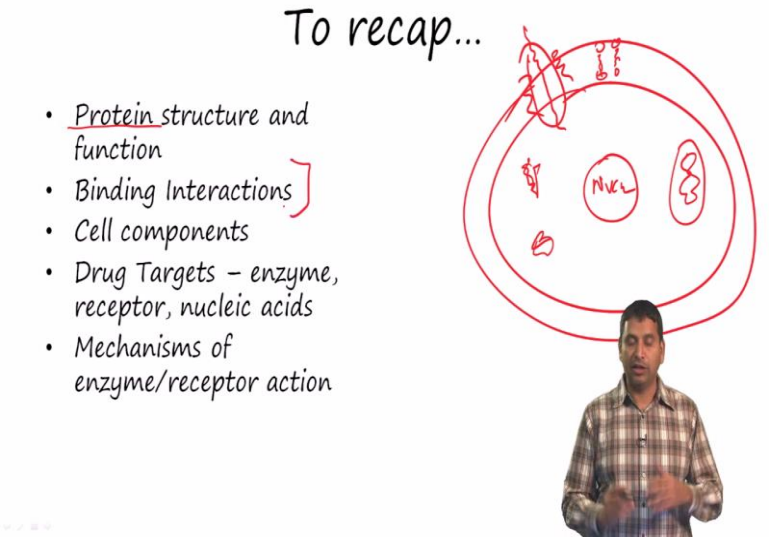

is you know within the protein as well as between the protein and a drug-like molecule or a drug. So broadly we looked at several types of binding interactions. It is the covalent interaction which is one of the strongest ones.

We also looked at hydrogen bonding and we looked at van der Waal's interactions and ionic interactions, salt bridge interactions and so on.

So this gives us an idea about what kind of interactions that we are sort of working with, right. And of course we looked at various components of the cell.

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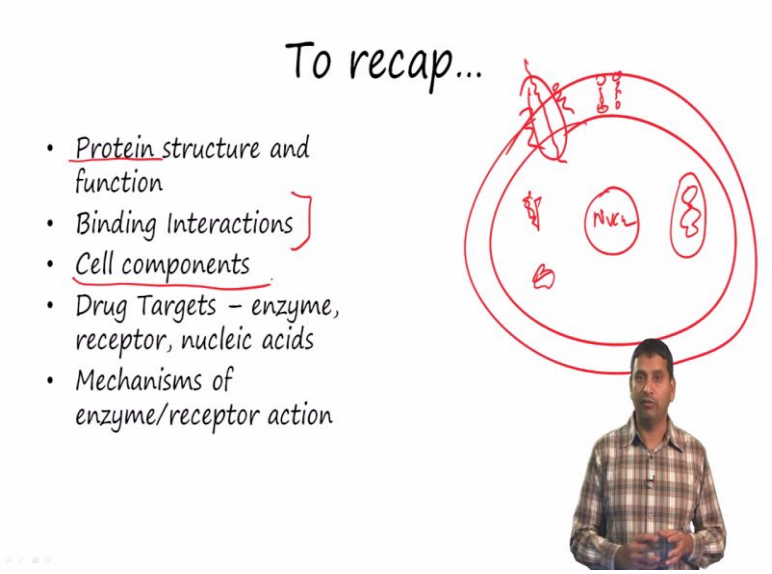

We have already seen that. You know we have seen that there is a nucleus; there is a mitochondria and so on.

And a majority of the drugs act one of the, on something called as a target. So drug does not act on the cell on the whole but instead it acts pretty much a specific target. Sometimes it can be more than one target but it is, it has some specificity and this target can be an enzyme which typically is a protein.

It can also be a receptor. So receptor is something that is on the surface which recognizes ligands and

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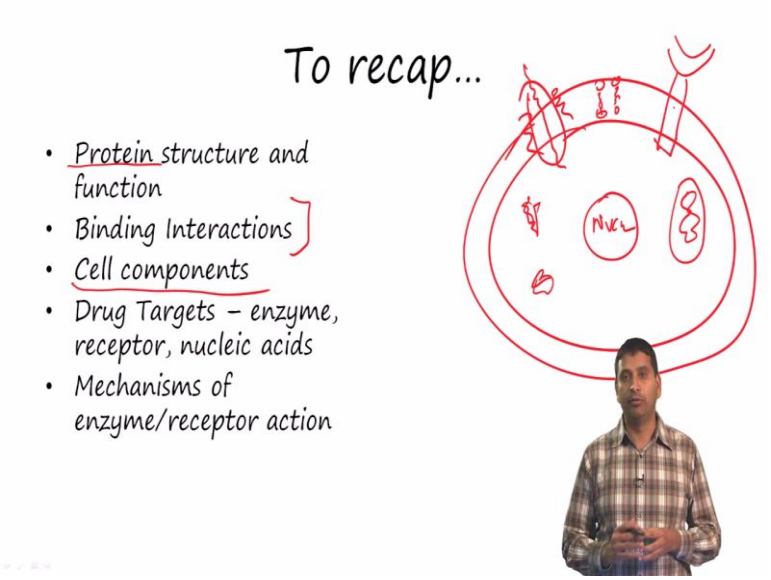

it helps with signal transmission. We have looked at both of these in detail. We have looked at how enzyme catalysis occurs. There are several theories of enzyme catalysis.

We have looked at how a receptor functions and how certain diseases you may want to increase the activity of a receptor, in the other case you; you may also want to decrease it and so on.

And then we looked at nucleic acids.

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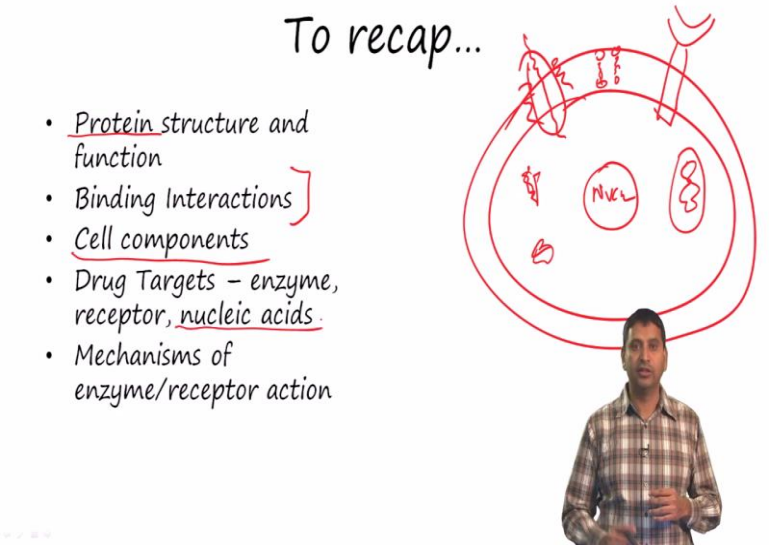

Nucleic acids are very important targets because they carry genetic information. DNA carries genetic information. RNA also carries information about how proteins are synthesized and RNAs themselves can be catalysts. So RNA is also a very important target.

And nucleic acids are typically targeted in cancers where, you know there is a rapidly dividing cell and so you may, you would prefer to, to hit the nucleic acids so that you can prevent the proliferation of the cell.

You can also have nucleic acids as targets in anti-bacterial agents. We have looked at several examples of those, Ok. Of course we spent some time in understanding

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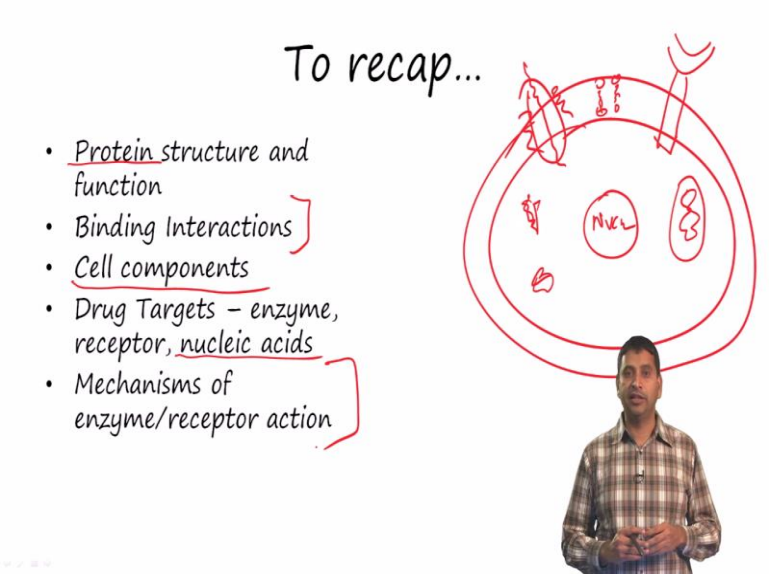

the mechanism of enzyme and mechanism of receptor action and so on.

So all this was done to build a framework. We built a very strong foundation on how the cell functions, how genetic information is transferred, how cells divide, how proteins are synthesized, how enzymes carry out their function, how receptors carry out their function.

We have also looked at some ways to quantify it. We have looked at Lineweaver-Burk plot and we have looked at various pharmacodynamics, that is how the receptor interacts with the, with the target ligand and so on. So all of this together provides us a very strong foundation.

Now in the next part we are going to look at another aspect of how this entire foundation is going to be used which is in pharmacokinetics. So after we understand this, all of this we also want to put this in perspective of the human body, Ok.

So human body is not a single cell, right. It is a combination of multiple cells and some of these cells can organize and form tissues and then you also have organs and so on and so forth.

So these are very important parts of the organism that we would need to understand in order for us to proceed further with new drug discovery. So in this context now let us look at what happens to a drug once it is administered, Ok.

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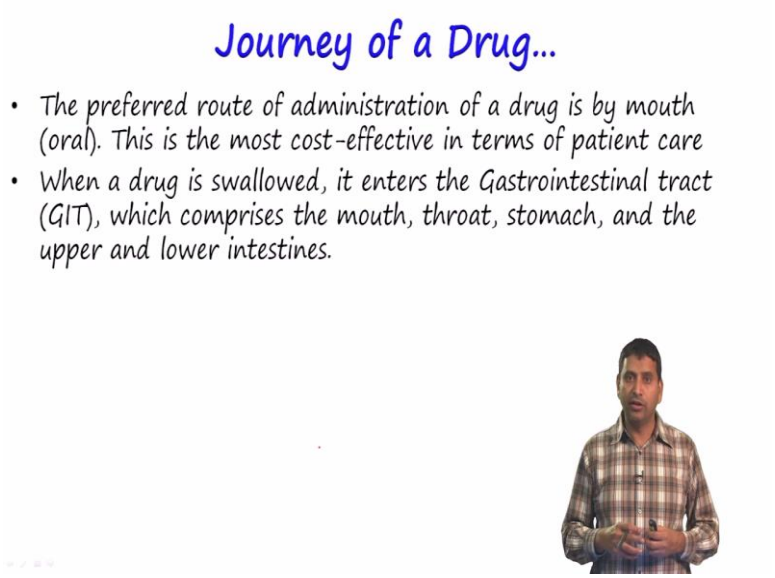

the, of course the preferred route of the administration of a drug is by mouth because that is clearly the most cost-effective and also people prefer to just swallow the drug rather than having an injection and so on.

So when the drug is swallowed it enters through the mouth, it enters the esophagus and it first enters the stomach, Ok.

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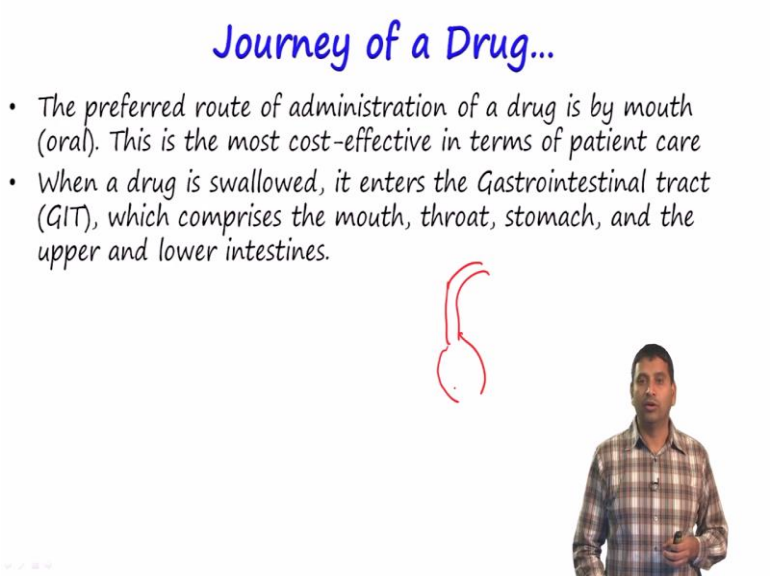

So this is just an approximate diagram, cartoon. It is not illustrative of the actual sizes of the stomach or the, or the intestines and so on.

So after it reaches to the stomach, it goes to the intestines. And there is a long intestine and the short intestine and so on. And so on and then it is excreted,

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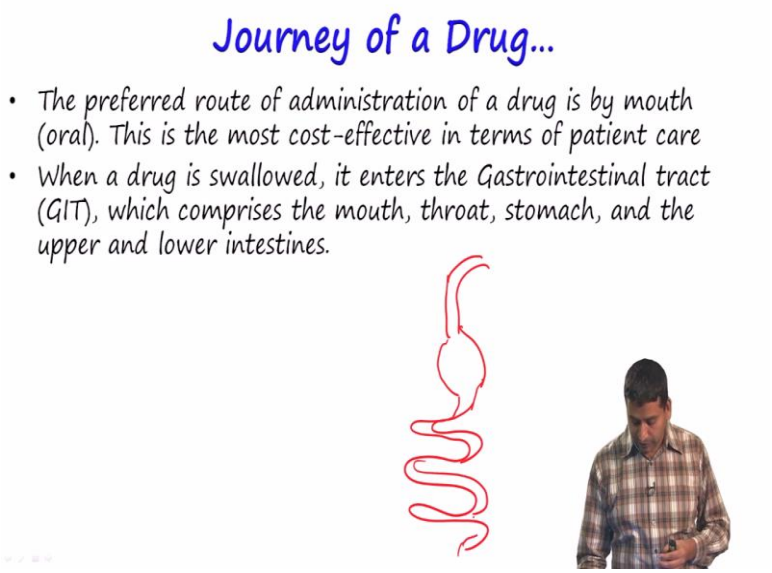

right.

So this is the journey of a drug. So it starts from the mouth, goes in, so in the stomach; the first place where it enters is the stomach, Ok. So this tract is called the GI tract

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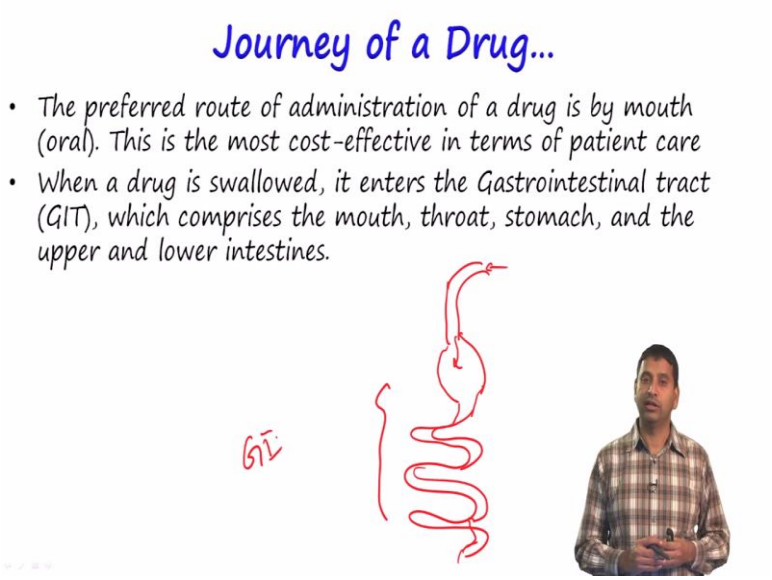

or the gastrointestinal tract, Ok. And it comprises of the mouth, throat, stomach, the upper and lower intestines.

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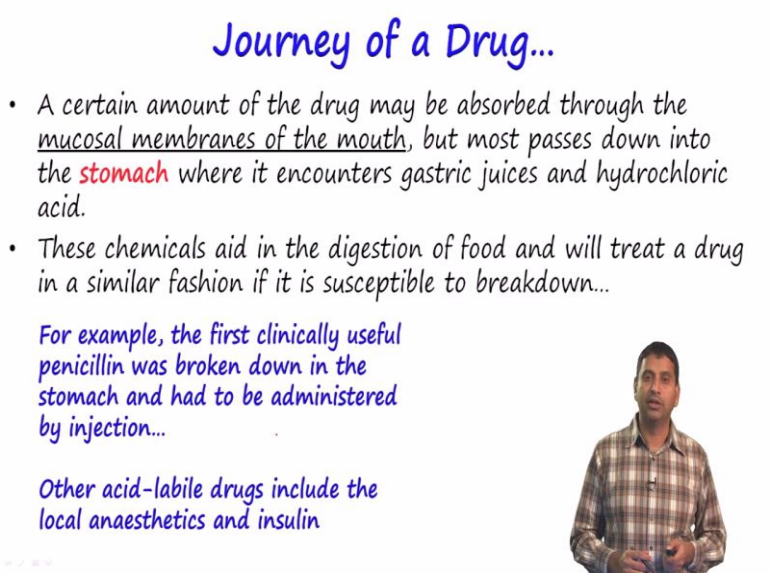

So the certain amount of the drug may actually be absorbed in mucosal membranes of the mouth but most of it passes down into the stomach.

In the stomach as we know there are gastric juices,

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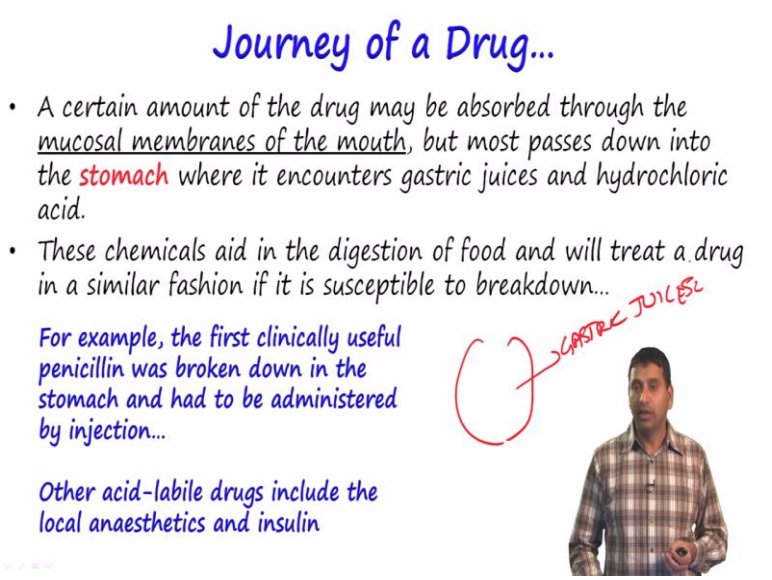

Ok who, which, whose pH is actually quite low, right. And the pH is maintained by, or the low pH is due to hydrochloric acid and so this is going to make the environment quite acidic, Ok. Now what this does is the combination of gastric juice and hydrochloric acid, it helps with digestion of the food. So drug is also exposed to this environment.

So similarly it is also going to be broken down, right. So for example the first clinically useful drug penicillin, when it is administered through the oral route is actually broken down in the stomach. It is extremely unstable in acidic medium. So even before it gets to the bacterium which is where it has to act, it actually has broken down. So this, these types of drugs are known as

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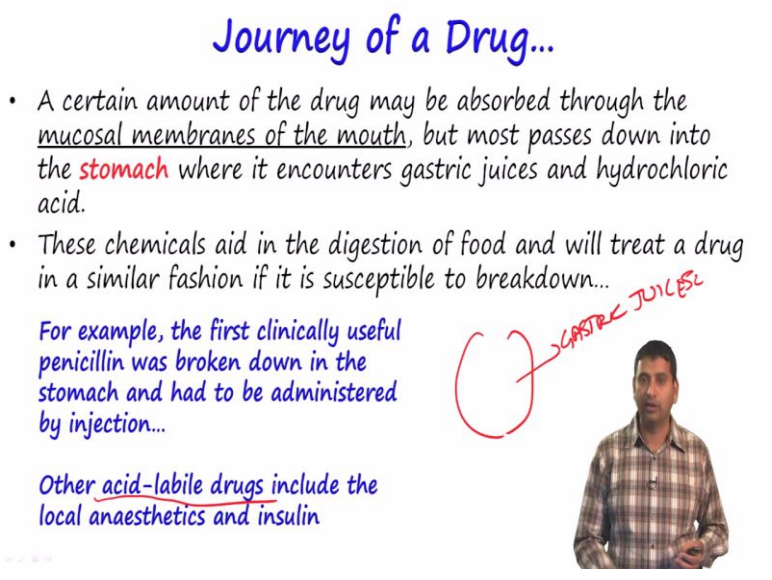

acid labile drugs.

And so acid labile drugs are not useful to be given orally and which also, some of the other examples are fairly large protein such as insulin or even local anaesthetics. So these are actually administered either through the blood or through inhalation.

So an important characteristic of a drug or a journey of a drug which is through the oral route will have to survive the stomach. So if it does survive, then it enters the upper intestine.

So we looked at it already, this is the stomach and then it goes into the upper intestine, Ok.

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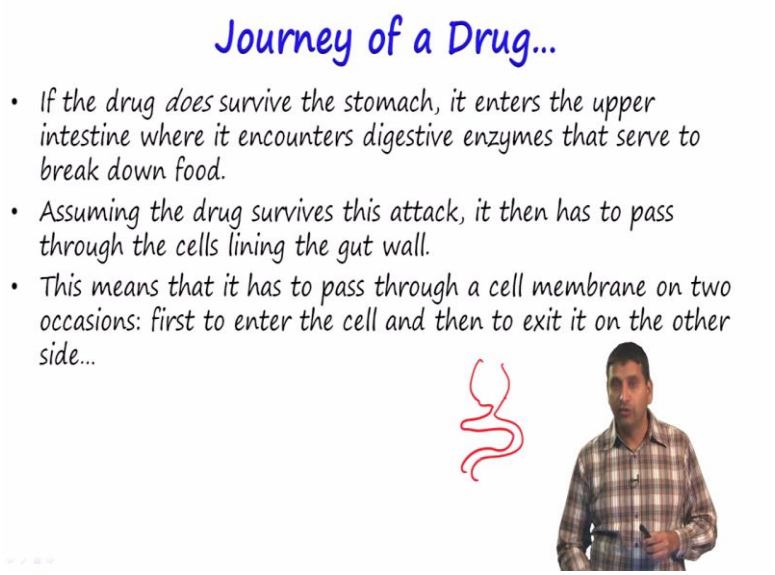

So in the upper intestine it encounters further digestive, digestive enzymes and this helps to break down the food further.

So here it will encounter a completely different set of enzymes compared to what the gastric juices have. And so assuming that the drug survives this attack then it passes through the cells lining the gut wall.

So on the, on the gut there is a lining through which

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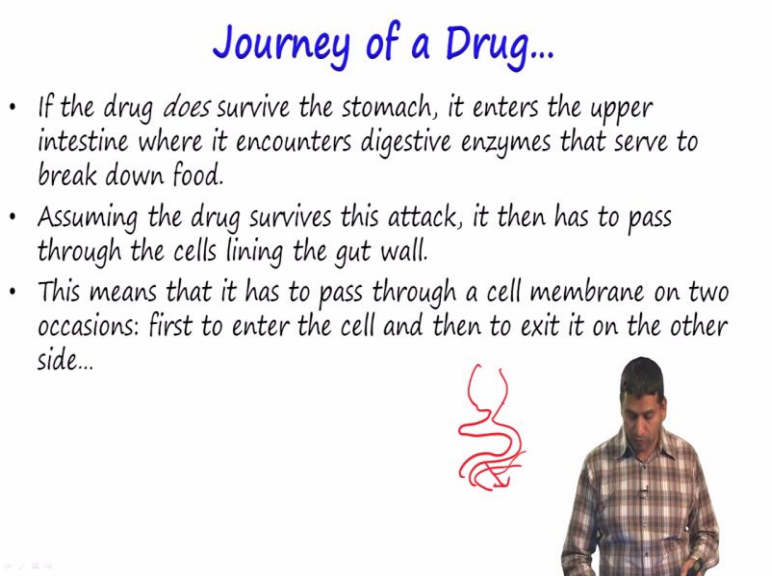

it has to pass. So here is the gut. In the gut there is a lining through which the drug molecule has to pass out,

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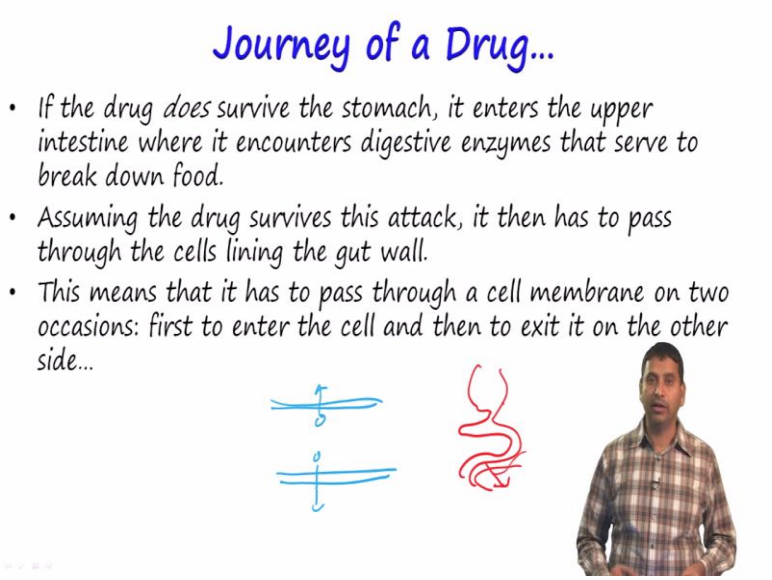

Ok. So this also means that has to pass through a membrane on two occasions.

First to enter the cell, that is here, first membrane and then it has to exit to the other side. So it is a fairly complex journey that we are trying to understand here.

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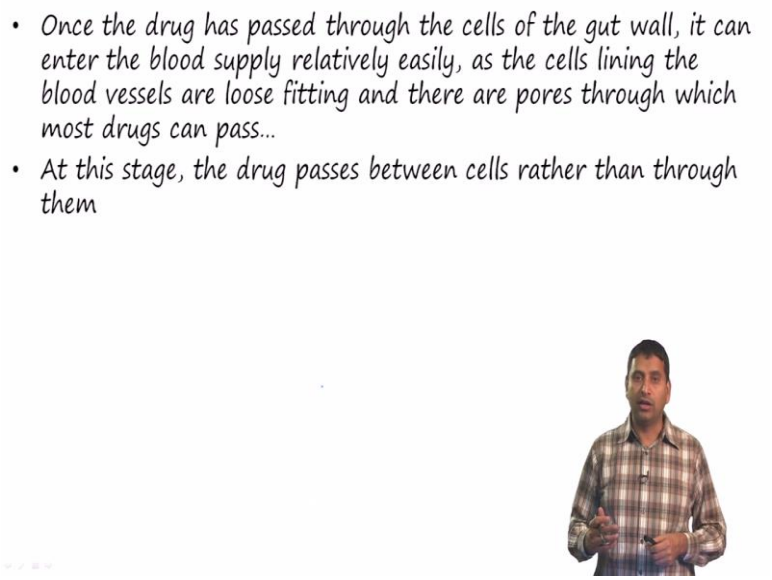

Once the drug has passed through the cells of the gut wall, it can then enter the blood supply relatively easily because the cells lining the blood vessels are loose fitting and therefore there are pores through which most drugs can pass.

So once you have the intestine lining over here, the drug enters and then the blood supply is pretty close. And so it just enters and gets into the

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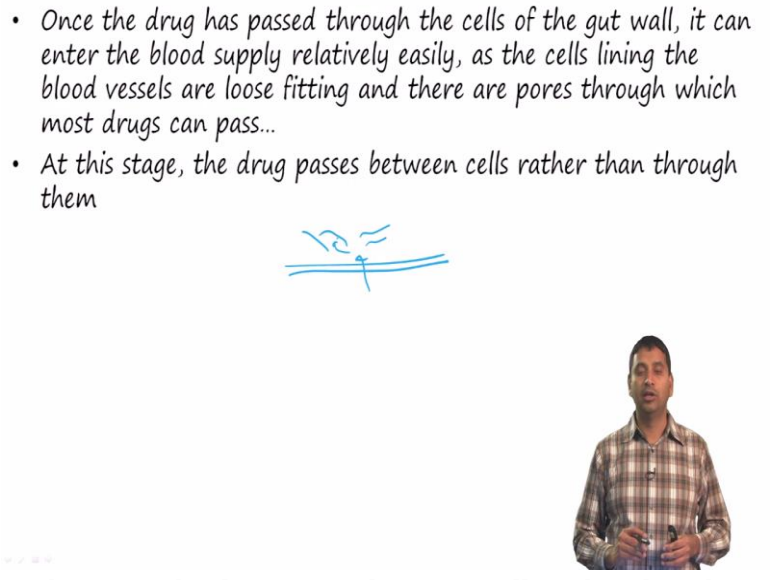

blood supply. So at this stage the drug passes between cells rather than through cells.

So you have a situation where there is a cell here, there is a gap, there is another cell, there is a gap and so on. So the drug actually,

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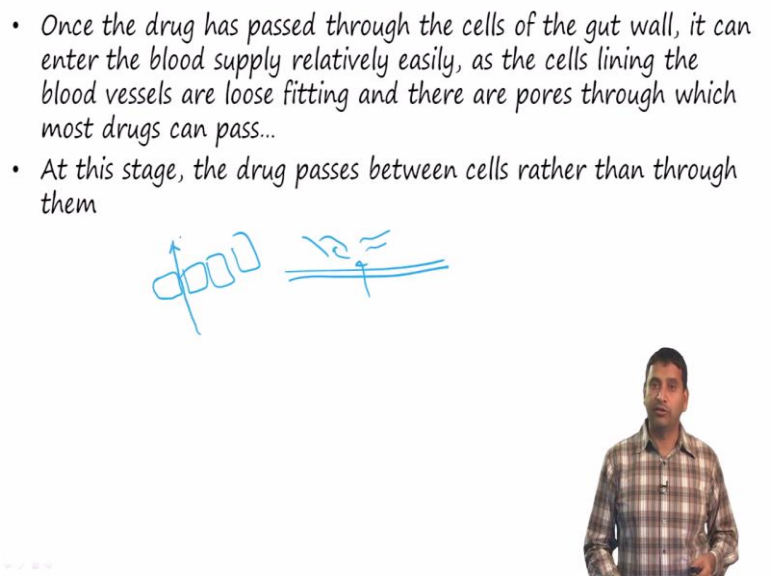

it passes between the cell rather than passing through them.

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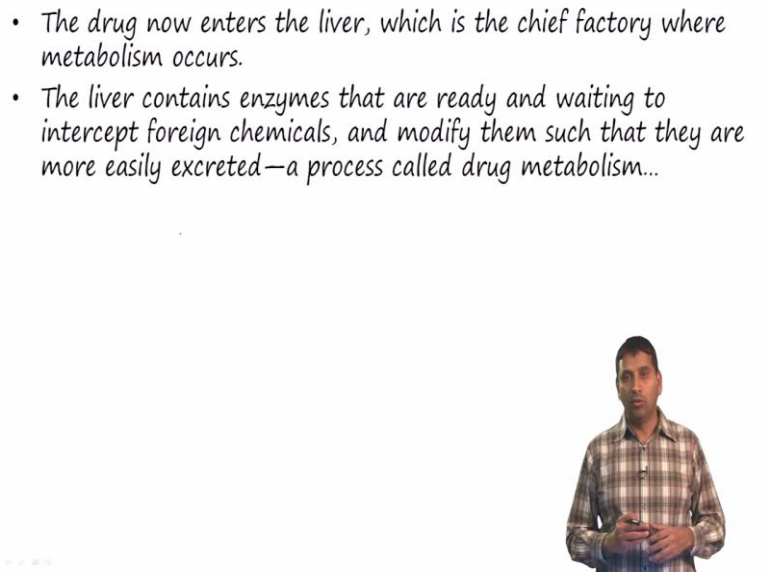

So now the drug enters the liver, Ok.

So liver is the, the major factory where metabolism occurs, Ok. So liver contains a huge range of enzymes which we will look at later, that are ready and waiting to intercept the foreign chemicals.

So keep in mind

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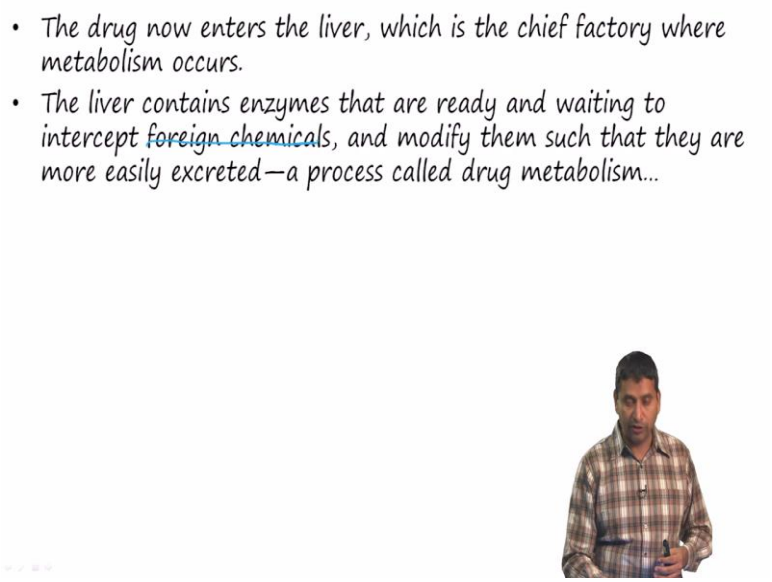

that as far as we are concerned the drug is a foreign chemical. Now the role of these enzymes is to actually modify these drugs, is to break them down, or put in something on it so that it is easily excreted. So the major role of the enzymes is to make the drug or the foreign molecule into easily excretable species. And this process is called as

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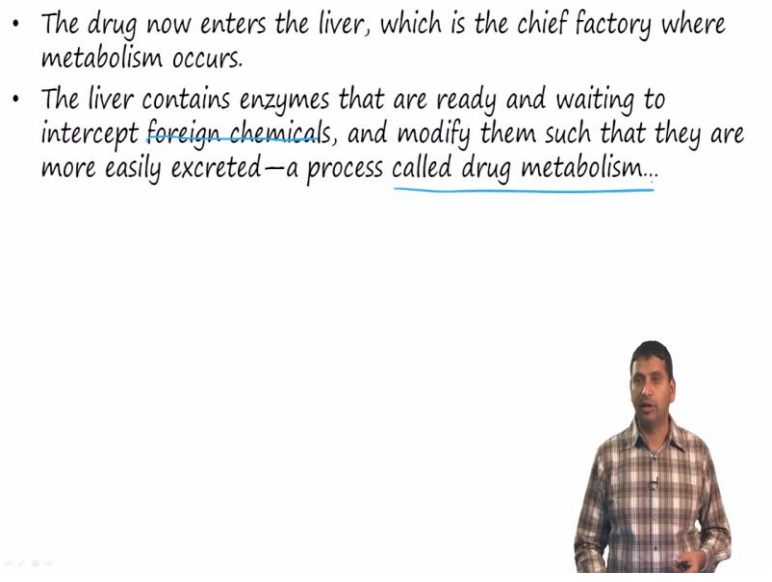

metabolism.

Now

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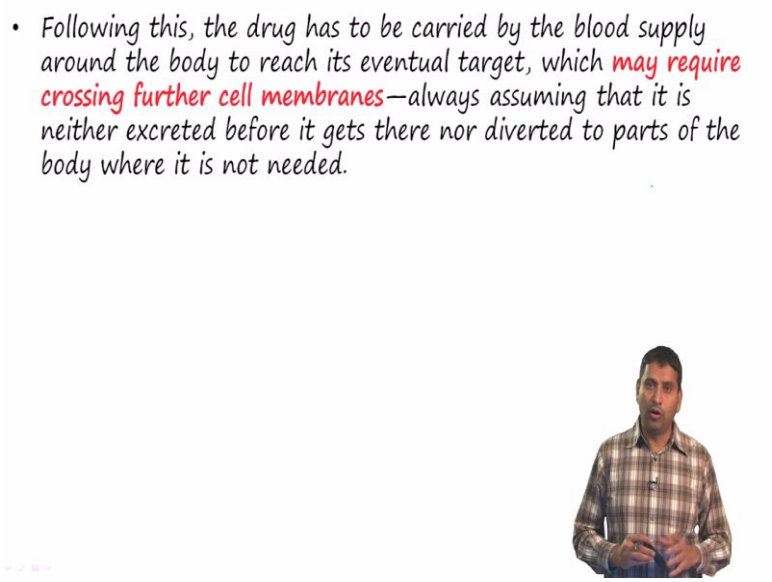

following this, the drug then has to be carried by the blood supply around the body to reach its eventual target. So keep in mind, we take an antibiotic for example because we have a bacterial infection.

So bacterial infection may be in a local area. That means it may be only in the gut or only the kidney and so on. So the drug has to be able to be transported to the area where the infection is present. Or, if for example we take an anticancer drug so the cancer may be in one part of the body, and the drug has to reach that part of the body for it to act on the cancer cells, right.

So here at the target it may require further crossing of cell membranes, Ok. So let us say, for example there is an area where there is a infection.

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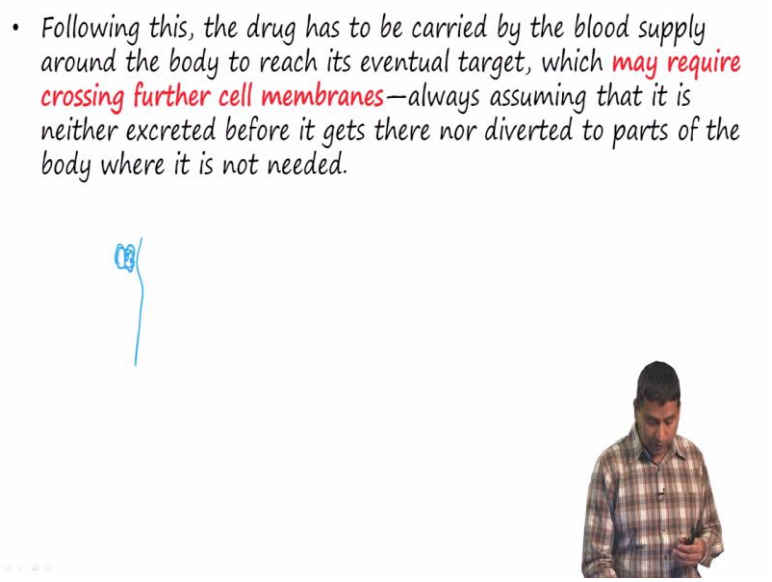

so this is a bacterial infection. So now the drug has to cross these membranes, get into the bacterium and let us say it is hitting the DNA of the bacterium, it is going

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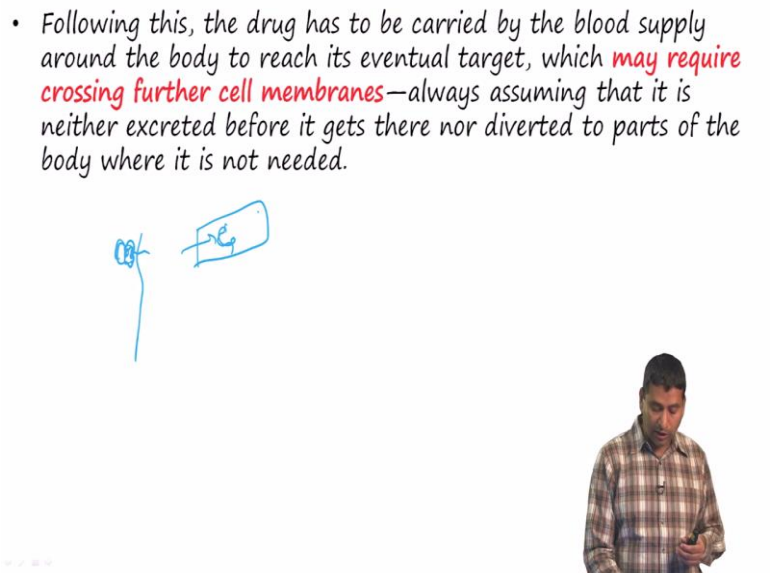

to have to get into the bacterium and then hit the DNA, right.

So therefore the drug will have to, may be, it may be necessary for the drug to cross further cell membranes before getting to the target. Now in this entire process we assume that it is not excreted before it gets

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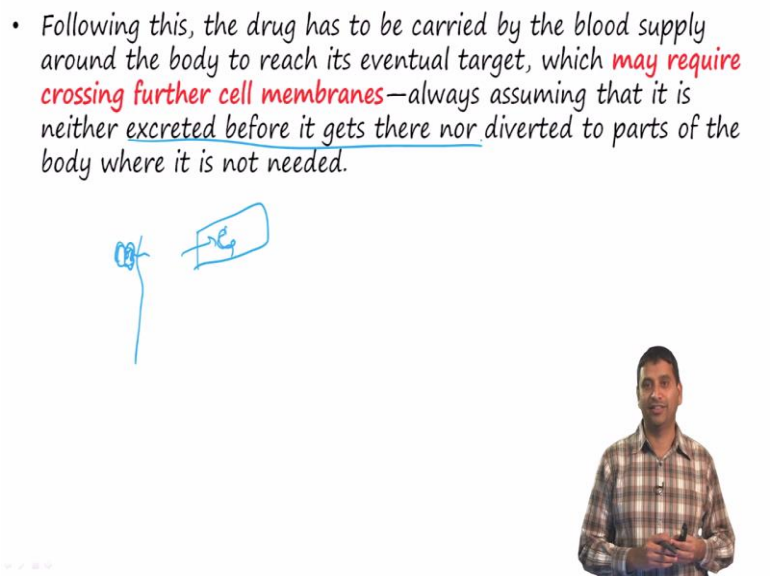

there, Ok. Or we also have to assume that it is not diverted to other parts of the body where it is not needed.

Let us say we have an infection in the, in the kidney but the drug gets diverted to the small intestine or it stays in the liver and so on. So that becomes a problem because it is not able to act at the area where it is supposed to act.

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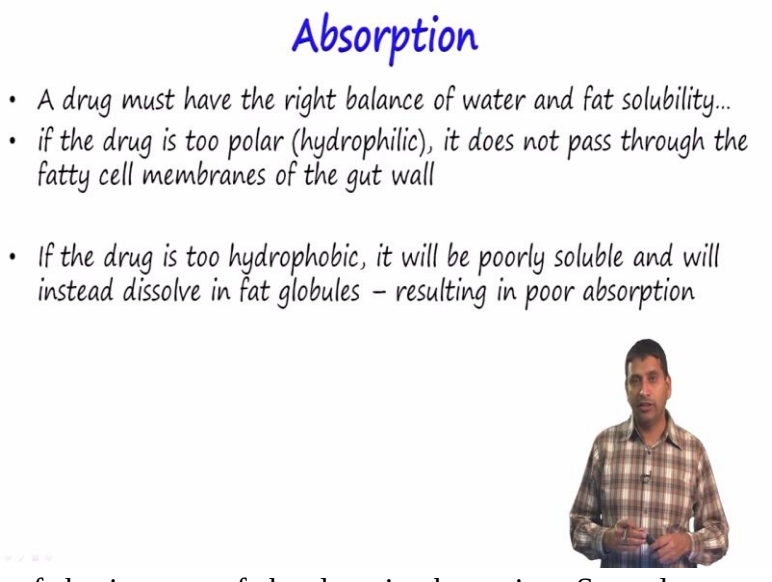

So the next part of the journey of the drug is absorption. So a drug must have the right balance of water and

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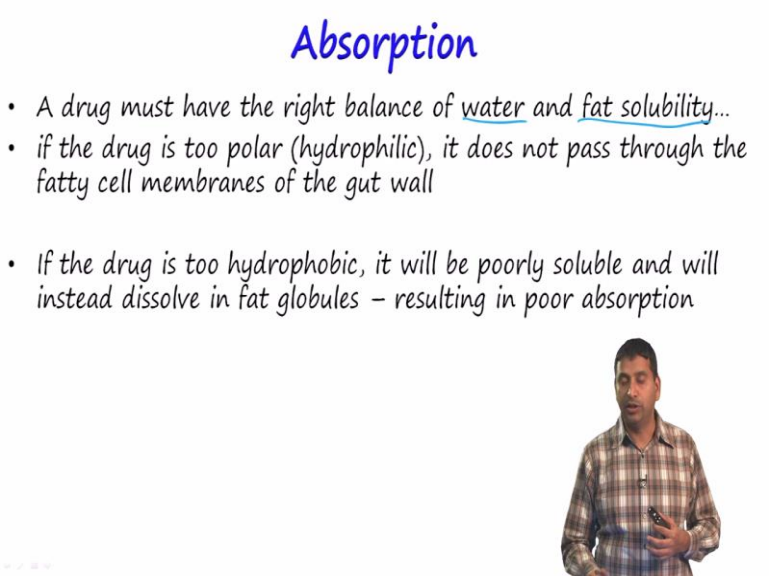

fat solubility, Ok. So later on in the course we will look at an important parameter known as partition coefficient or log P and we will look at it in more detail as how to determine it and so on.

But we should have the right balance of water and fat solubility. If the drug is too polar, that is if it is too hydrophilic then

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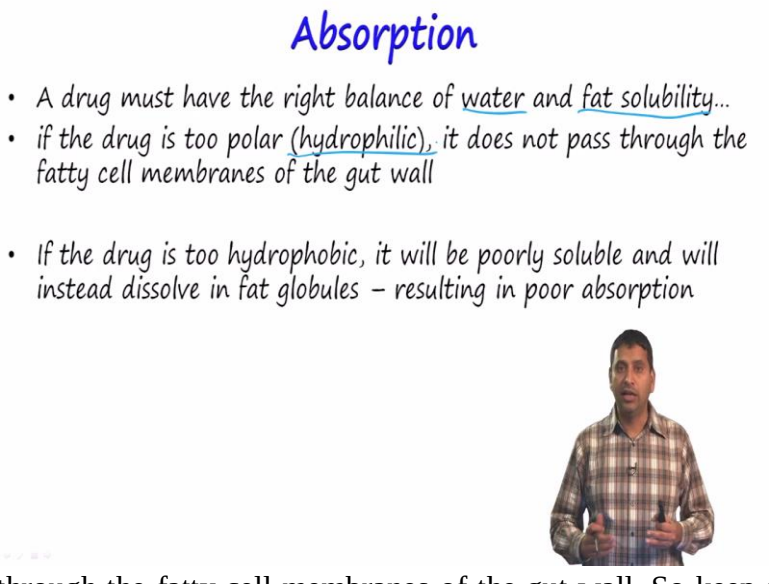

it does not pass through the fatty cell membranes of the gut wall. So keep in mind it has to cross this gut wall that we are describing. So it has to get into this membrane, spend some time here

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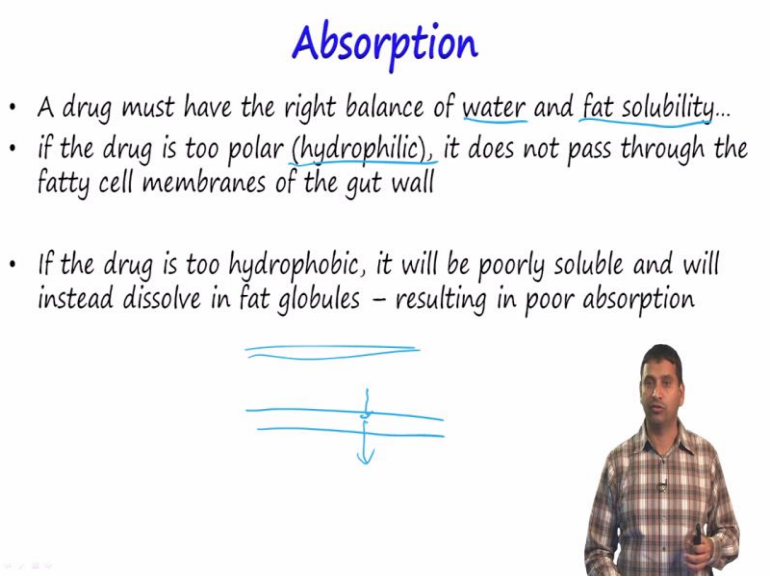

and then cross. So if it is unable to get into the membrane then it is going to be excreted.

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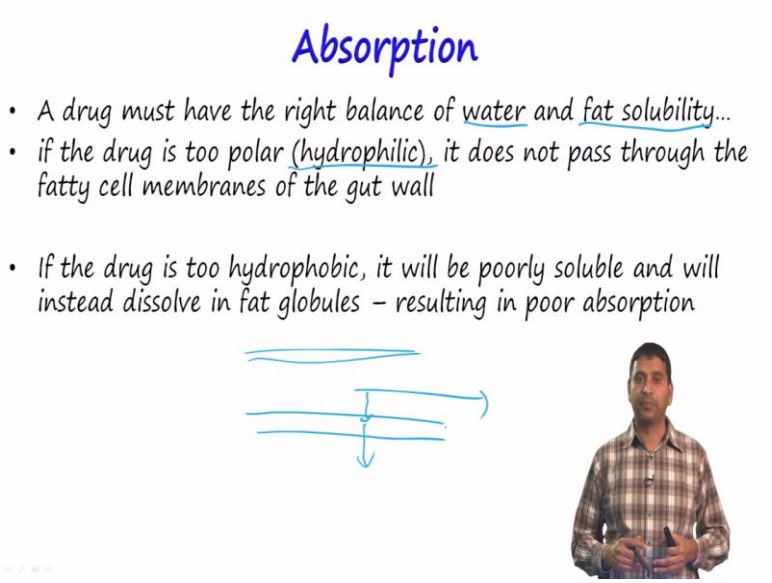

If on the contrary, if the drug is too hydrophobic it will be poorly soluble and what happens is it ends up dissolving in these fat globules,

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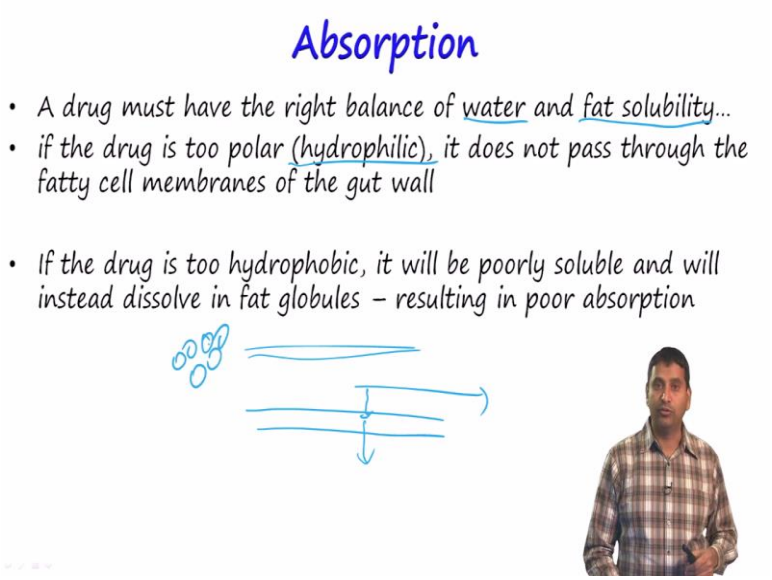

Ok so fat globules are present, you know in the, in various parts of the body and, then it, the drug will then partition into these fat globules.

Again this is not very useful because the fat globules are not the area of the disease. You may want to hit the, you may want the drug to act on, in the kidney. So this will lead to poor absorption.

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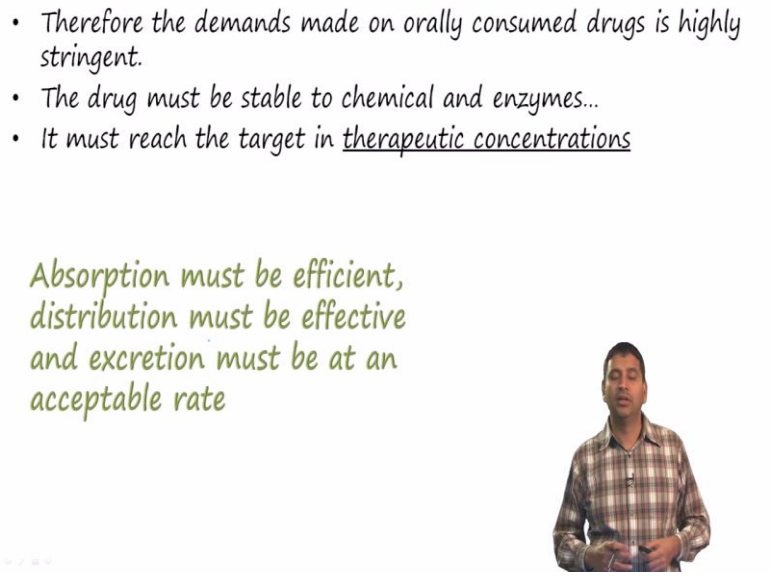

Therefore the demands made on a orally consumed drug is extremely high, right. So the drug must be stable to chemical and enzymes.

For example it should be stable in the stomach to the digestive enzymes then it should be stable in the gut because if it is going to get destroyed there then it is going to get excreted and it has to cross membranes very properly.

It must also reach the target in therapeutic concentrations, Ok. So we need to understand this better. We have looked at parameters such as IC_{50},

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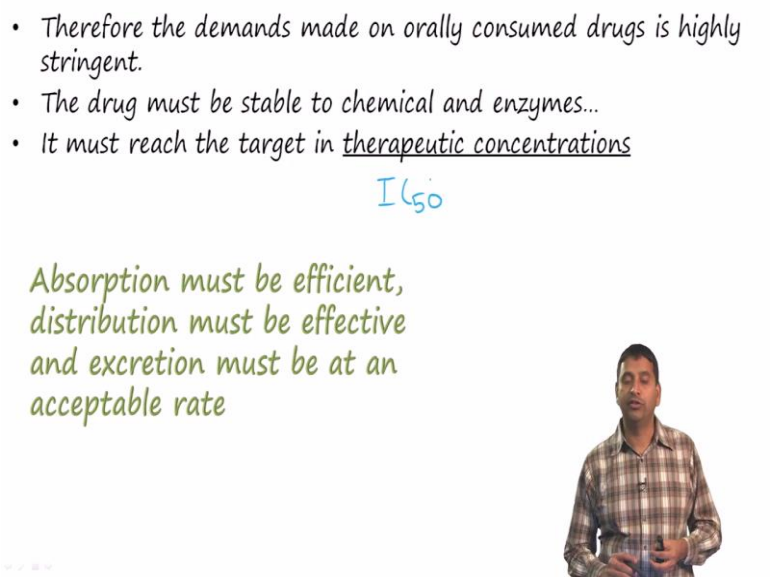

which is basically the concentration of the drug required to inhibit 50 percent of let us say an enzyme activity, Ok. So now,

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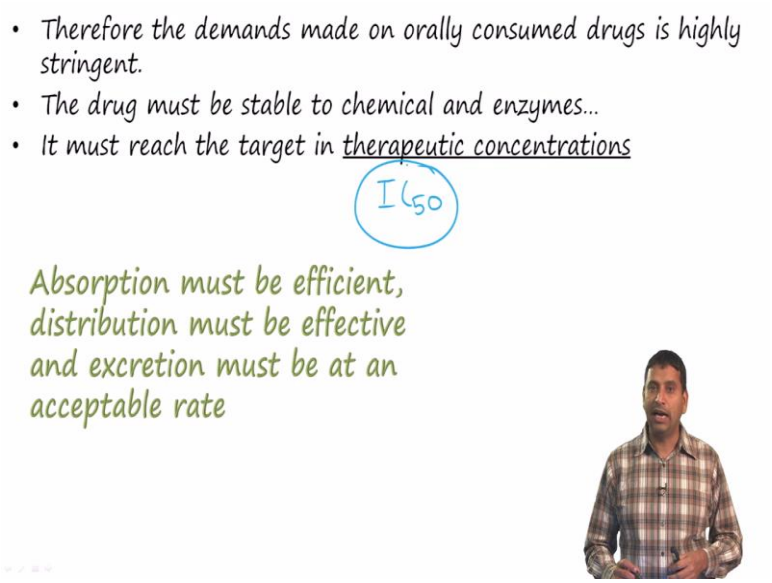

at 50 percent of that concentration, of this, let us say IC_{50} is some 10 micro molar.

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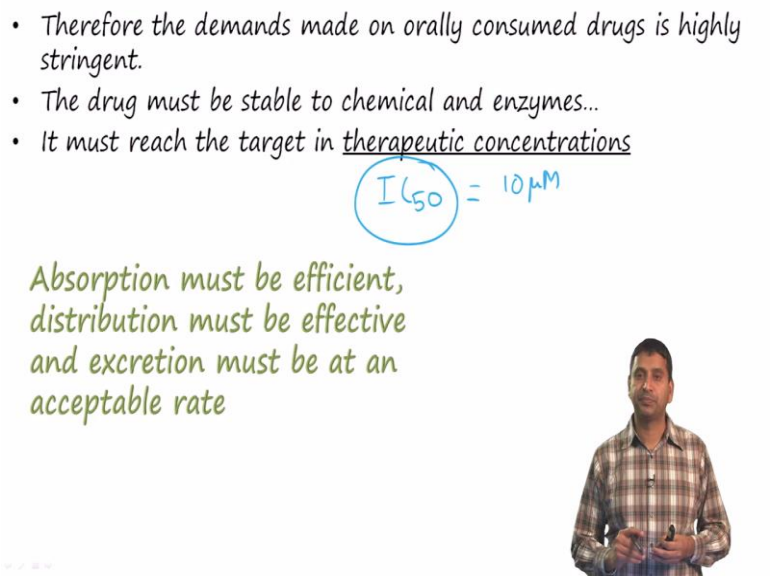

Now this drug has to reach the site at 10 micro molar concentration at least for you to see a 50% percent reduction in the activity of the enzyme, Ok. So after crossing through the stomach, passing through the gut and getting into the blood and then reaching the target, that concentration has to be at therapeutic level.

So at this, let us say if the IC_{50} is 10 micro molar and only 1 micro molar of the drug

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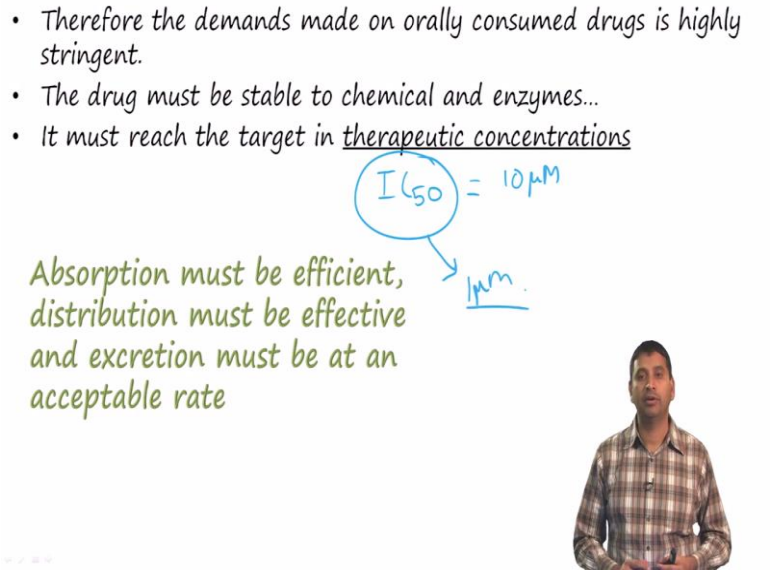

ends up at the site of interest then it is not a therapeutic concentration and therefore the drug may not be effective, right.

So a number of parameters have to be considered while looking at how the drug is going to act. And how it is, you know whether it is orally active or not. So absorption must be efficient. Distribution must be effective and excretion must be at an acceptable rate, Ok.

So let us look at this term called

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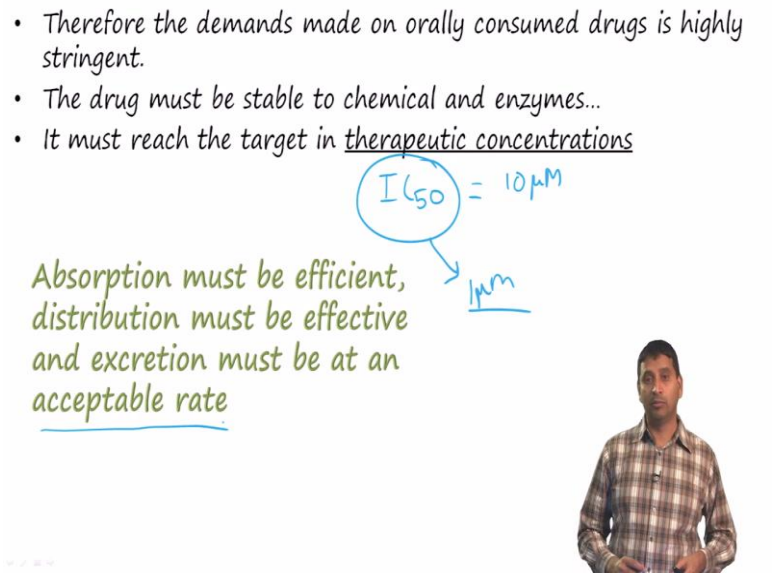

acceptable rate. So let us say we take a drug which stays in our body for days or months, Ok. Now what may happen is that it may become toxic over a period of time. So we look at that shortly. But the absorption must be efficient, right which means that we should get a lot of the drug into the blood stream or it should get into the blood supply very well.

That distribution must be effective that means it should be distributed to the area of our interest rather than entire body. Because, sometimes the drug need not be spread across the body because it has to reach the target at therapeutic concentration.

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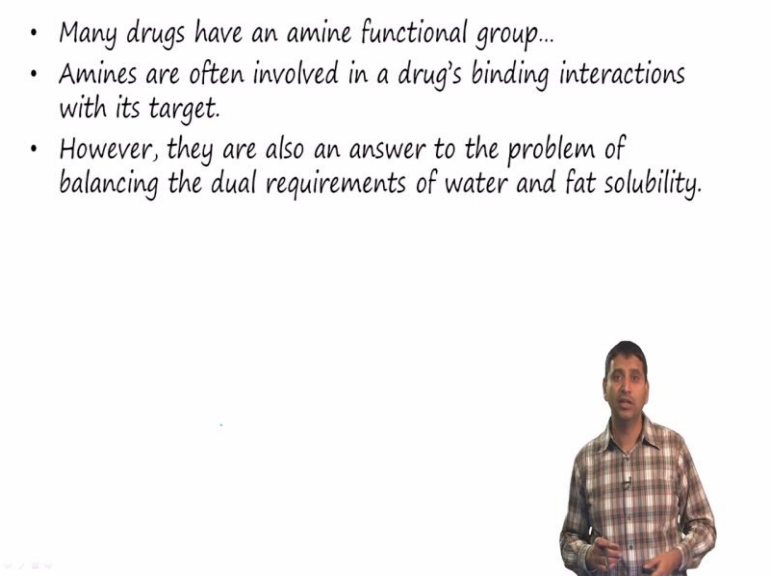

So many drugs have an amine functional group, Ok. So what is an amine?

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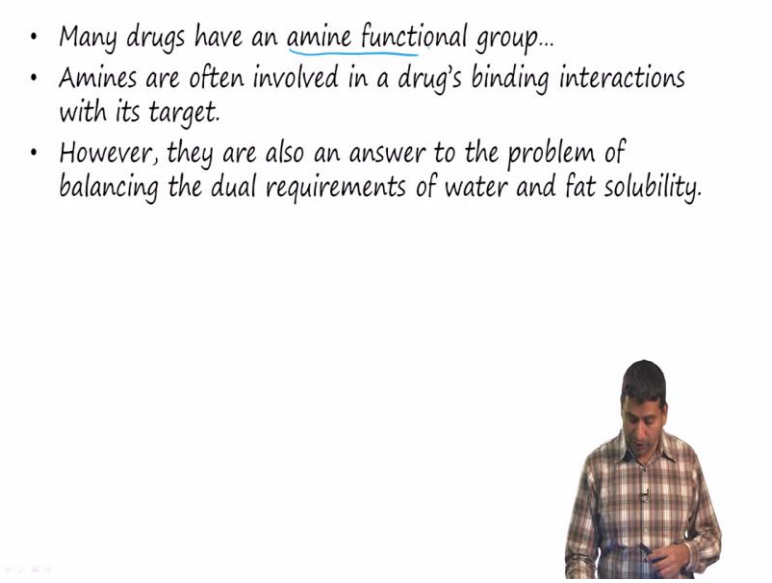

Amine is RNH_2; this is a primary

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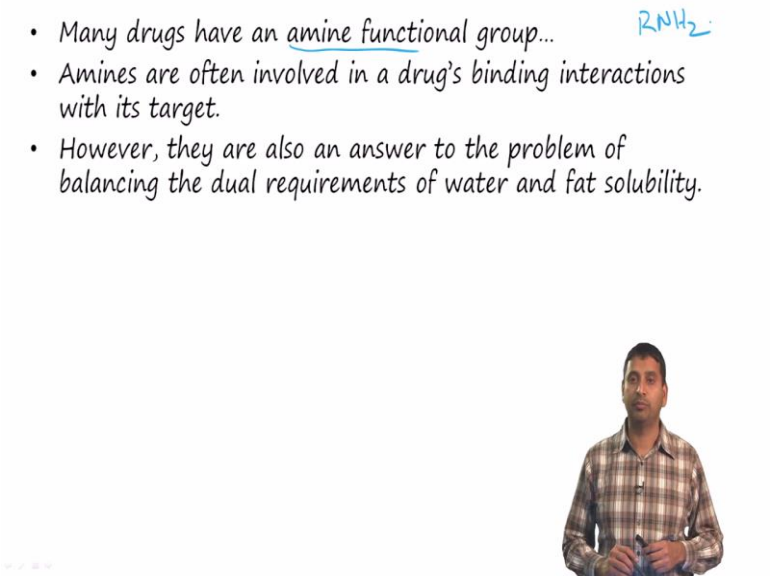

amine, Ok. Amines are often involved in drug's binding interactions.

We ourselves have looked at, for example in an enzyme there may be a carboxylate and NH_3 plus can actually have

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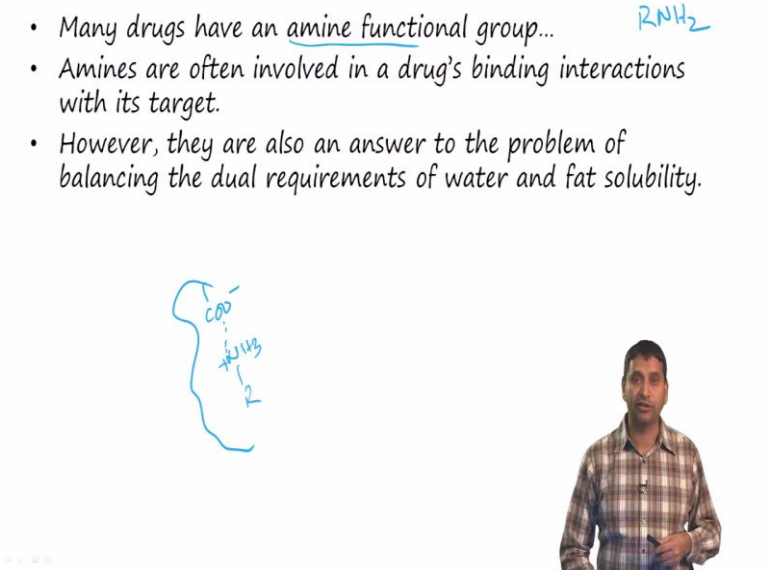

an interaction here, right. So amines are very important in many drugs because of exactly what I have drawn, which is that they can balance the two requirements.

So they can be neutral in the form of RNH_2, but they can also be protonated

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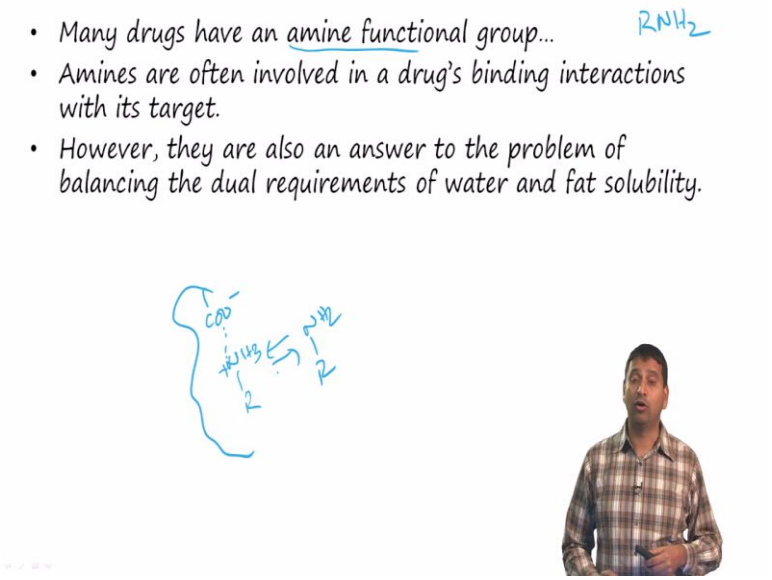

to form RNH_3. So when are in the neutral form they

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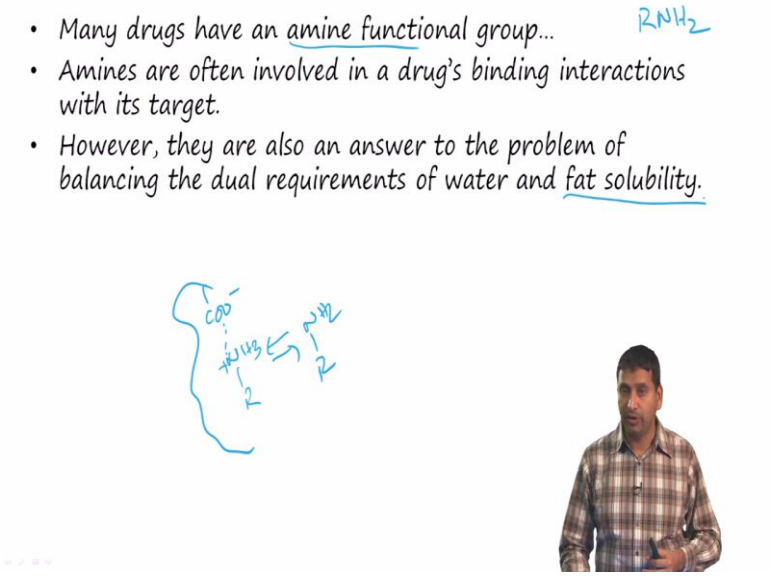

can actually be fat soluble and when they are protonated they can actually

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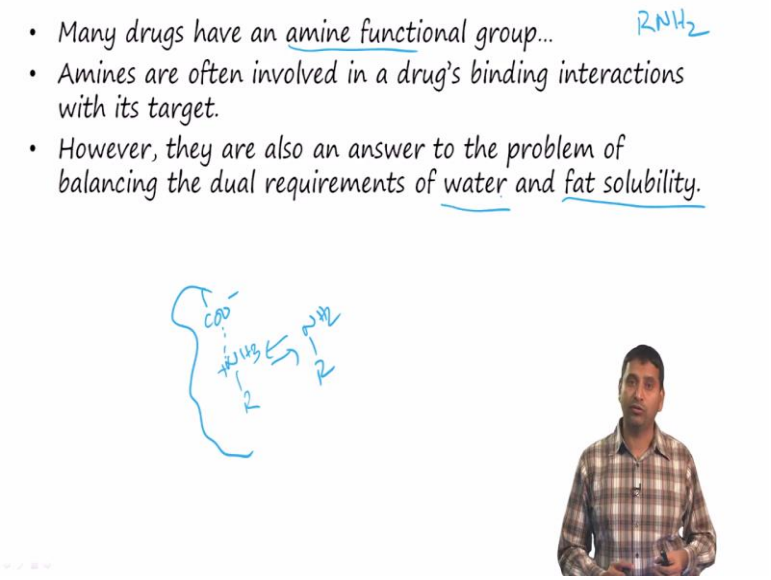

be water soluble. So this balancing of the requirements can be achieved by amines, which is why amines are very commonly found in many drugs. Furthermore amines are also excellent

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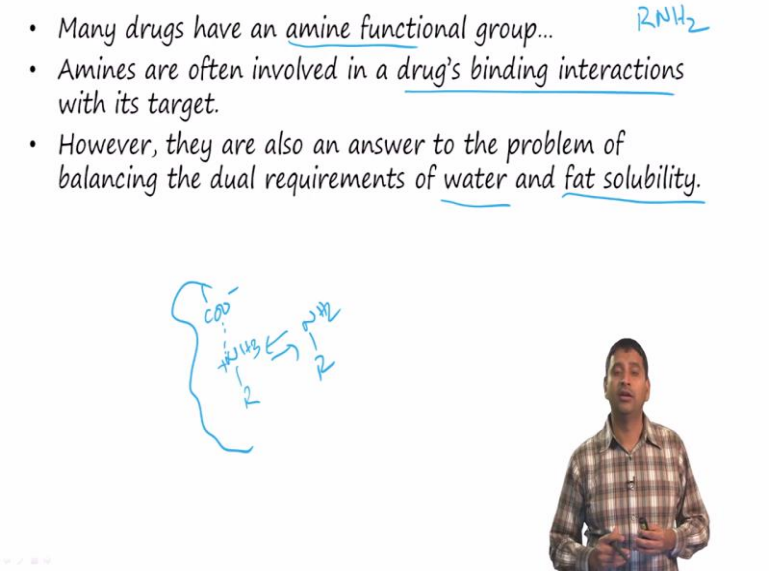

in binding interactions.

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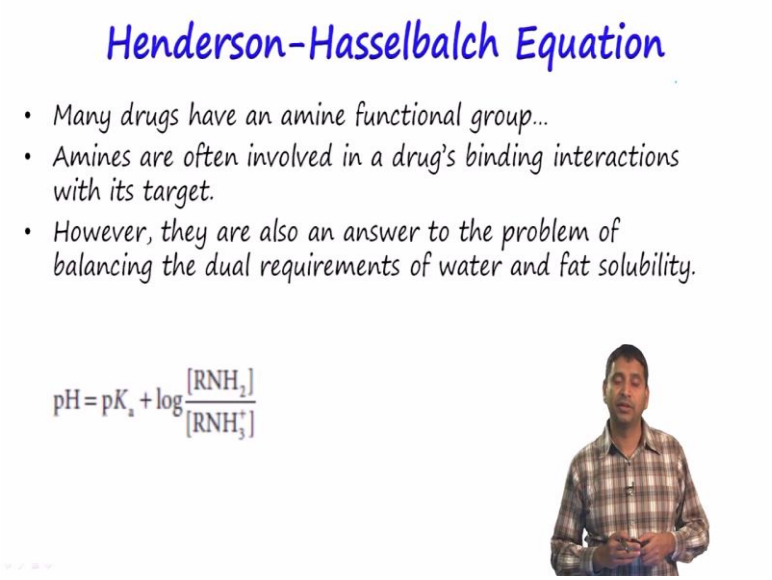

Now let us understand the Henderson Hasselbalch equation. We have already looked at some of this in the past. Now since many amines have a functional group, let us focus on the Henderson Hasselbalch equation for an amine, Ok. So amine, the pH of the solution is nothing but pKa plus log of concentration of RNH_2

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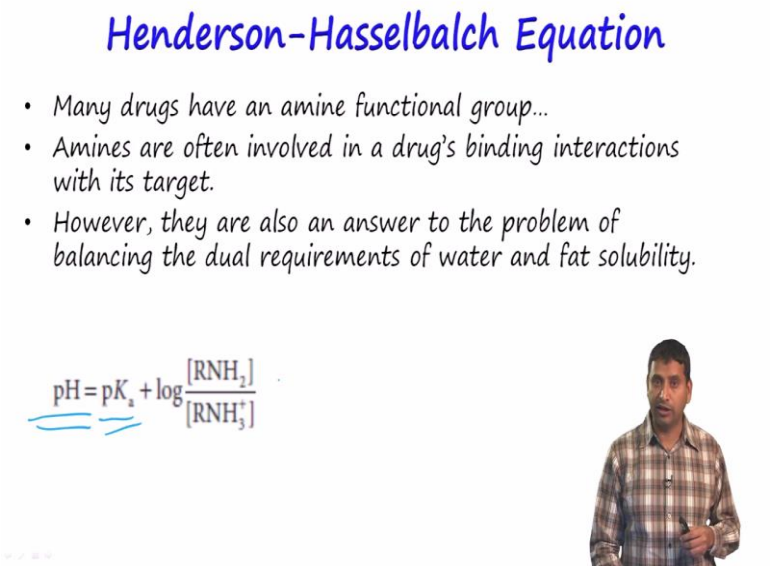

divided by concentration of RNH_3 plus.

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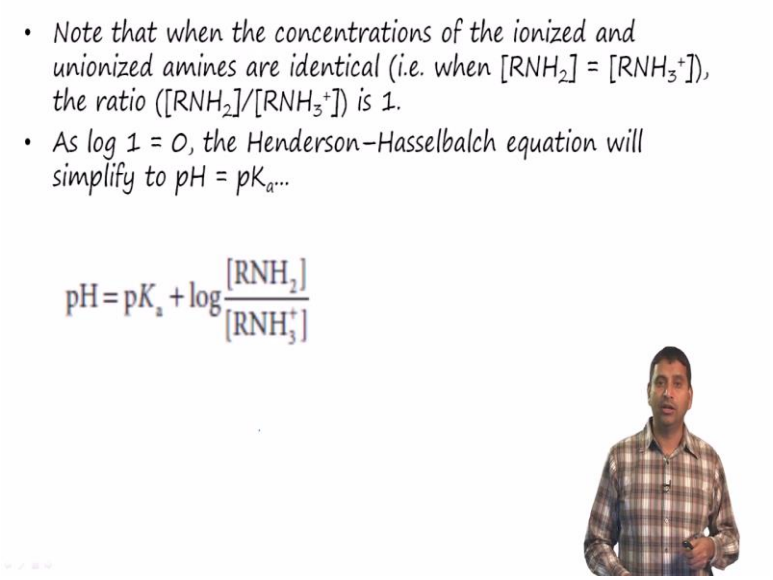
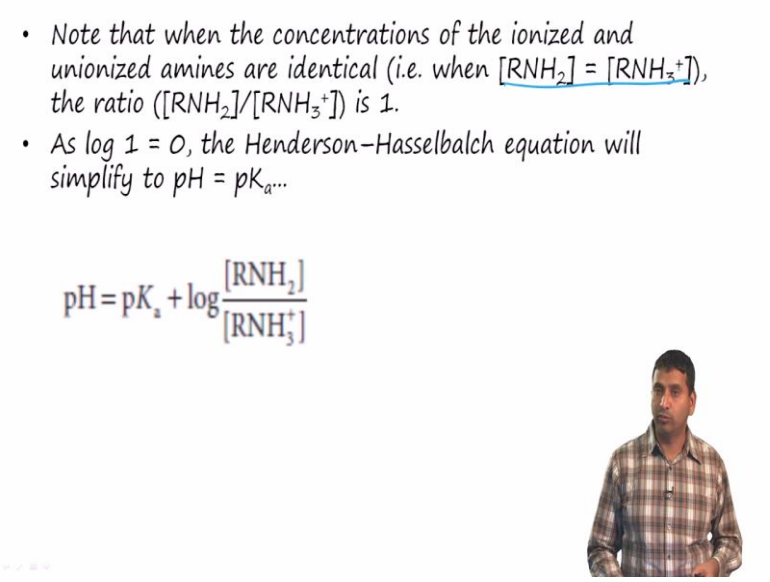


Note that when the concentration of the ionized and unionized amines are identical that is R NH_2



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equals RNH_3 plus then this ratio becomes 1.

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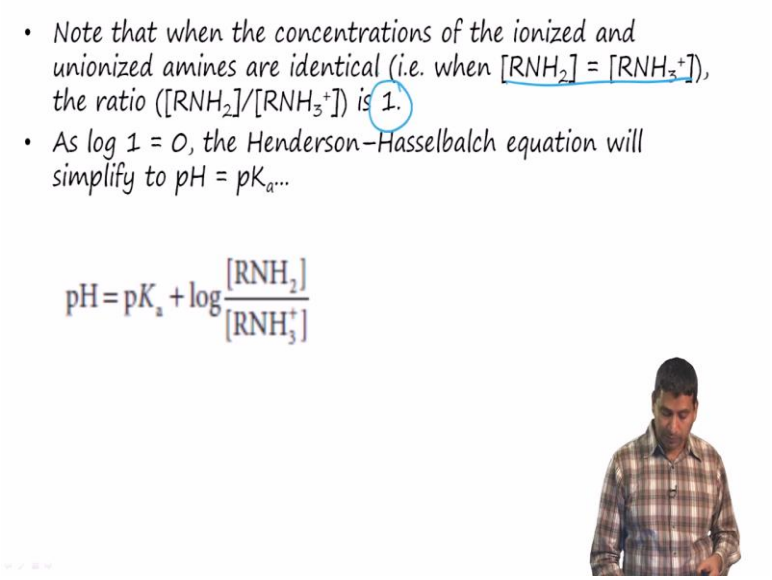

And since we know that log 1 is 0,

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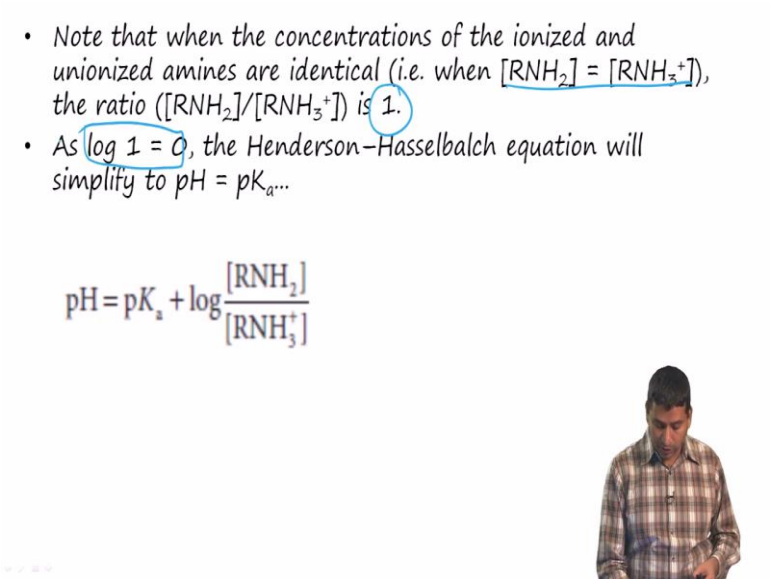

this term becomes pH equals pKa, Ok.

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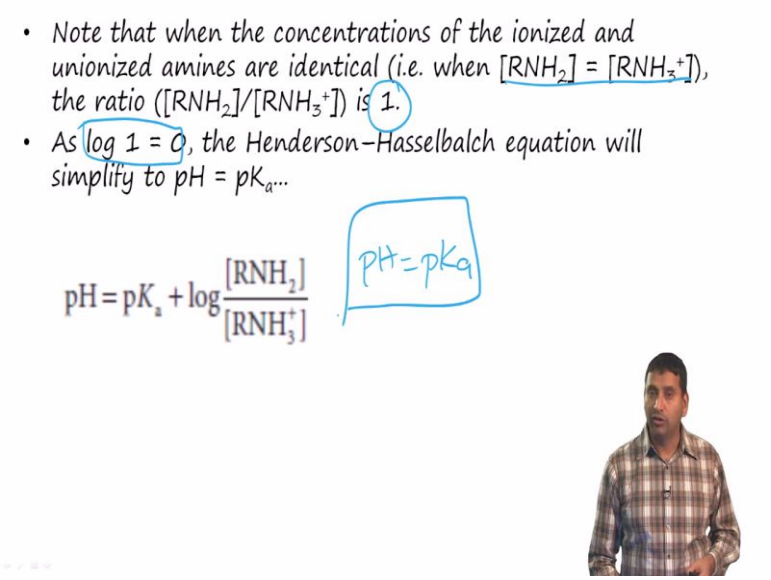

So at a pH which is equal to the pKa you will find 50 percent

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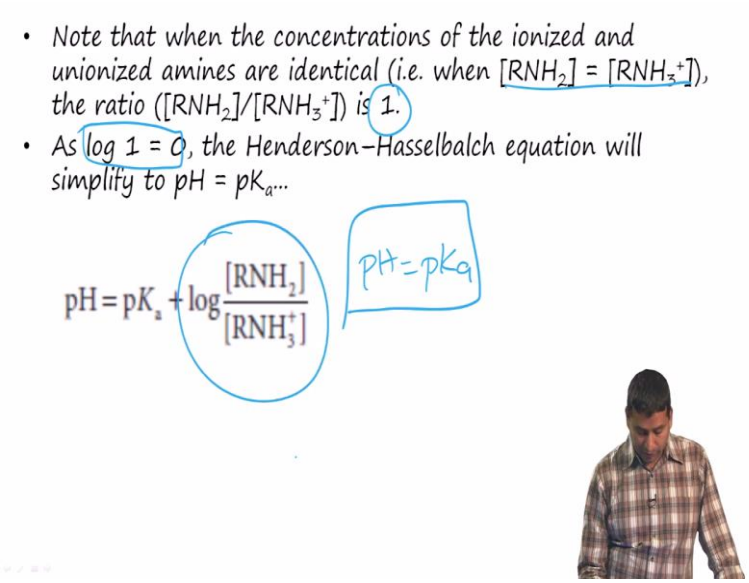

RNH_2 and 50 percent RNH_3 plus,

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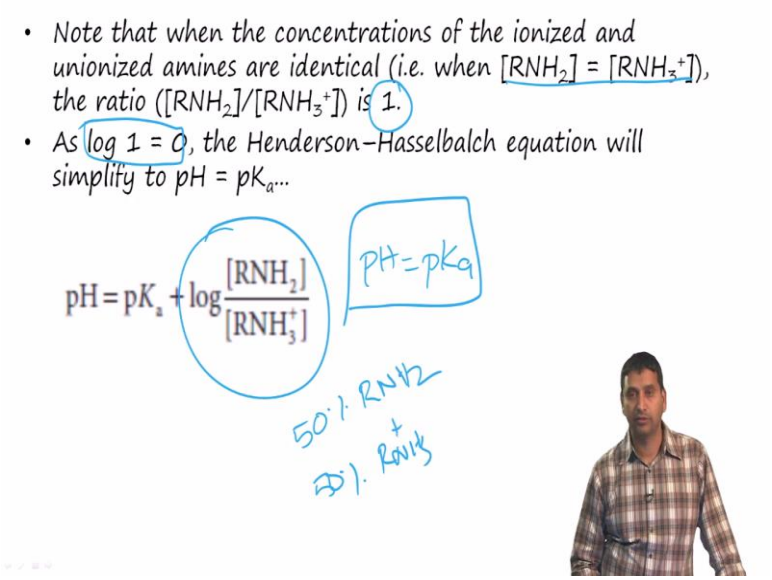

Ok. So this is very useful to know because when a drug is traveling through various compartments it will encounter quite acidic pH, it will encounter fairly little bit basic pH, and so we can find out what is the ratio of, or we can predict what would be the ratio of the ionized to unionized forms using this equation.

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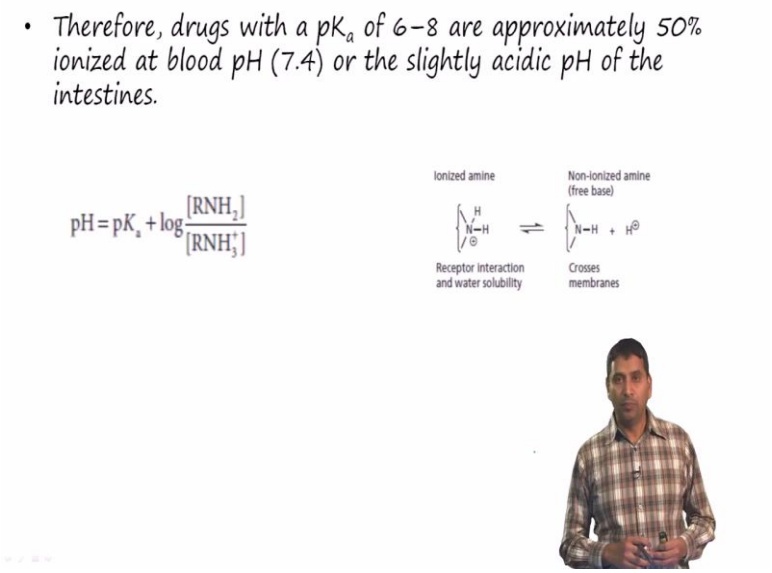

So in situations where we use amines the pKa of these amines

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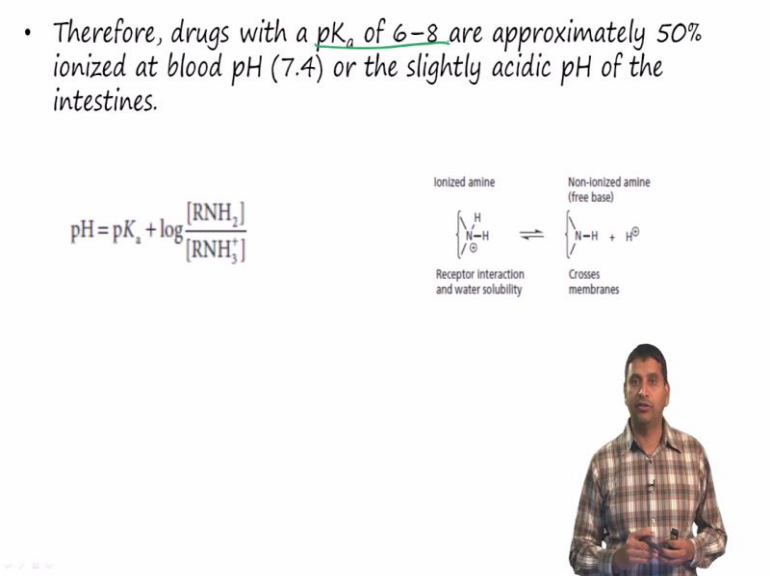

is typically between 6 and 8, which means in normal neutral pH,

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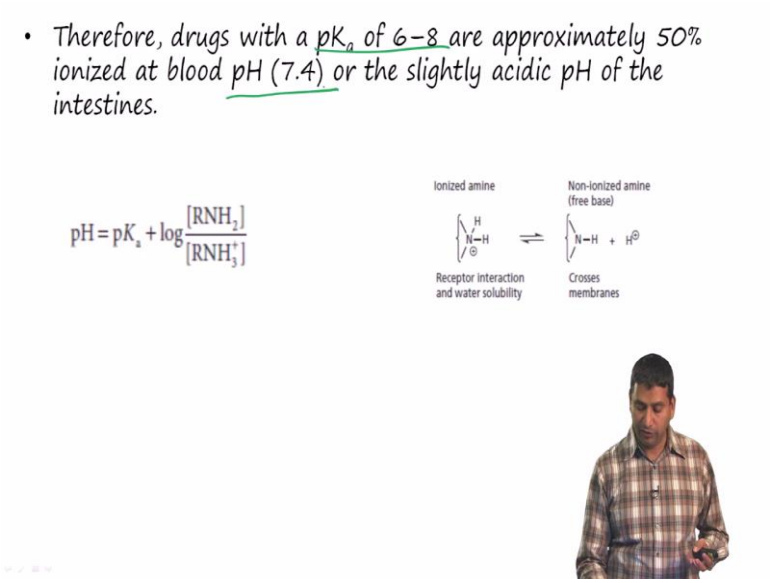

they are approximately 50 percent

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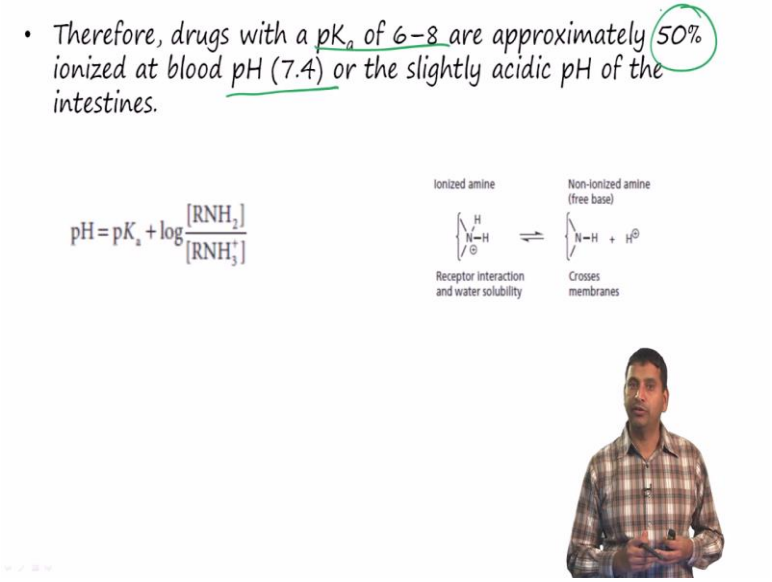

ionized, Ok. So here is the, for example a situation where the receptor interaction

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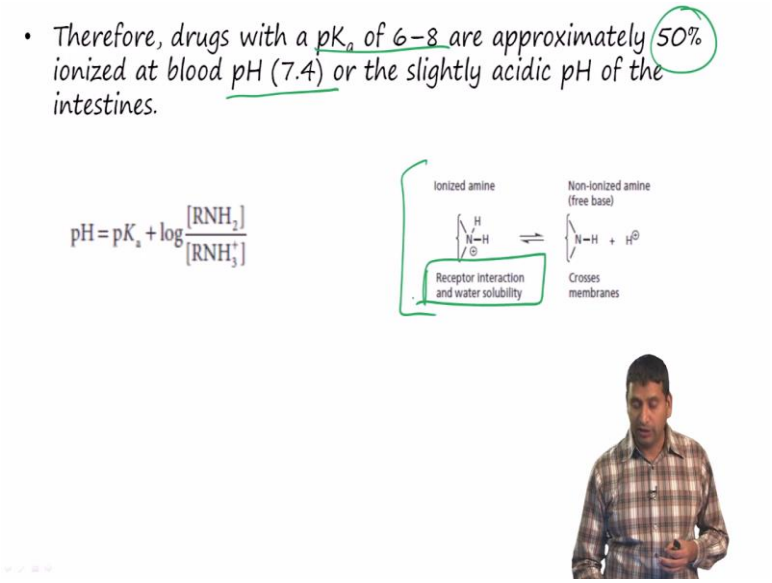

can occur because it has an RNH_3 or RNH_2 plus cation is formed and if the receptor has a negative charge on the surface, then it can interact with it.

And here is

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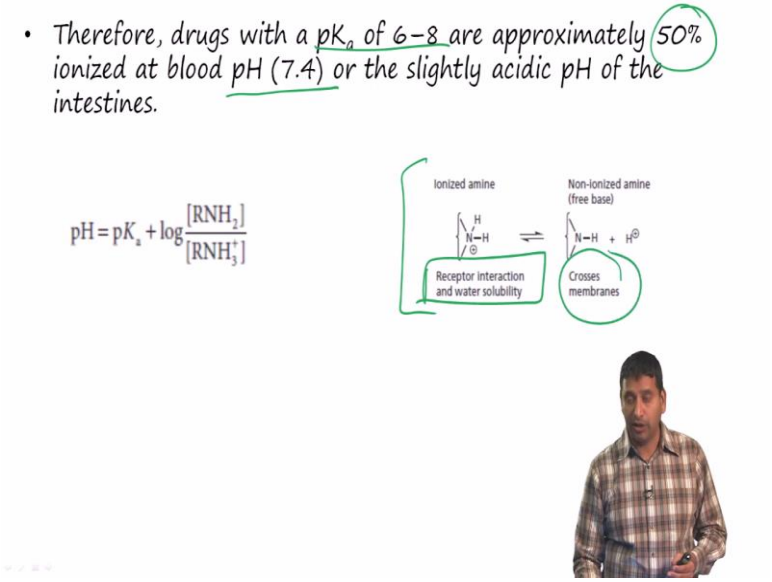

a situation where it is in the free amine form or the neutral amine form. Here it can help with crossing membranes because membranes, as we know have high levels of lipids. So neutral molecules can cross membranes

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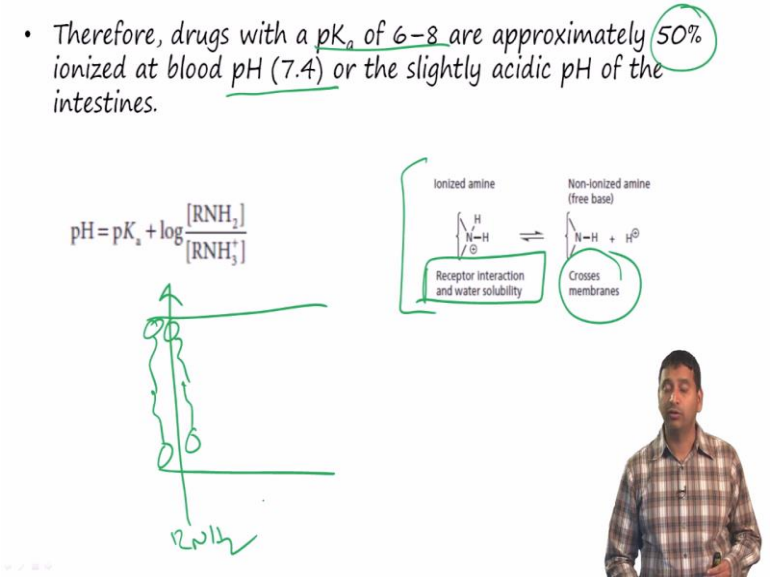

very well. So amines are very versatile functional groups because of these properties.

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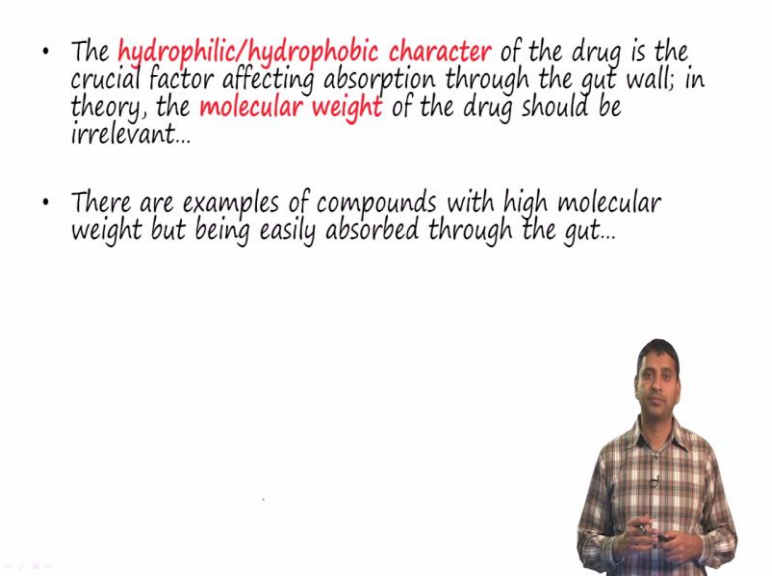

So the hydrophilic or hydrophobic character of the drug is a crucial factor in affecting absorption, Ok. So in theory the molecular weight of the drug,

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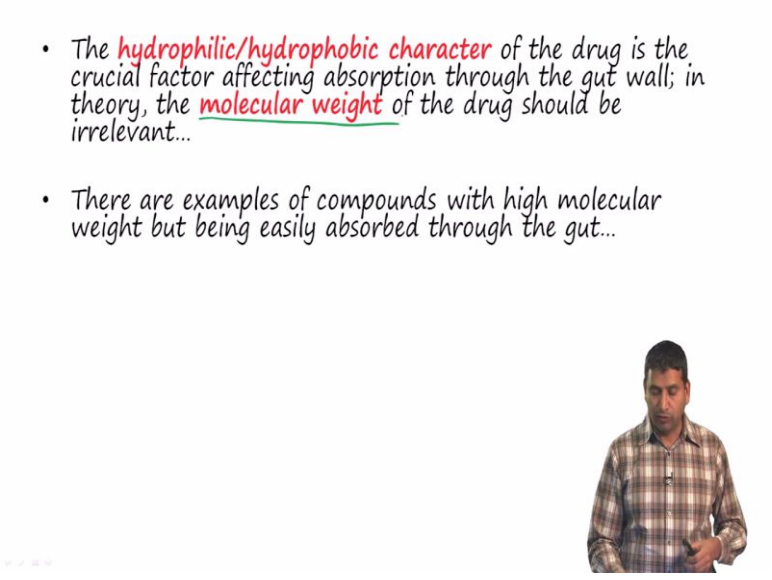

so how big, how heavy the drug is, is not very relevant, Ok.

So there are many examples of compounds which have high molecular weight but can be easily absorbed through the gut. So the hydrophobicity is an, is more important in, in affecting how well the absorption occurs.

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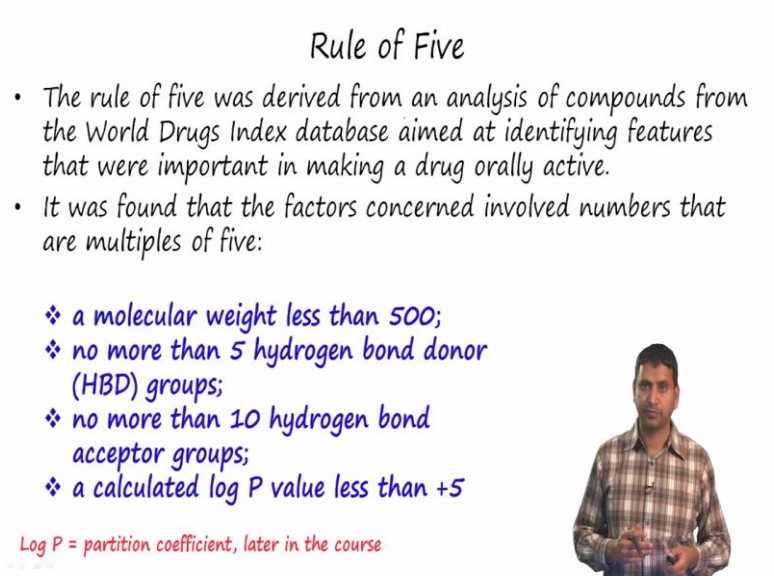

So Lipinski came up with his Rule of Five.

What he did was, he and his co-workers did was that they looked at the World Drug's index database, Ok where

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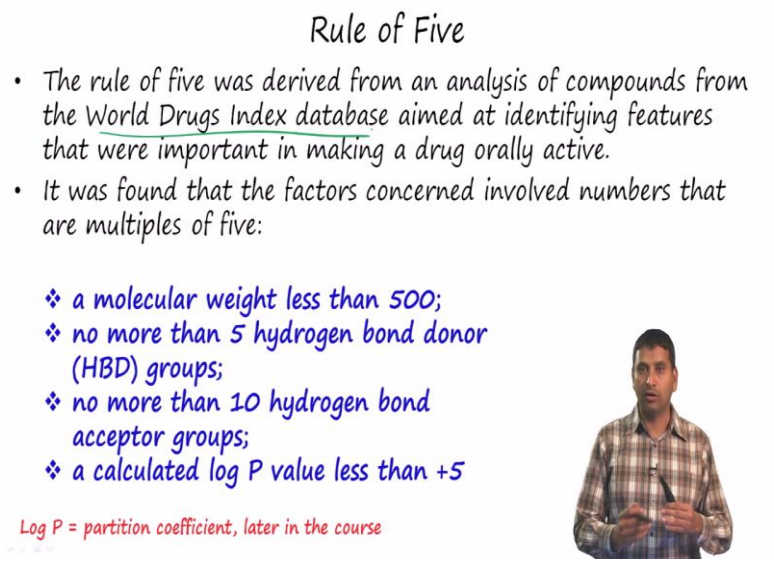

they found, they had a compilation of the drugs that were used clinically, which were orally active and using this they found that they were able to identify certain characteristics which were common to these orally active compounds, Ok.

So if you are able to identify these common features then it is likely that if you design a compound which has similar characteristics then it may be orally bioavailable, Ok. So one of the things was

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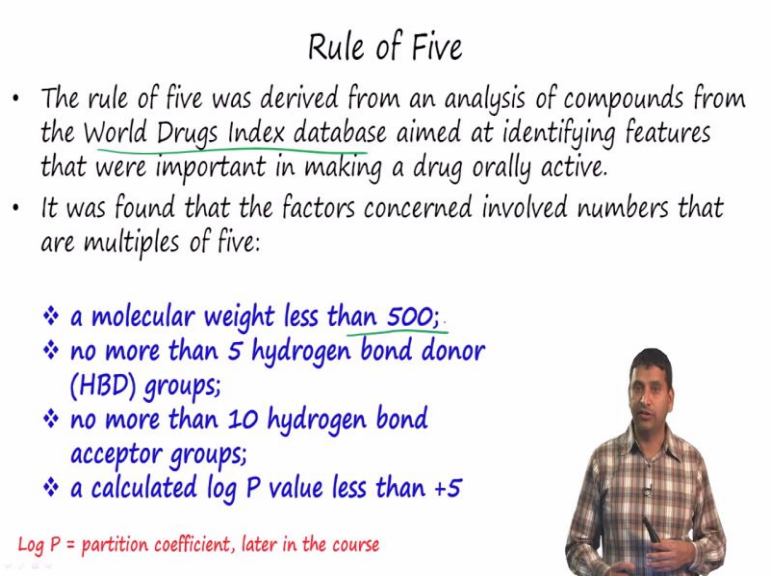

molecular weight less than 500, although we just discussed that molecular weight is not super important but it is one of the common features of this analysis.

And then not more than 5

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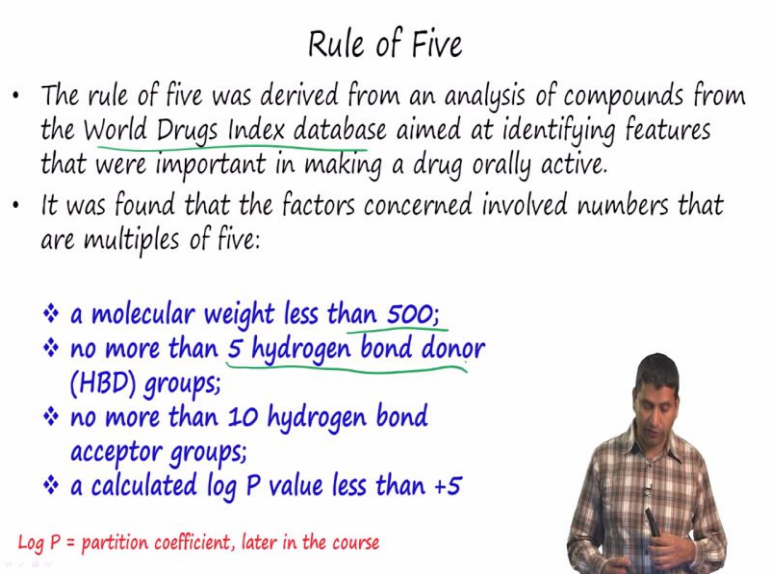

hydrogen bond donor groups, we have already looked that in detail what hydrogen bond donor groups are. Then not more than

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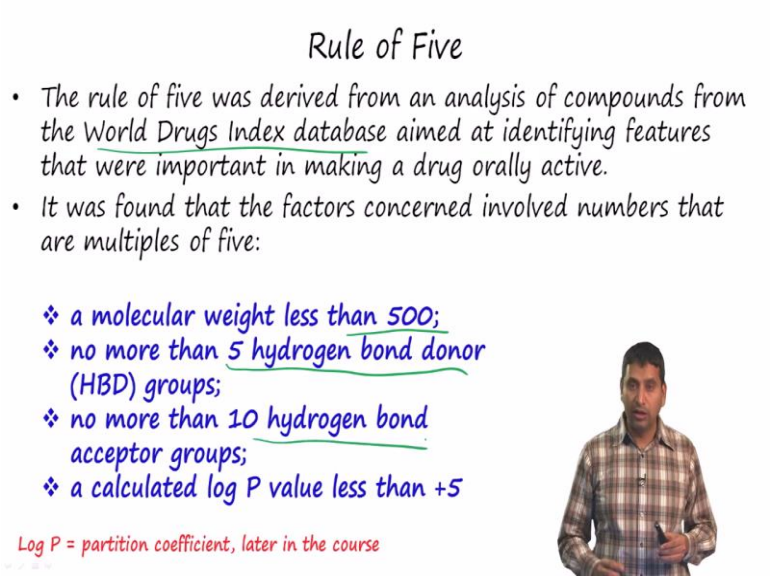

10 hydrogen bond acceptors, acceptor groups and there is also a calculated log P value of less than plus 5,

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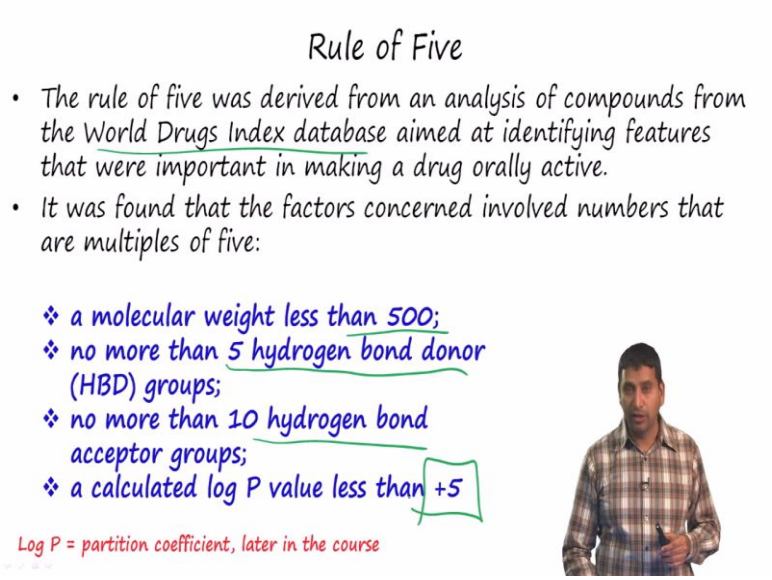

Ok. So keep this concept in your mind. We shall come back to log P values subsequently in the course.

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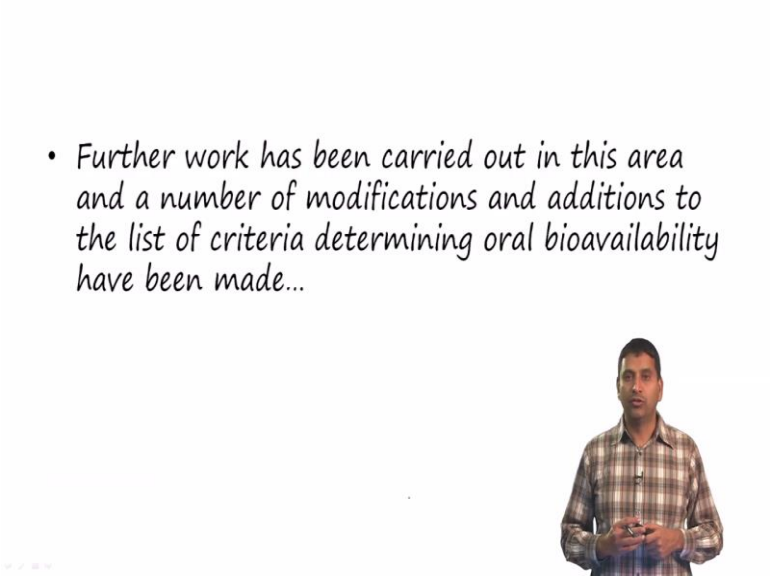

So of course, there have been a number of modifications and additions that have been done to this criteria and we will not be looking at these in detail but there are modern or better methods that are available today wherein we can have slightly better or in fact improved predictive value of whether a molecule is orally bioavailable or not.

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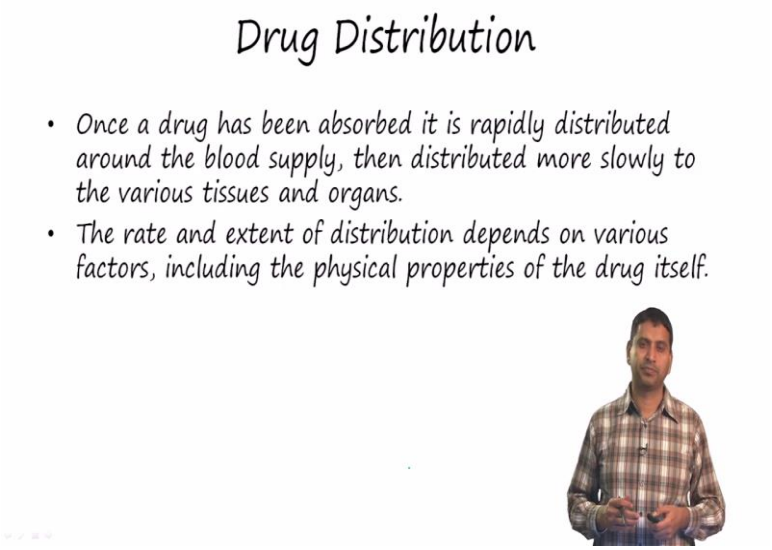

The next concept is drug distribution, Ok. So we have already seen that once the drug is absorbed then it is taken by the blood supply, around by the blood supply and now wherever the blood supply is present it is going to perhaps cross

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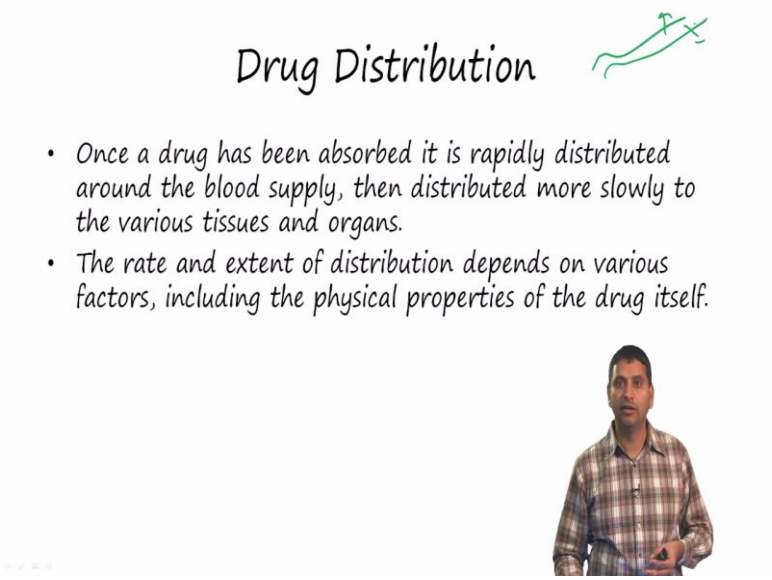

this and go out, Ok.

So the distribution too is more, it is quite slow towards various tissues and organs. So the rate and extent of distribution depends on a number of factors, Ok so which include the physical properties

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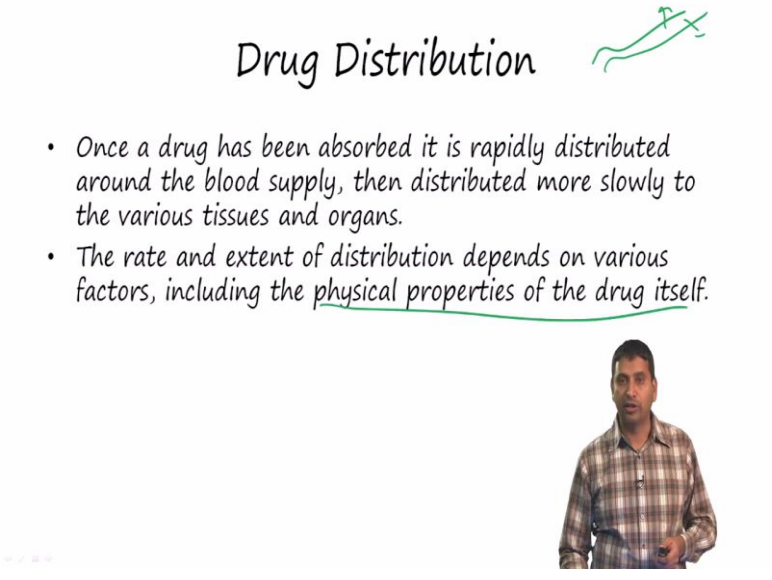

of the drug itself.

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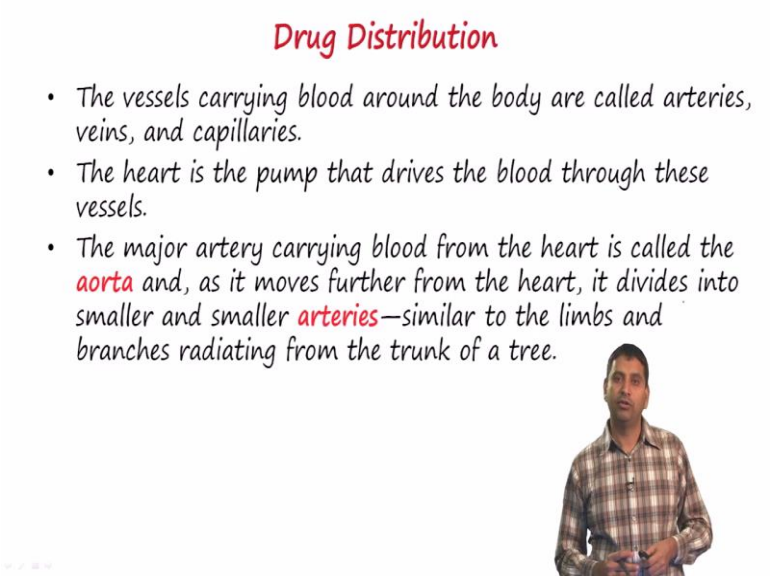

So let us look at them, Ok. Before we go there let us look at what happens in a blood vessel. So the blood vessels, the vessels that carry out the blood are called, carry around the blood are called arteries, Ok or veins and there are

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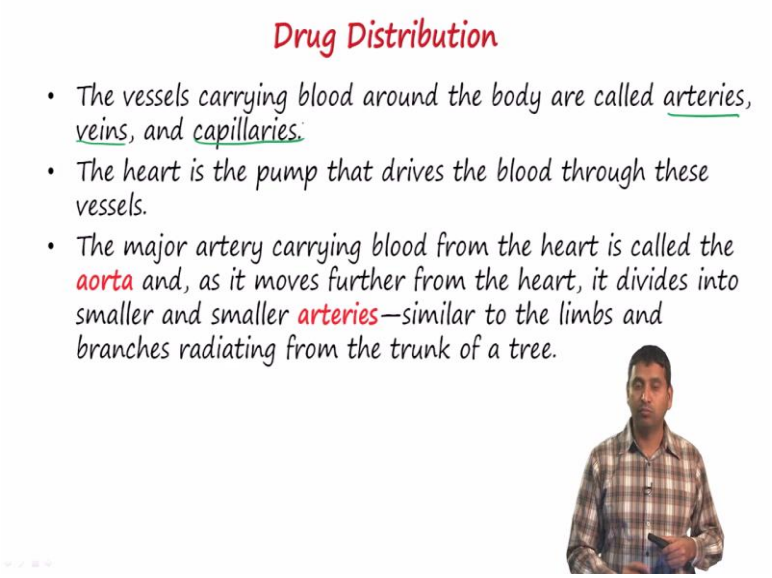

very small vessels which are called as capillaries, Ok

So as we all know, heart is the pump that drives the blood through these vessels and then the major artery that carries the blood from the heart is called aorta and as it moves further from the heart it divides into smaller and smaller branches and so on, right.

So this is

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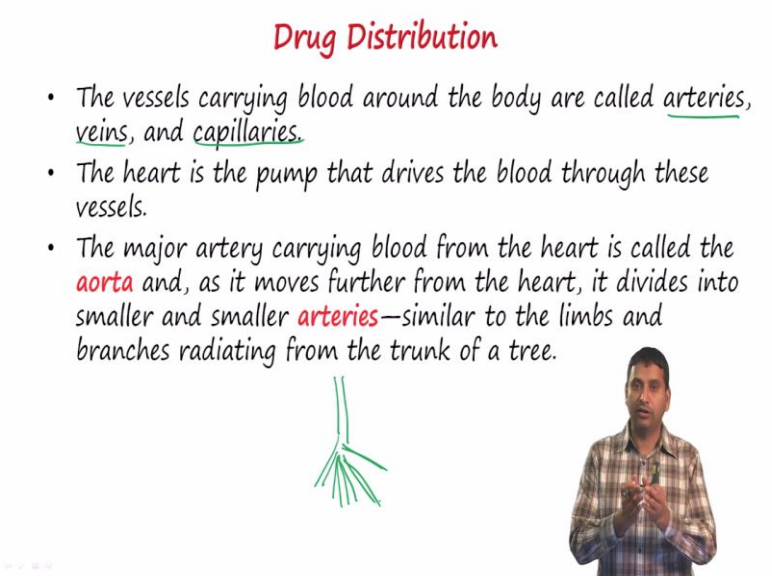

somewhat analogous to how the, from the trunk of the tree the branches of the tree are radiating out and similar to this, the arteries are smaller and they branch out from the major aorta.

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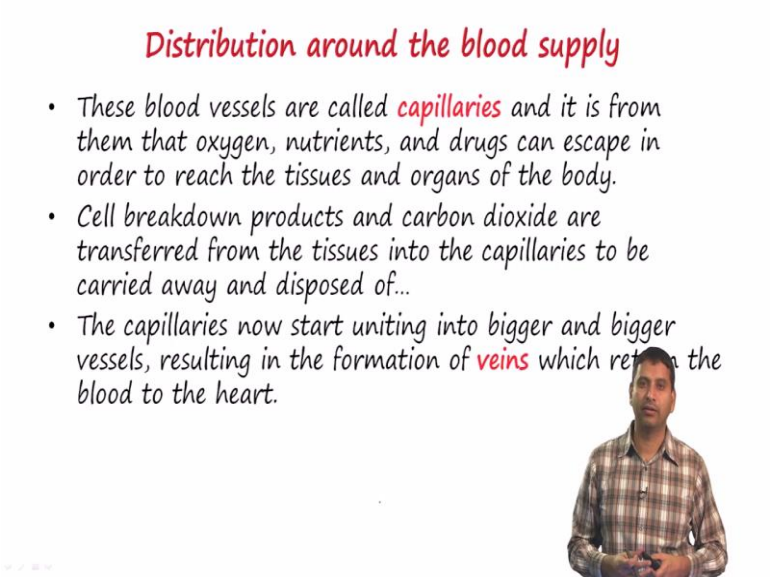

And then it becomes smaller and smaller and these blood vessels are called capillaries, Ok. It is from these that oxygen, nutrients and drugs can escape into the neighboring area, Ok. So this, the tissues are bathed in this kind of capillaries

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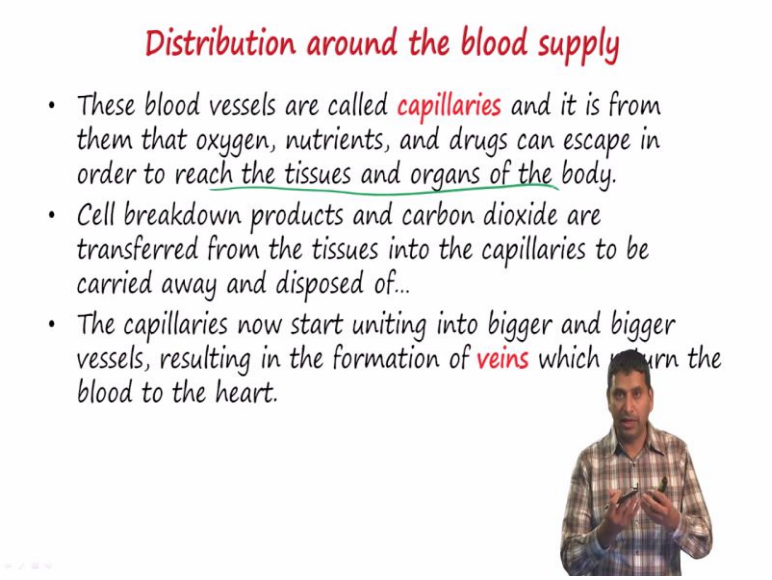

from which they can absorb these important nutrients.

Then cells also break down products, so for example carbon dioxide or other metabolites that are broken down. Those are in turn transferred from the tissues into these capillaries again

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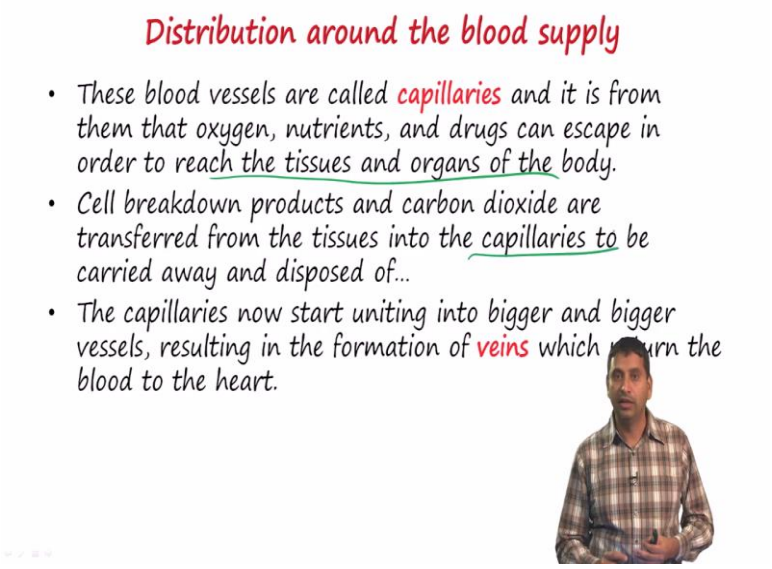

and then these capillaries are again going to converge and they start uniting into bigger and bigger vessels and these result in the

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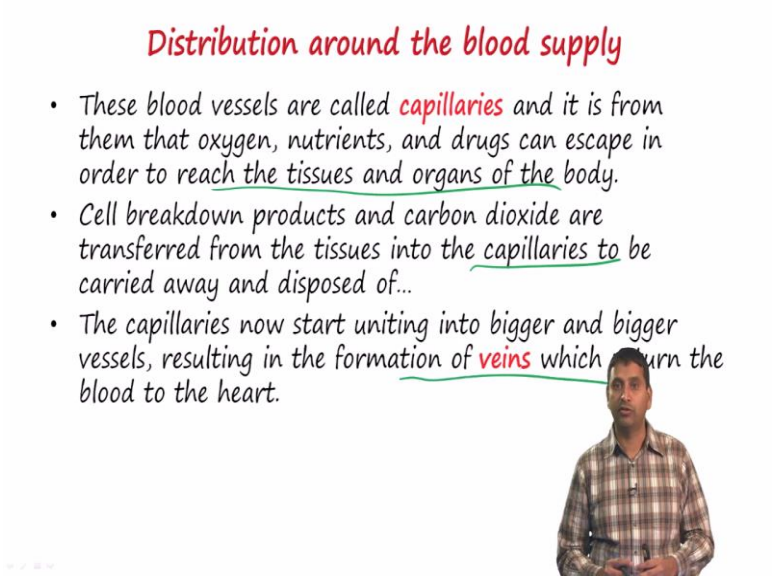

formation of veins.

And these veins again connect back to the heart and then before, and then it is reoxygenated and then it is again pumped back. So there is a connection between the heart and the lung obviously because lung is the place where oxygen is passed to the blood.

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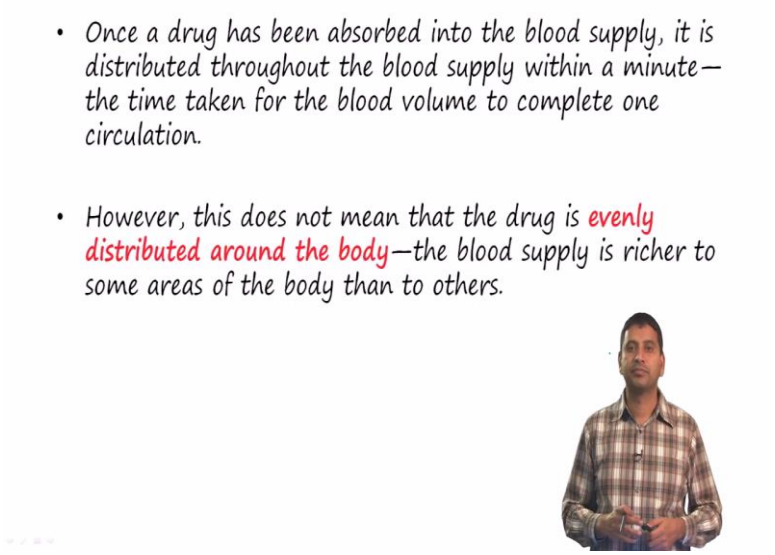

So once the drug has been absorbed into the blood supply it is distributed throughout the blood supply within a minute or two, Ok. So it is the time that is taken for the blood to complete one circulation.

However this does not mean that the drug is evenly distributed across the body. So the blood supply is richer to some areas. So for example if the person is running then the blood supply is perhaps more to, to the muscles which are involved in running and so on,

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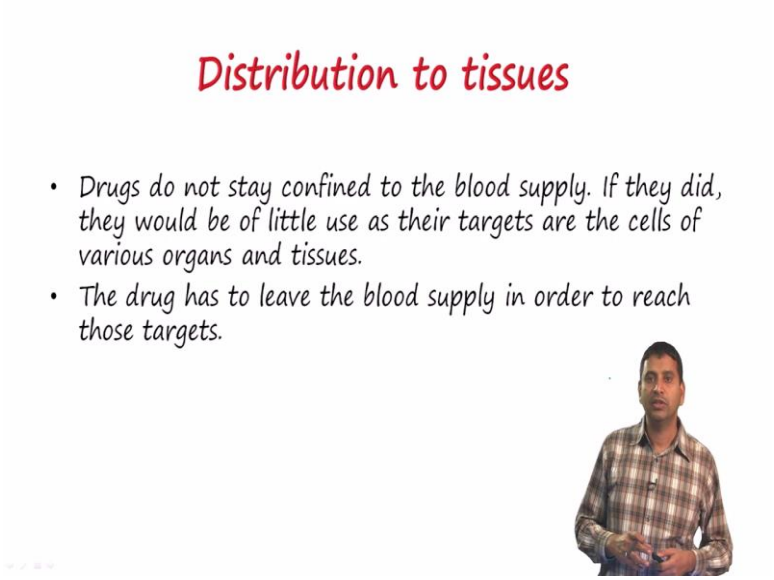

right.

So therefore drugs do not stay confined to the blood supply. They remain in the blood for a very short time and after that they are passed on to the tissues. Because if they remain in the blood they are not very useful because hardly there are very few drugs that act in the blood, right. Beyond that you may want the drug to reach a particular target which is further away from the arteries or veins, Ok.

So the drug has to leave the blood supply in order to reach these targets,

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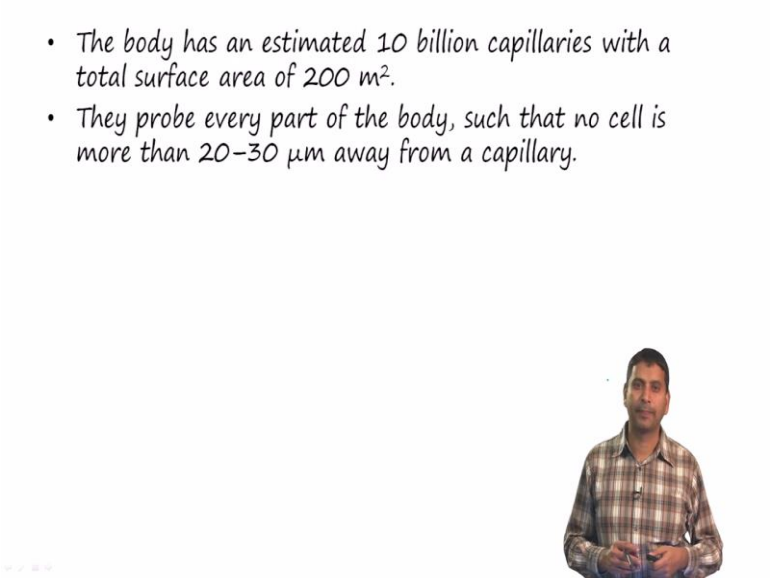

Ok. So the body has an estimated 10 billion capillaries

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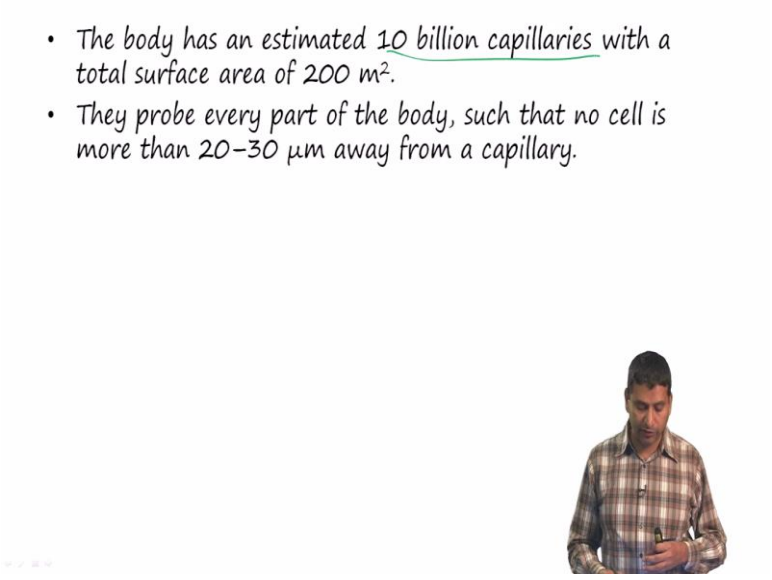

with a total surface area of 200 square meters, Ok. They probe every part of the body such that no cell is more than 20 to 30

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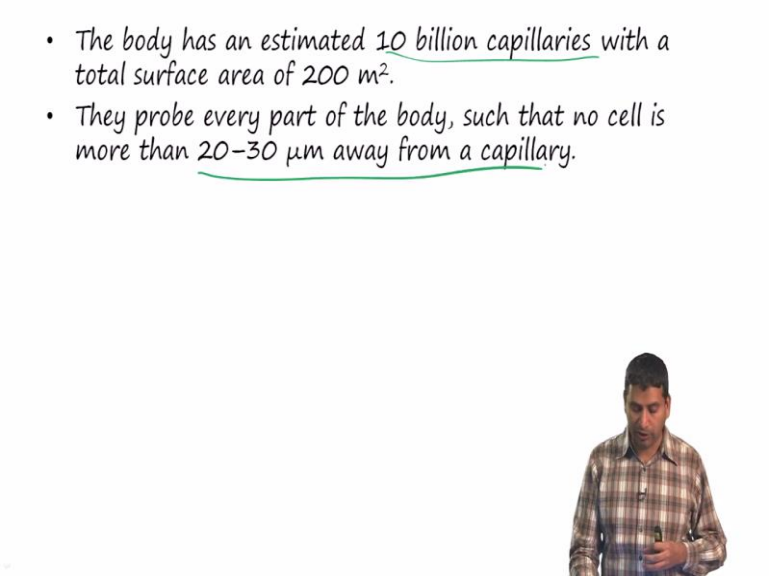

microns away from a capillary.

So imagine this we have a very large body and in this large body each capillary is only 20 to 30 microns away from a cell, Ok. So the blood is, blood supply is pretty good and once the drug gets into the blood supply it is going to get it as close to the target as possible.

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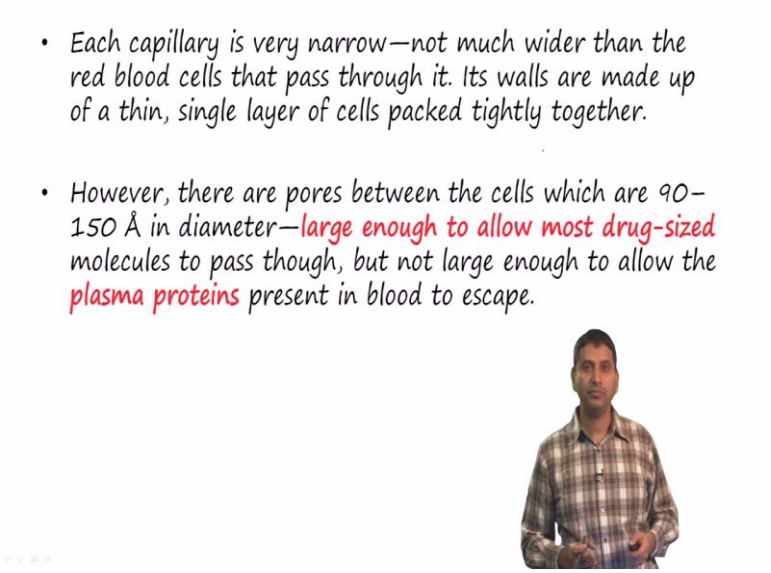

Each capillary is very narrow, not much wider than a red blood cell and its walls are made up of a thin single layer of cells packed very

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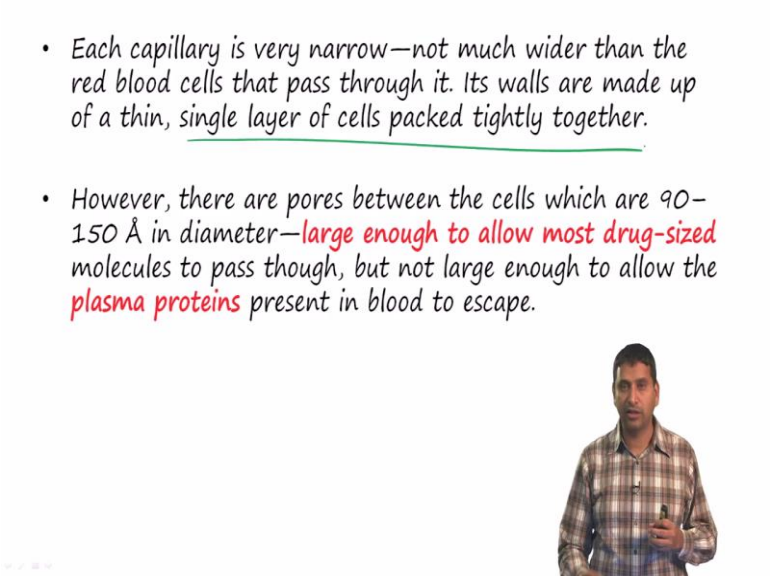

tightly together, Ok.

But there are pores between these cells. So you have these cells like this, and then there are these pores between these cells

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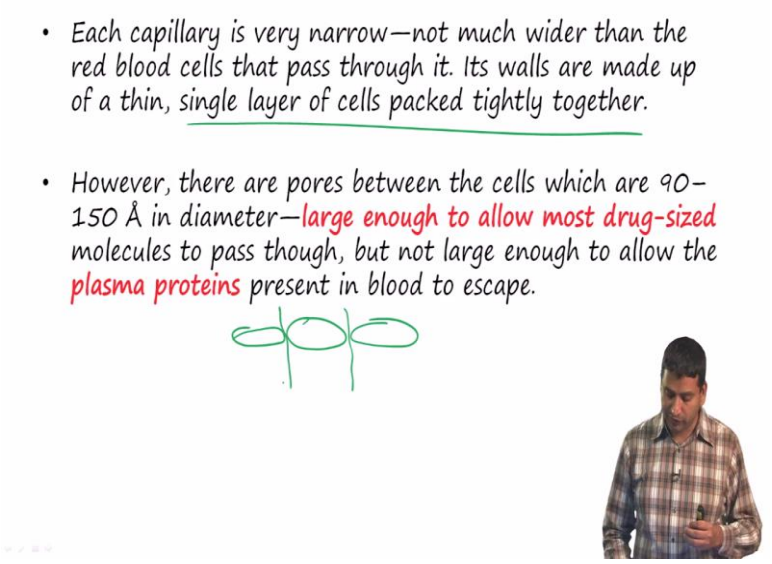

and these are somewhere between 90 to 150 Angstrom

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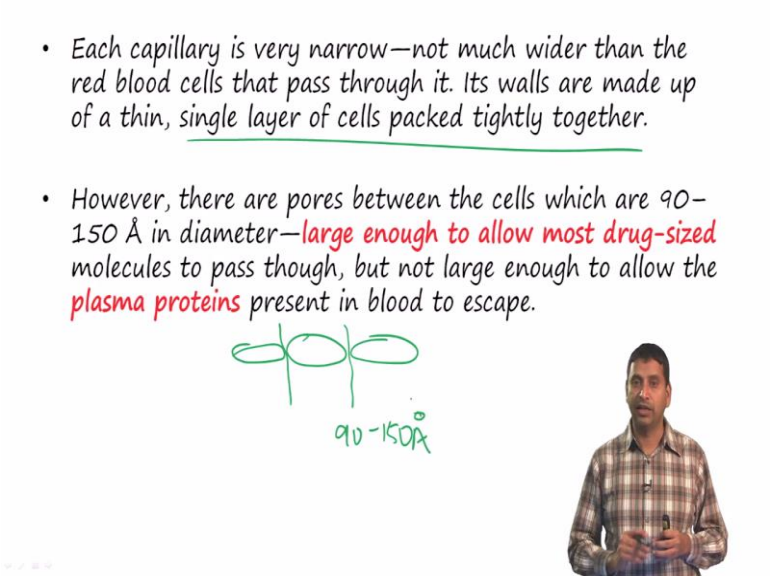

in length and these are large enough to allow most drug-size molecules to pass through.

So if you, for example take a small drug like penicillin it may be a few Angstrom in size in diameter and therefore it is easy for it to pass through.

But large molecules such as proteins and plasma proteins are, continue to remain in the blood and they do not leak into the tissue.

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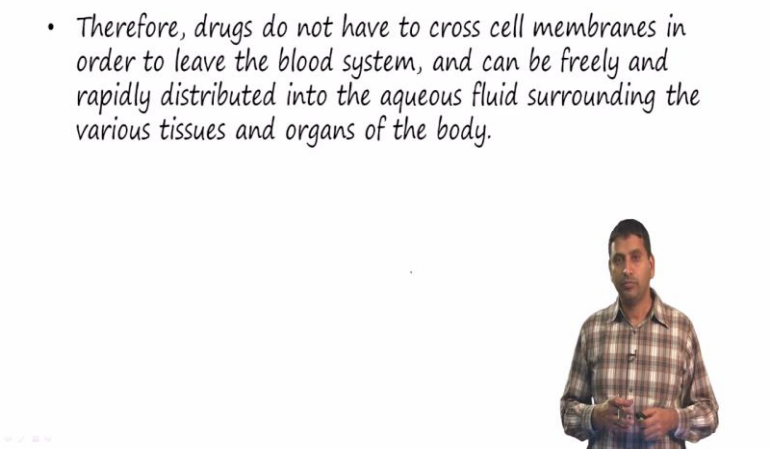

So therefore drugs do not have to cross cell membranes in order to leave the blood system.

So once the, the capillaries are there, after this they can just through diffusion permeate out through

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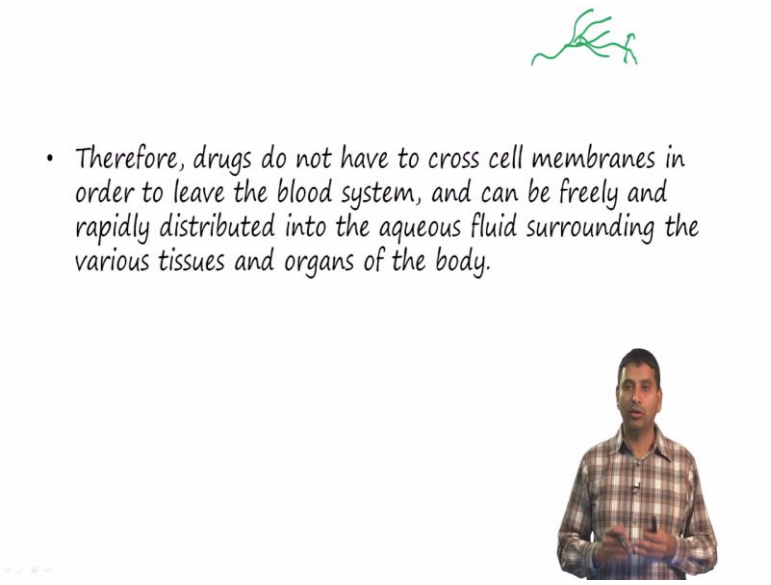

those gaps, Ok and they can be freely and rapidly distributed into the aqueous fluid surrounding the various tissues and organs of the body.

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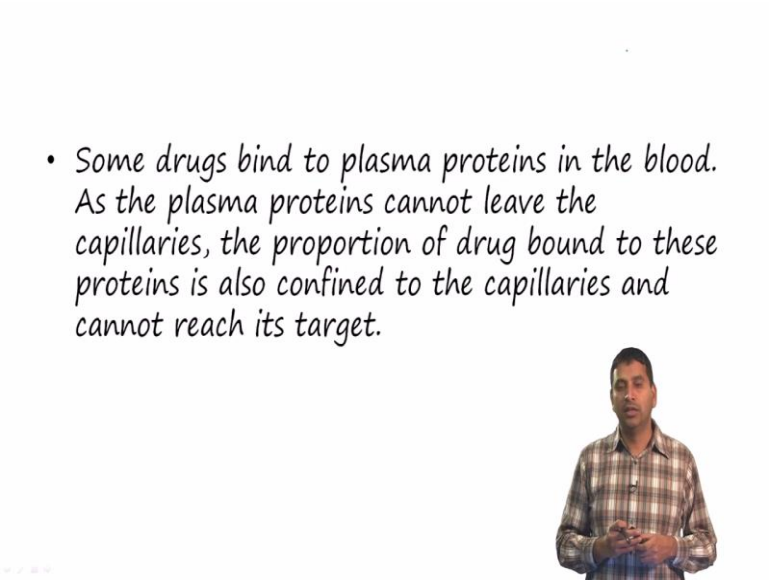

There are some drugs which bind to plasma protein, Ok. So the blood contains number of proteins in it and these are called as plasma proteins and these proteins, they do not leave the capillaries, Ok. So there are some drugs which go and bind to these plasma proteins.

So you have this plasma protein and let us say here is your drug and what happens is that it actually binds to it,

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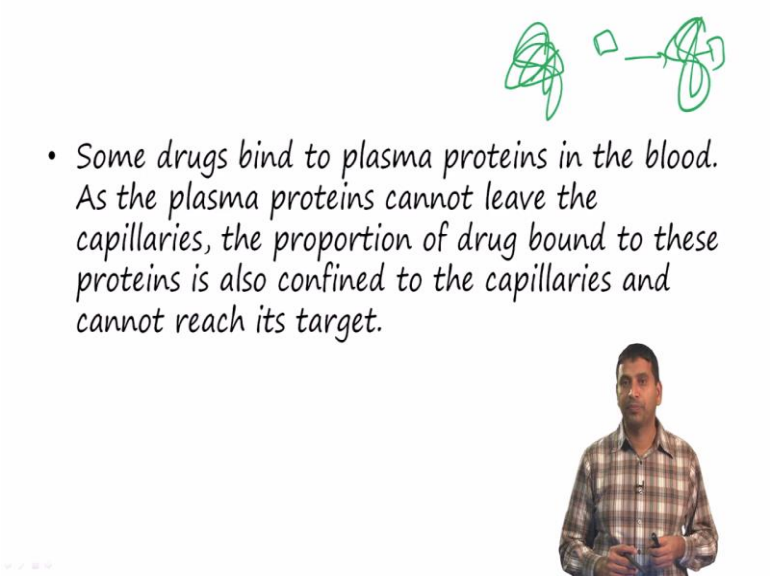

right. Once it binds then the drug is actually stuck or confined to the capillaries, so then it does not reach the target.