**Medicinal Chemistry**
**Professor Dr. Harinath Chakrapani**
**Department of Chemistry**
**Indian Institute of Science Education and Research, Pune**
**Lecture No 33**
**Pharmacokinetics Part II**

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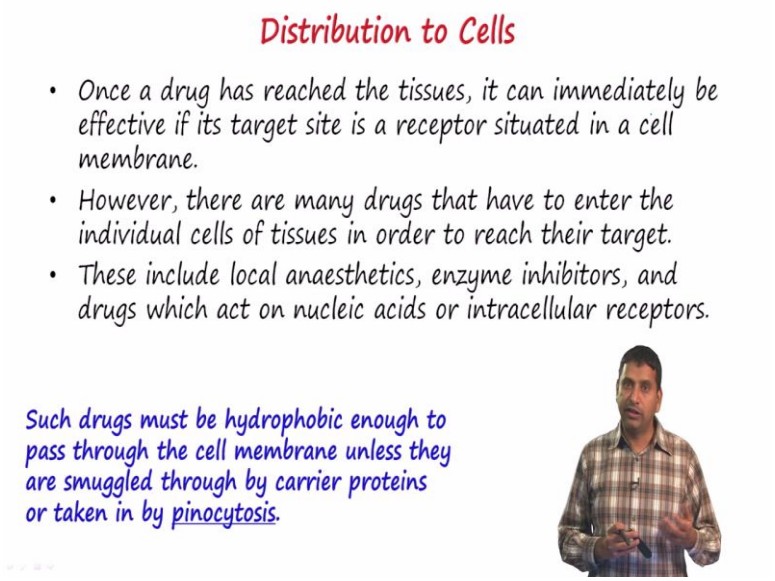


Next, let us look at how distribution to cells occur, Ok. So once a drug has reached the tissue it can be immediately effective if the target site is a receptor situated on the cell membrane. So we already know that if the target for a drug is a receptor,

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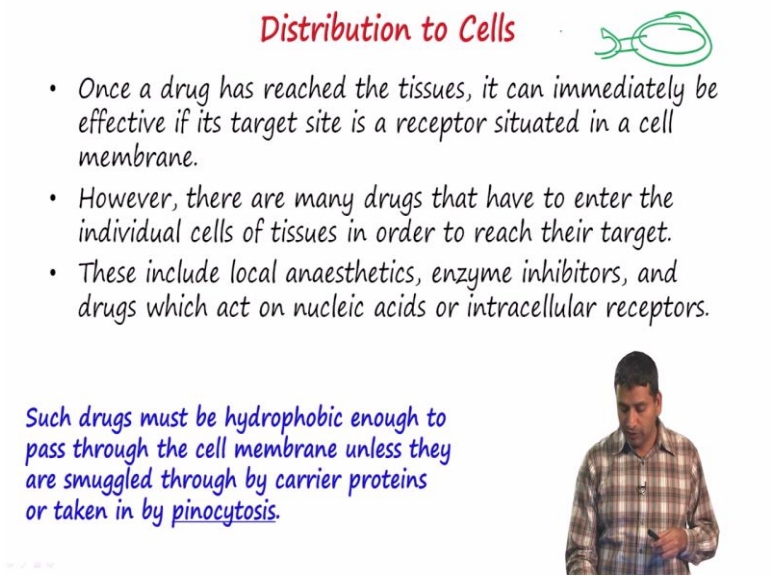


right so this acts on this and immediately there is a signal that is

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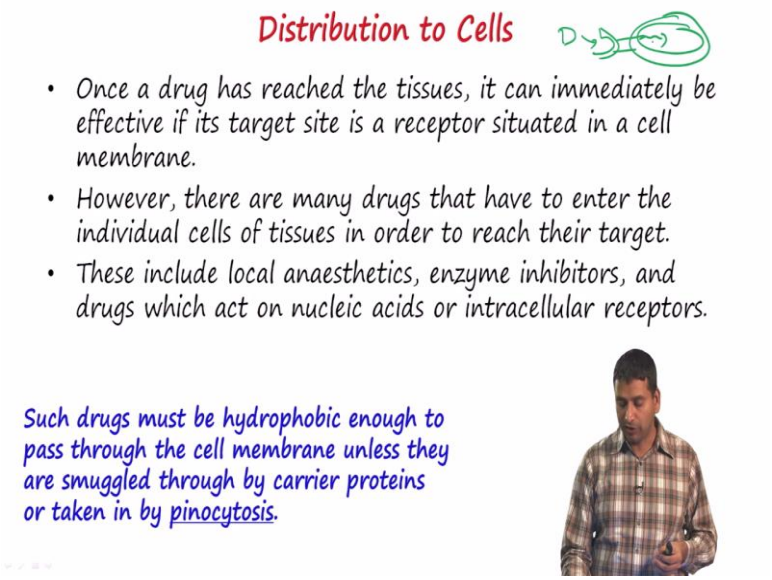


passed on and that can lead to, for example neurotransmission and that will be the desired outcome, Ok.

But there are many drugs that have to enter the individual cells. Ok of these tissues in order to reach their targets. So in this case what happens is the drug, let us say the target is here, the drug has to get across this membrane and then

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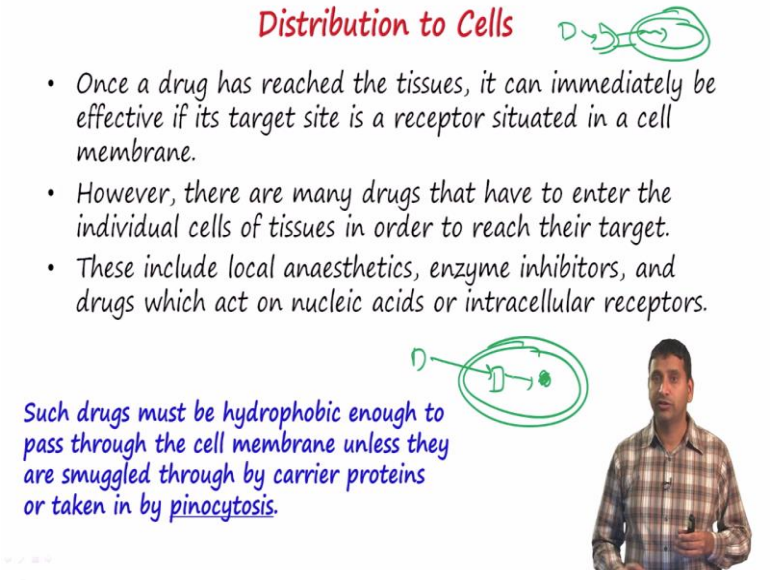


act on its target, Ok.

So some of these include local anaesthetics, enzyme inhibitors because enzymes are present within a cell and so if you design a molecule or a small molecule as an inhibitor of an enzyme

then it has to get across the cell membrane, go hit the enzyme, then bind to it and then inhibit it, Ok.

And of course there are drugs which act on the nucleic acids, right. And those again have to get across the cell membrane and in the case of mammalian cells, they have to get across the nuclear membrane, get into the nucleus and then bind to it. And we already looked that not all receptors are extracellular receptors. And there are some important intracellular receptors which drugs can hit.

So again to act on these, the molecule has to get across the cell membrane, right. So such drugs which has to pass cells have to be hydrophobic enough to pass through the cell membrane. We have already looked at number of examples of why the molecule should be hydrophobic.

And unless they are smuggled through by what is known as carrier proteins, right, so carrier proteins can, what they can do is they can bind to the drug and take it along with it; when the protein gets across the membrane, they can take along with this small molecule.
Or the last process, last way they are taken in is by a process known as pinocytosis. Let us now look at what pinocytosis is that occasionally there are polar groups with high molecular weight that can cross the cells of the gut, Ok without actually passing through the membrane. So this process is known as pinocytosis,

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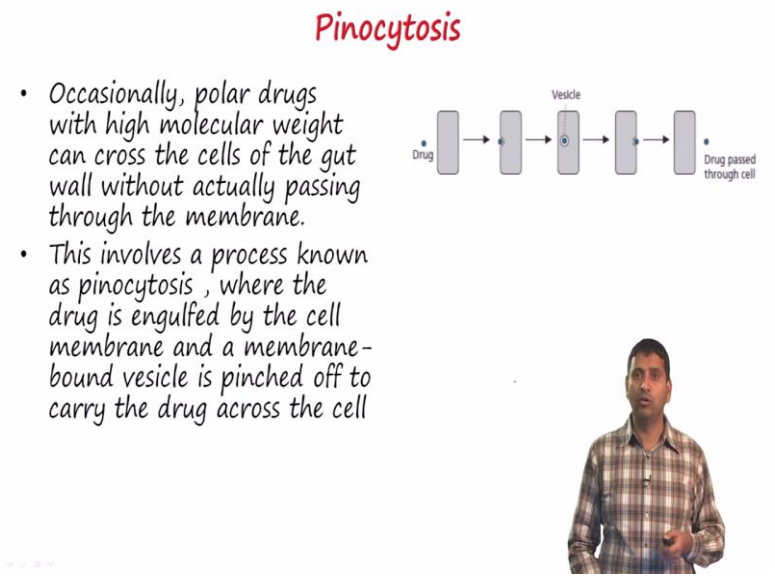

right. So the cartoon that shows it is, describes it is shown here.

Say you have a drug molecule that goes and interacts with this membrane and then there is a invagination in

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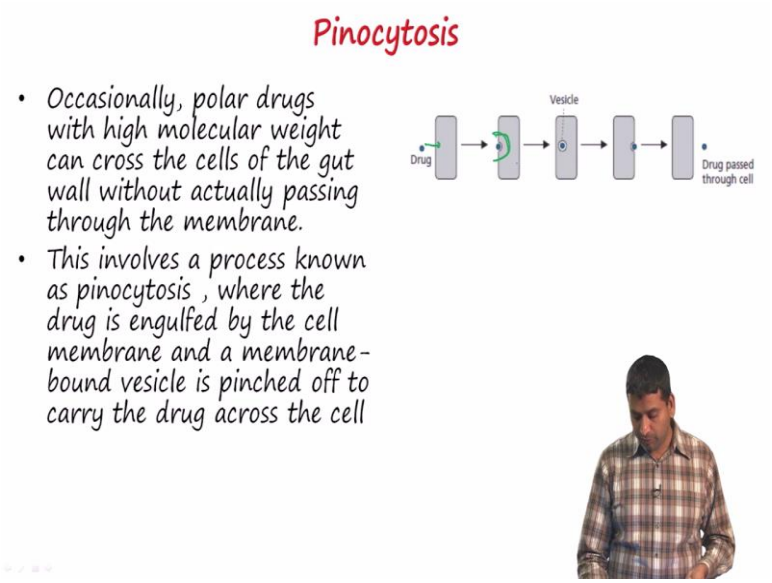


the membrane which then

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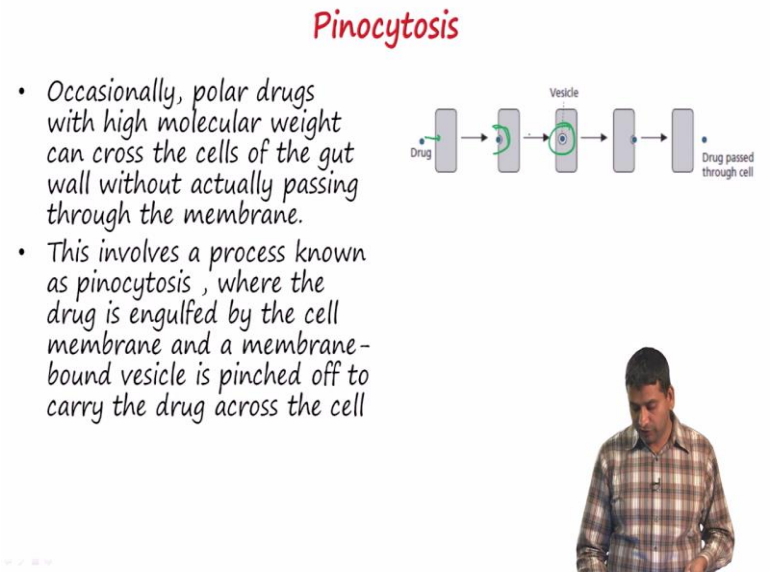


forms a vesicle and then subsequently it is transported to the other side and then the drug is

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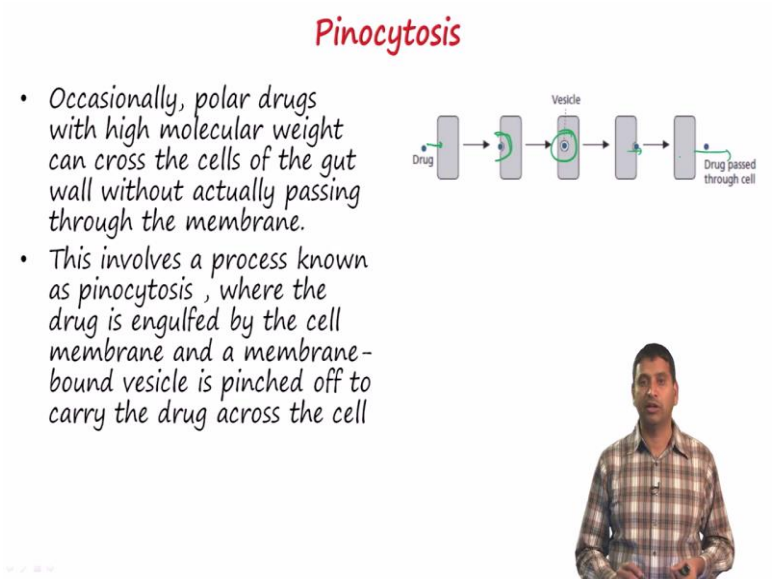


passed through the cell, Ok. So it is a process by which the drug is engulfed and pinched off to carry the drug to the other side.

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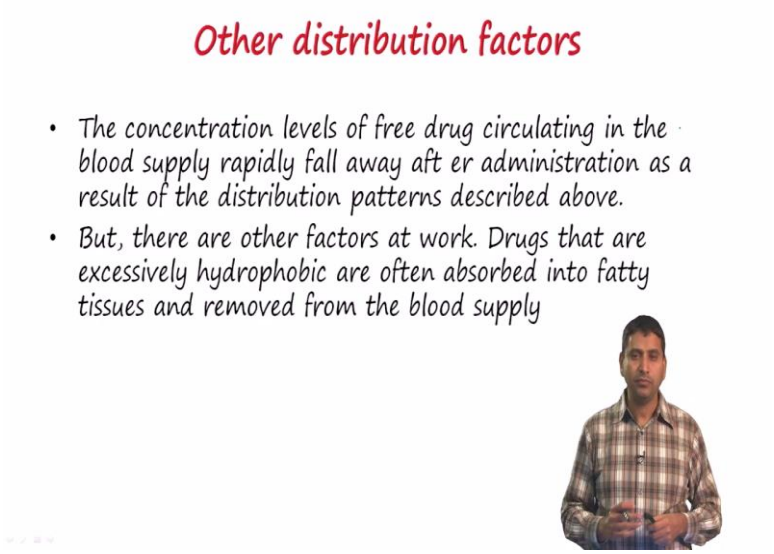


So there are other factors of course that are important. The concentration levels of the free drug circulating in the blood supply rapidly fall away after administration of, as result of the distribution patterns described above. So what it means is that, once you administer the drug then the drug concentration of the drug in the blood will go up.

So let us say on the y axis we have concentration of drug. In the blood, so at t equals 0, it is 0 then it goes up,

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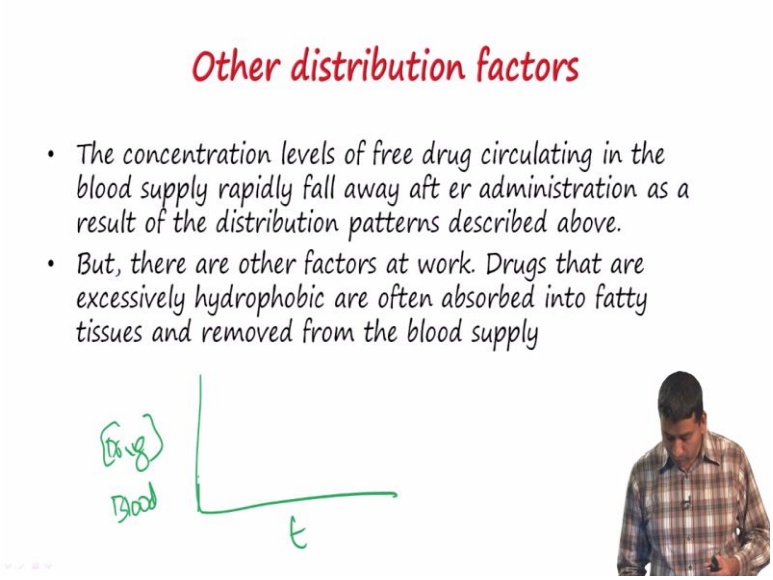


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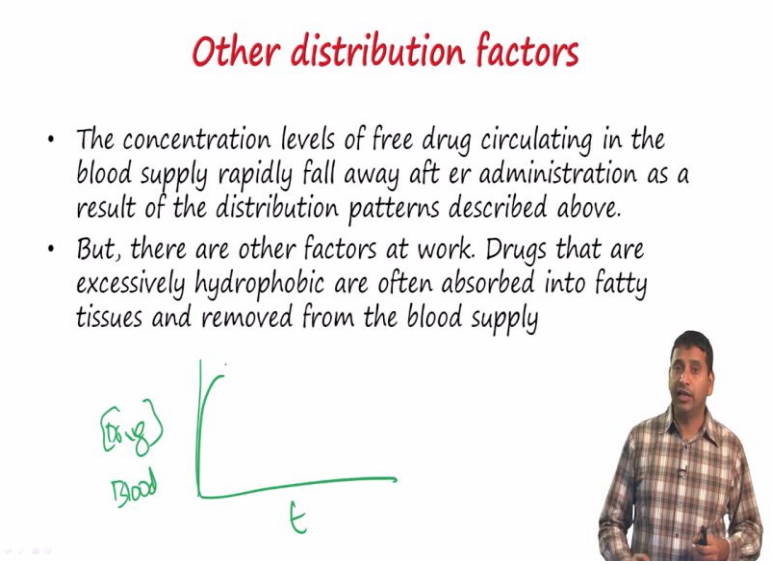


and then after some time what happens is that it starts distributing through these capillaries it gets across and starts going into various tissues. So it will, is expected to

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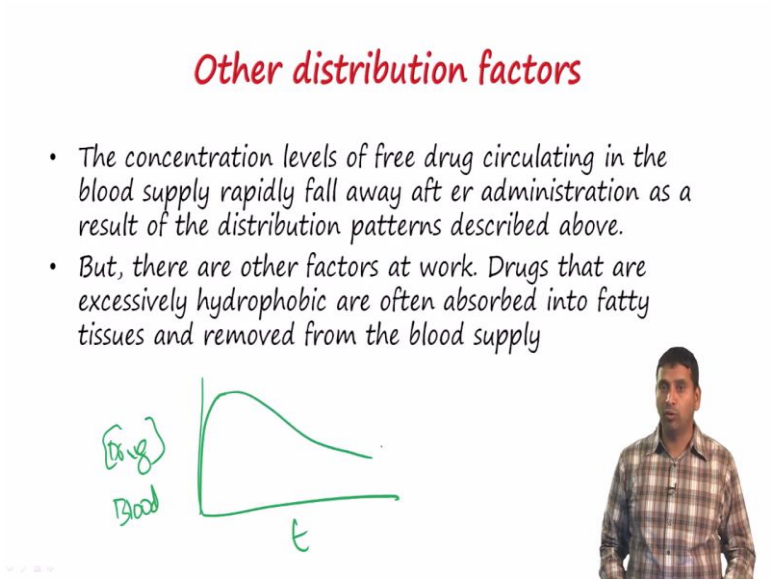


go down over a period of time, Ok.

But drugs that are excessively hydrophobic are absorbed into fatty tissues and they are removed from the blood supply. So they are not available to pass around inside the blood, right.

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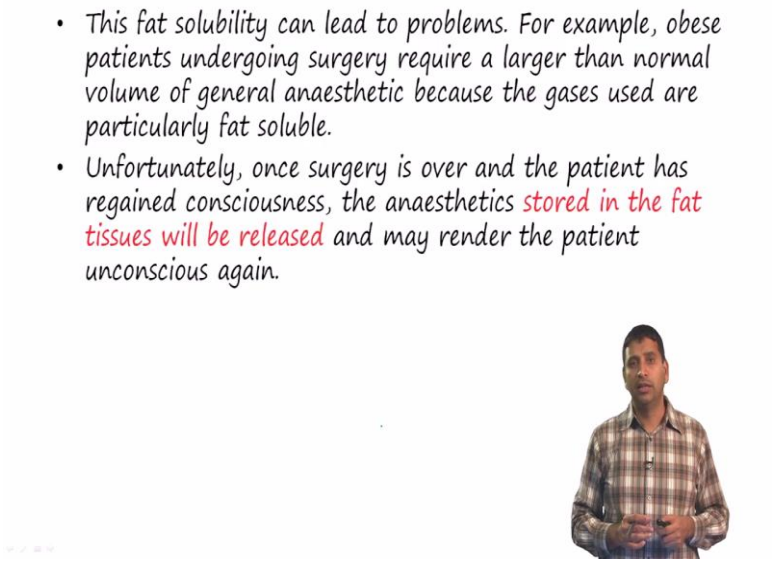


And, so fat solubility can lead to many various problems, Ok.

So we looked at it earlier that a highly hydrophobic molecule can get into fat globules, right and for example in obese patients, these are people who are excessively fat, beyond, you know the normal range and sometimes they undergo surgery, Ok.

And what happens is that when they undergo the surgery they require larger than normal amount of general anaesthesics because their body weight is excessively high.
So when you give this general anaesthetic,

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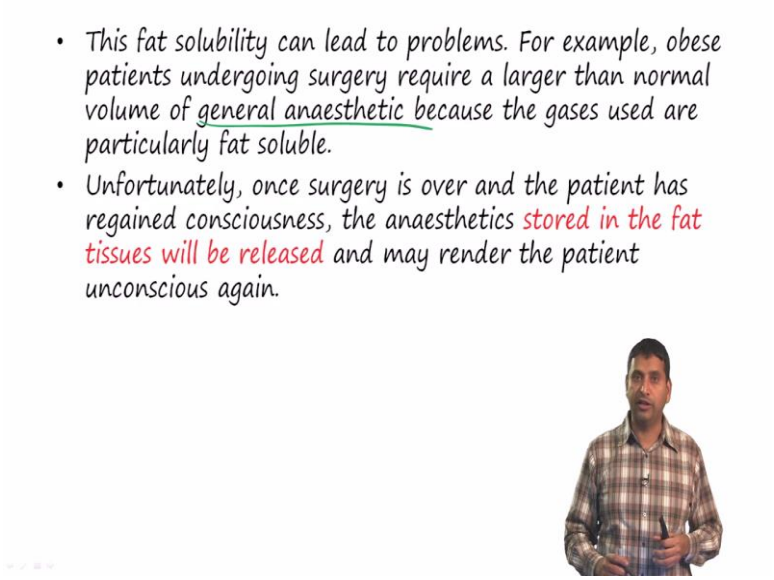


because general anaesthetics typically contain these gases which are particularly fat-soluble, Ok. So what happens is that after the surgery this anaesthetic gets across the body and gets into the fat area, area where there is lot of fat, Ok.

So once the surgery is completed then the patient will regain consciousness because this anaesthetic is not available anymore. But then because there is lot of anaesthetic stored in the fatty tissues, they will then be released slowly and then because of that the patient can become unconscious again.

So therefore when we are administering a general anaesthetic to particularly obese people one needs to keep this in mind when they are doing it.

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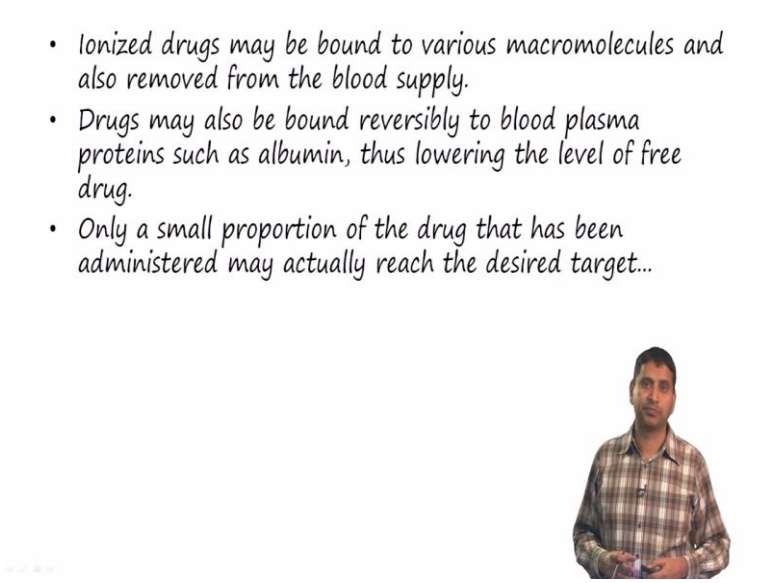


Ionized drugs again may have other problems, Ok. They may bind to various macromolecules and also they may be removed from the blood supply, Ok. So once you have removed from the blood supply then it is not very useful. So drugs may also bind reversibly to blood plasma.

So there is a very important albumin protein

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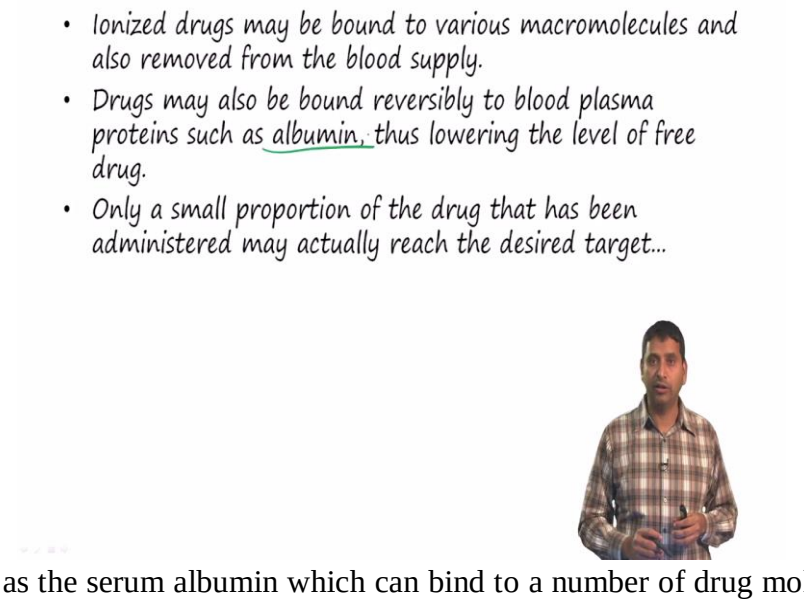


which is called as the serum albumin which can bind to a number of drug molecules and this lowers the level of free drug that is available to

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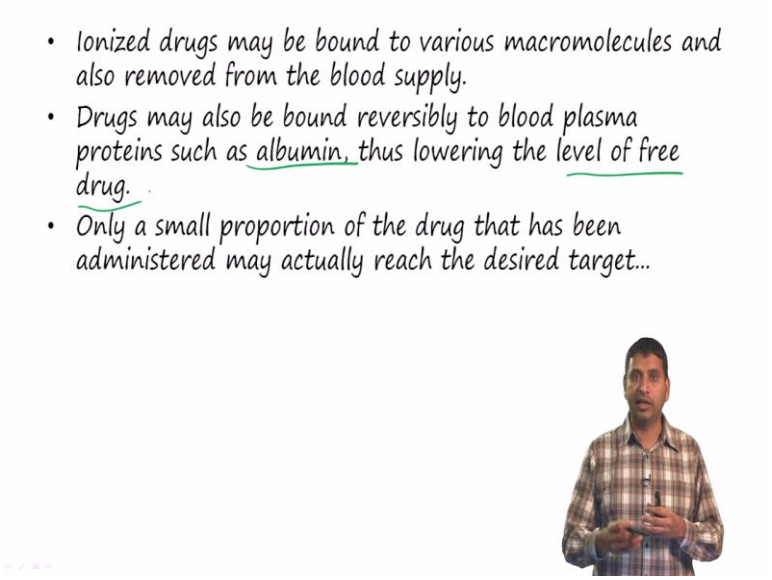


interact with the target.

So only a small proportion of the drug that has been administered may actually reach the desired target. So in this entire

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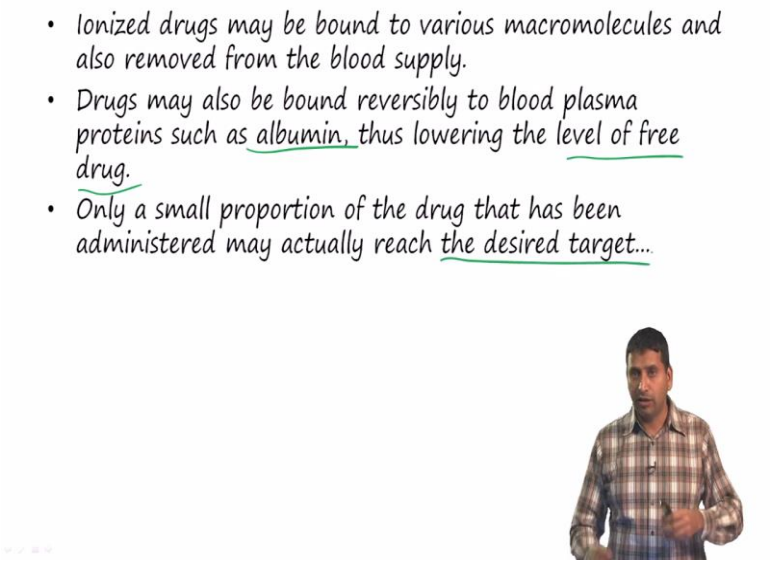


description that we have looked at today what we are trying to explain to you or what I am trying to explain to you is that once we take a capsule or a pill it gets into the stomach, it gets into the intestine and then it gets into the blood supply and so on.

But only a fraction of the drug may actually reach the desired target. So a large amount of the drug may actually be either excreted or going or being transported to a region which is not very important and so on,

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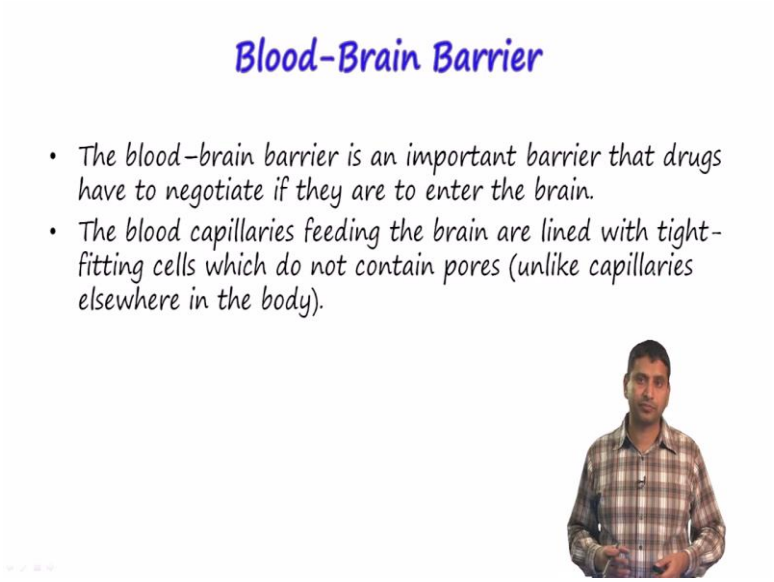


Ok.

Now there is another important factor when we are considering various organs in the body. One of the most important organs that we have is the brain and the brain is actually protected quite a bit from the rest of the body, so by what is known as a blood brain barrier,

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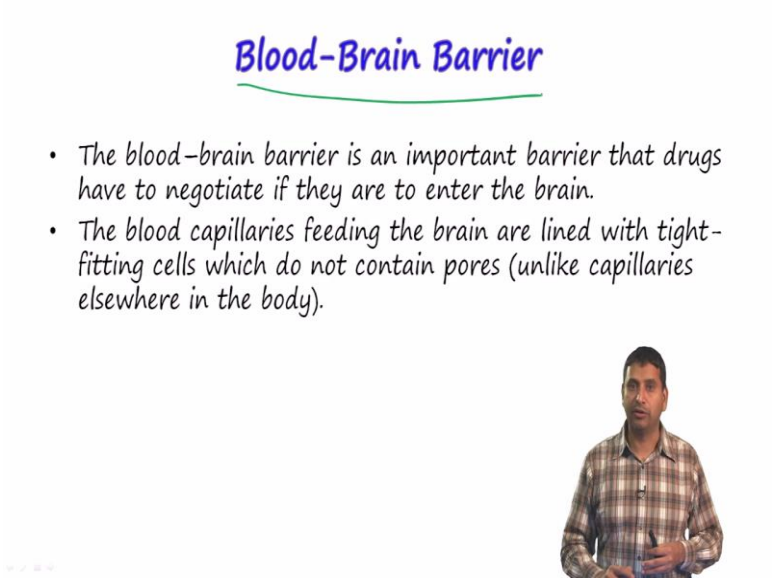


Ok.

So what happens is that if one wants to send a drug to the brain then it has to cross what is known as a blood brain barrier or it has to negotiate this barrier. So the blood capillaries that feed the brain are lined with very tight filling cells. So normally we were looking at the intestine lining cells. There are many pores through which

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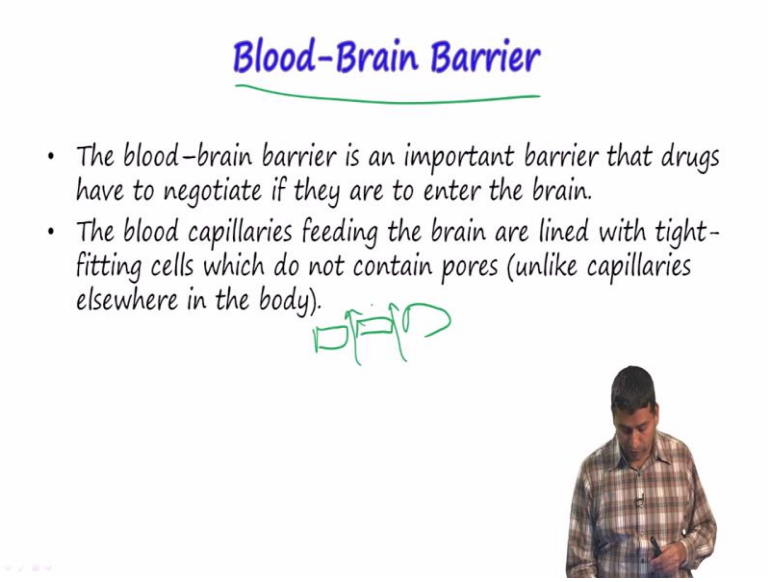


it goes.

But in the brain these are actually very tightly filled and therefore there are no pores that

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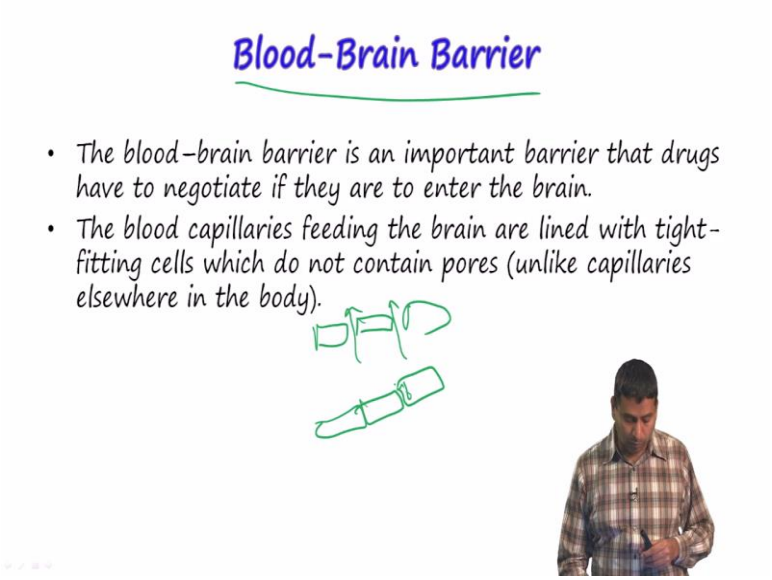


are really available for the drug to pass through,

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- Moreover, the capillaries are coated with a fatty layer formed from nearby cells, providing an extra fatty barrier through which drugs have to cross.
- Drugs entering the brain have to dissolve through the cell membranes of the capillaries and also through the fatty cells coating the capillaries.

Ok. So the capillaries are coated with a fatty layer, Ok so there is also formed from nearby cells and this provides an extra fatty barrier through which drugs have to cross.

So not only do they have to cross the membrane but they also have to cross this extra fatty layer. So drugs entering the brain have to dissolve through the cell membrane of the capillary and also through the fatty cells coated

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- Moreover, the capillaries are coated with a fatty layer formed from nearby cells, providing an extra fatty barrier through which drugs have to cross.
- Drugs entering the brain have to dissolve through the cell membranes of the capillaries and also through the fatty cells coating the capillaries.

with these capillaries.

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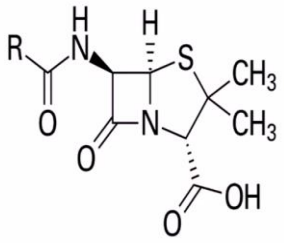
Polar drugs, such as penicillin, do not enter the brain easily.




So for example the drug that we looked at is penicillin, so penicillin is not, does not enter the brain easily because it is quite polar.

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- The existence of the blood–brain barrier makes it possible to design drugs that will act at various parts of the body (e.g. the heart) and have no activity in the brain, thus reducing any central nervous system (CNS) side effects.

So the existence of the blood brain barrier makes it possible to design drugs that will affect various parts of the body but have no activity on the brain.

Because this is very important because the brain is quite susceptible to side effects, right. So if the drug is designed such that it does not cross the blood brain barrier then the central nervous system is actually

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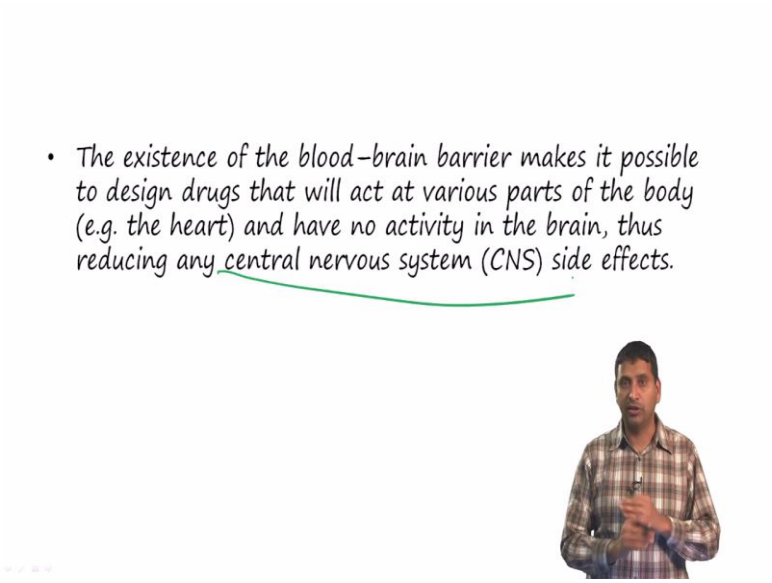


spared of the side effects.

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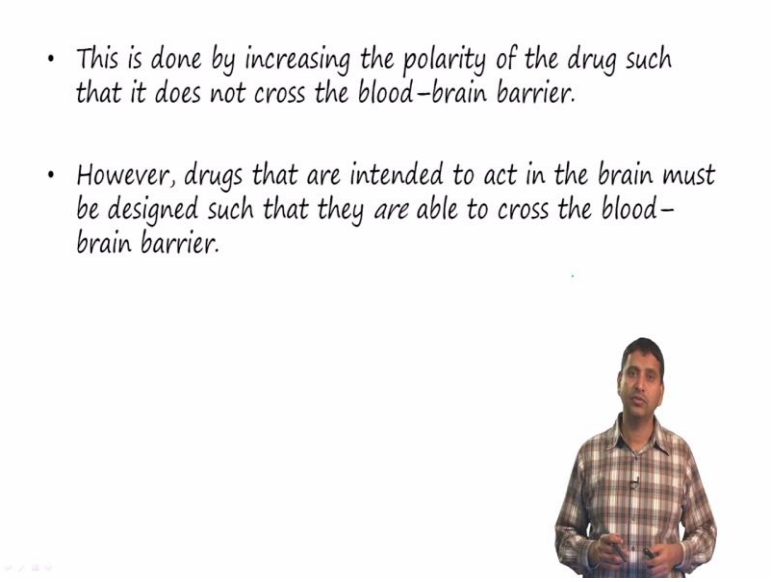


Now the way we can do it is to increase the polarity of the drug such that it does not cross the

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- This is done by increasing the polarity of the drug such that it does not cross the blood–brain barrier.
- However, drugs that are intended to act in the brain must be designed such that they are able to cross the blood–brain barrier.

blood brain barrier, Ok. However keep in mind that if we have to make a drug that is supposed to go to the brain then we should be able to design it in such that they are able to cross the blood brain barrier,

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- Some polar drugs can cross the blood–brain barrier with the aid of carrier proteins, while others (e.g. insulin) can cross by the process of pinocytosis described previously.
- The ability to cross the blood–brain barrier has an important bearing on the analgesic activity of opioids

Ok.

So some polar drugs can actually cross the blood brain barrier with the help of what are known as carrier proteins, Ok while others can actually go across by the process of pinocytosis which was described

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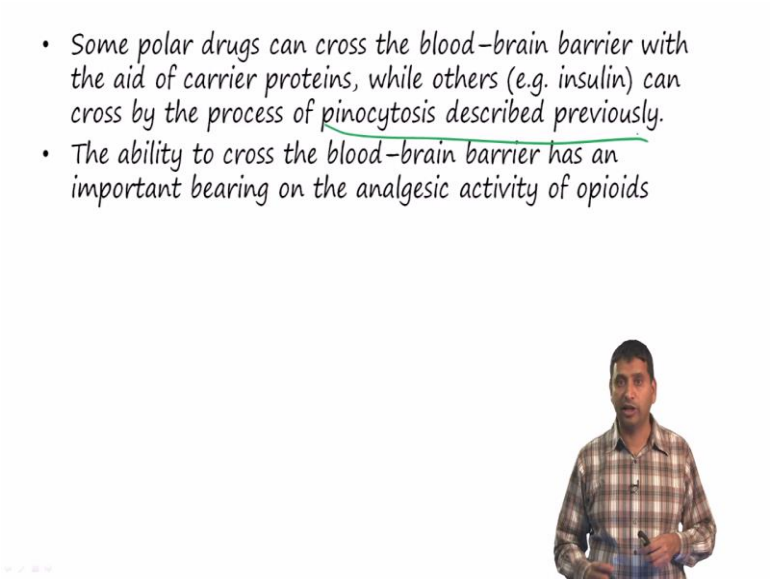


previously. The ability to cross the blood brain barrier has an important bearing on analgesic activity of opiods,

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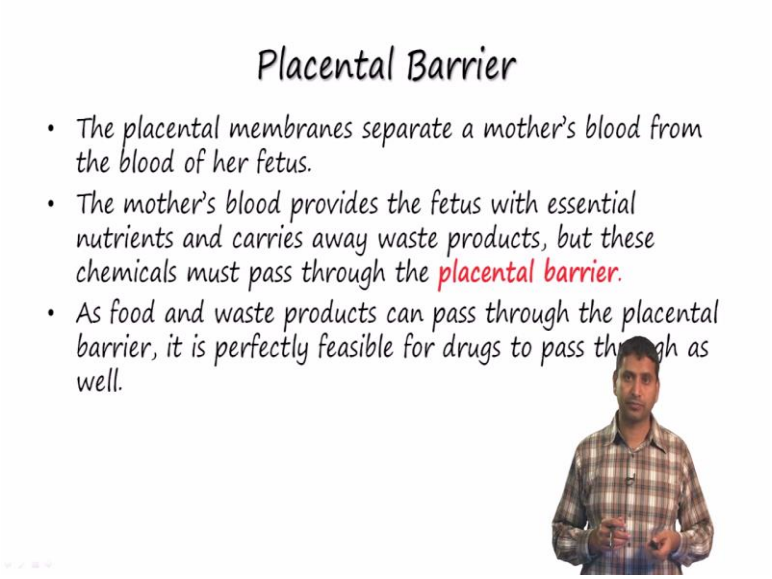


Ok.

Now there is another barrier especially in pregnant women where the fetus is growing and the fetus must be spared of number of processes that happen in the mother. So the placental membrane forms a very important barrier.

So the placental membrane separates the mother's blood from the blood of her fetus. So the mother's blood provides the fetus with essential nutrients like oxygen and all other nutrients and it also carries away waste products

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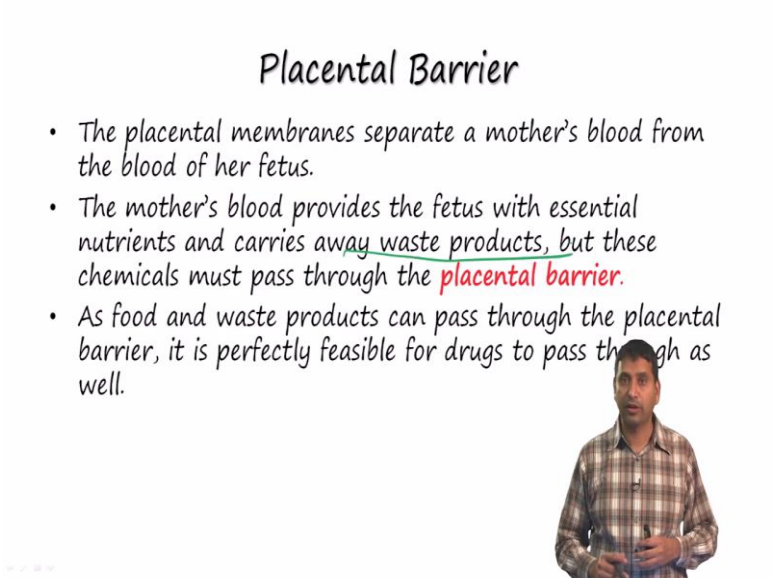


from the fetus, Ok.

But these chemicals must pass through what is known as the placental barrier. So as the food and waste products can pass through this barrier it is perfectly feasible for drugs also to pass through this.

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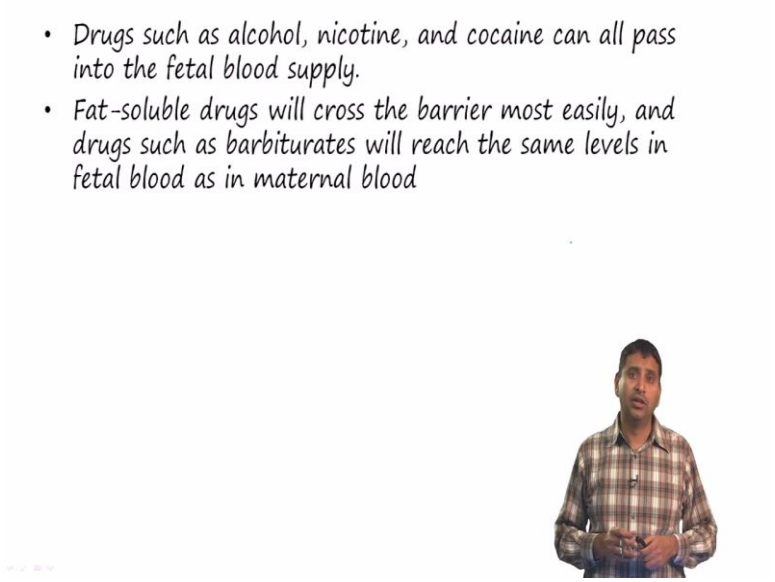


So many drugs such as alcohol, nicotine or cocaine can all pass through the fetal blood supply, Ok.

And fat soluble drugs will cross the barrier very easily, right and drugs such as barbiturates which are sometimes, which are consumed as addictive agents will reach the same level in

the fetal blood as in the maternal blood. So these are very dangerous to be consuming during pregnancy,

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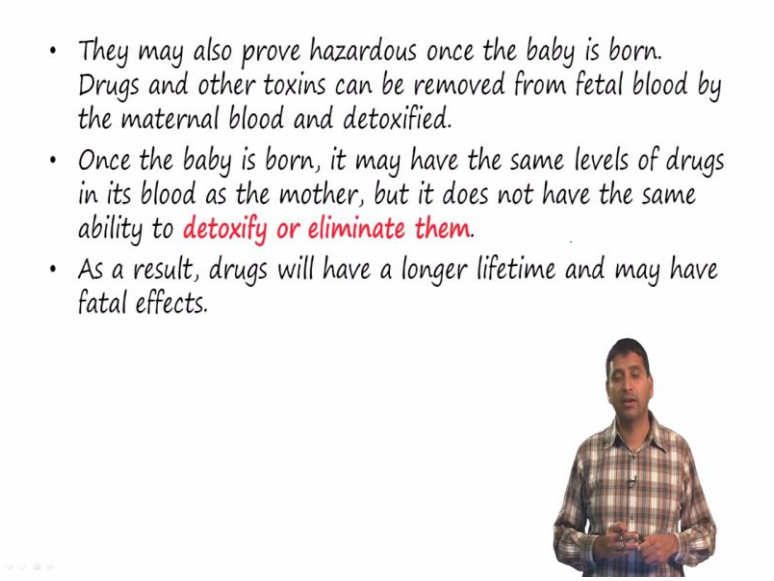


right.

So some of these are not known or not obvious but sometimes they may prove hazardous once the baby is born, Ok. So once these drugs or toxins enter the fetus, the mother's blood can pick it back up and detoxify it.

But once the baby is born it may still have some of the levels of the drug in its blood but it does not have the mechanism to detoxify or eliminate them. So it is possible that

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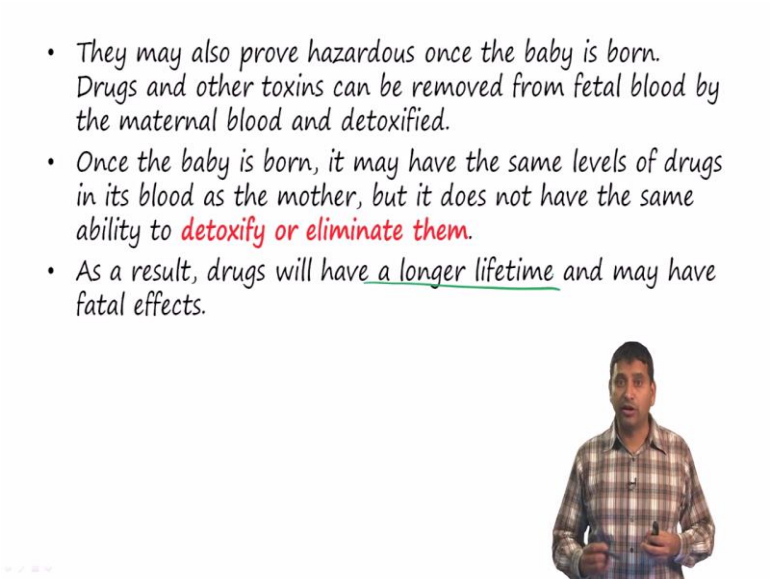


the drugs with a long half life, or a lifetime may have fatal effects on the fetus.

So these are some things that we need to consider when we are dealing with pregnancy or drugs that are going to have an effect on the mother who is carrying a fetus.

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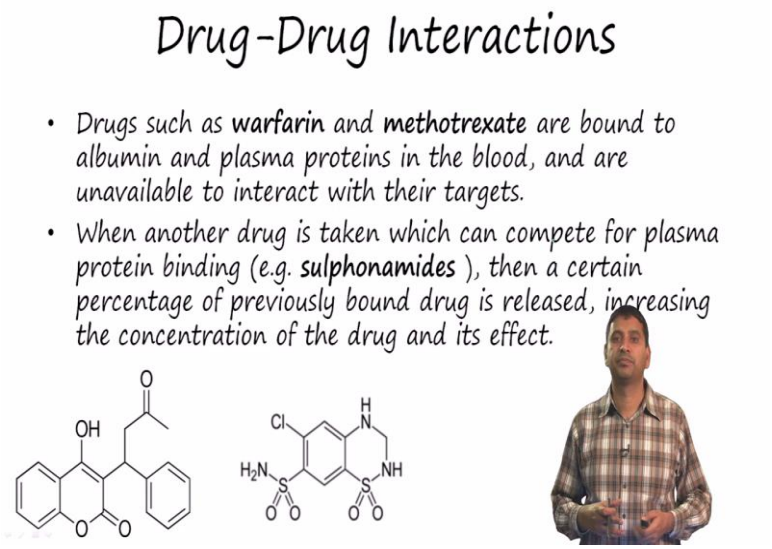


Another important aspect is the interaction between drugs, Ok. So drugs such as warfarin whose structure is shown here are bound to albumin, an plasma protein. We already looked at this, that plasma proteins can bind to certain drugs and therefore they are not available to interact with their targets.

But now when you take another drug, Ok, this drug can actually come and compete for the plasma protein binding. So the example here is sulphonamides

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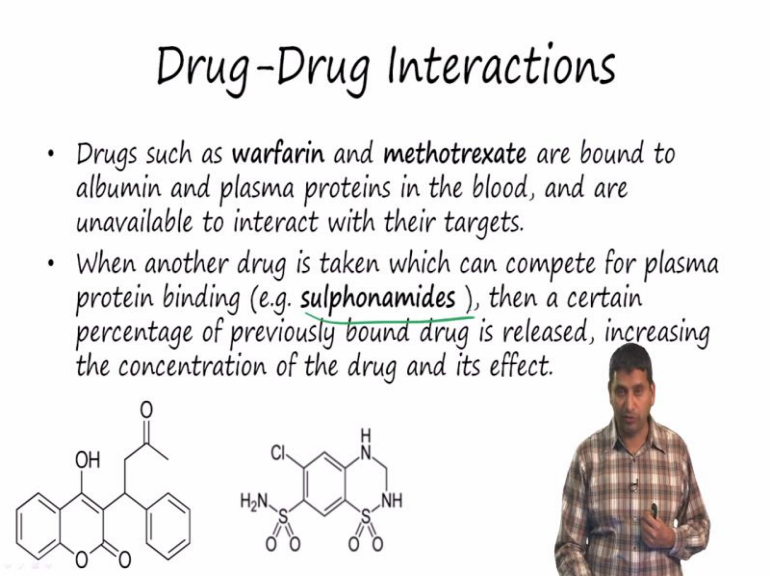


which were used as anti-bacterial agents. Now once the bound, the drug is bound here,

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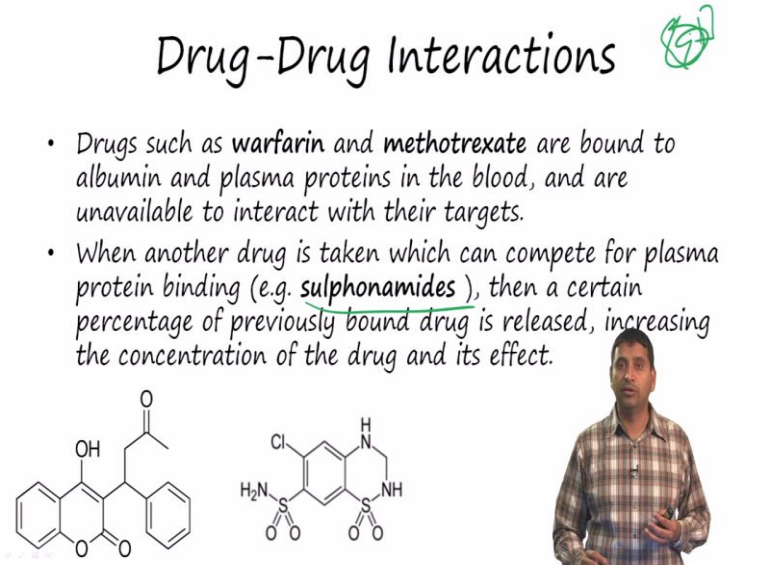


when there is a competition from another drug this first drug starts to get out, Ok.

So once the previously bound drug is released, the increased concentration of the drug is actually results, right. So this drug, the warfarin may actually have an effect which is unexpected when you take it with sulphonamides

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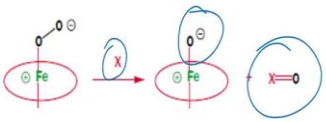
- Oxygen molecules are transferred from haemoglobin to other haems, such as the enzyme P450, and to a wide range of oxidizing agents.
- Almost any molecule we ingest that isn't a nutrient—a drug molecule, for example—is destroyed by oxidation.




Clayden, 2000

molecule behind.