Medicinal Chemistry
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Lecture No 39
Drug Administration Routes Part - 1

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Welcome back. In the past few lectures we have been looking at how drugs are administered and how they are metabolized once it gets in. So we looked at various aspects of ADME.

In today's lecture we are going to look at some aspects of excretion that is how drug is got rid of and various aspects of how drug is actually administered to the person. And how those variations can have some tremendous impact on how the drug actually works.

So just

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- Absorption, distribution, metabolism, and excretion.
- Phase I & Phase II metabolism...

to recap, we have looked at the concept of ADME. So we have looked at absorption, about how the drug is actually getting into the body and hitting the target that we wanted to hit.

We looked at distribution about how the drug sort of, which parts of the body it is going to distribute and so on. And we have spent quite a bit of time on metabolism. We have looked at Phase 1 and Phase 2 metabolism.

So the last part of ADME is excretion, so which we will start with today. And then we will move on to various other topics related to how to administer a drug and so on.

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The first pass effect

- Drugs that are taken orally pass directly to the liver once they enter the blood supply.
- Here, they are exposed to drug metabolism before they are distributed around the rest of the body, and so a certain percentage of the drug is transformed before it has the chance to reach its target.
- This is known as the first pass effect

So before we go forward let us understand what the first pass effect is.

So what happens when you take a drug orally is that it goes into the stomach and then from the stomach it gets degraded to some, in some part to metabolites and then it goes into the upper intestine and, as well as in the stomach it is absorbed to the blood, right.

So once it gets into the blood, it has to go to the liver, right. So in the liver, it is exposed to various metabolism pathways such as Cytochromes P450.

So before they are distributed around rest of the body certain percent of the drug is actually transformed to some metabolite. So this effect is known as the first pass effect.

So

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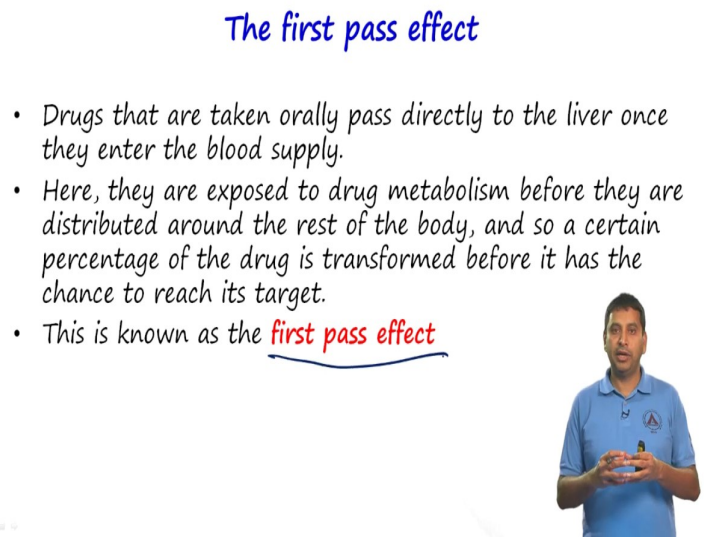

depending on how well the drug is actually metabolized you will find that the drug actually remains to a large extent intact if it is able to survive the first pass effect, Ok.

So if the drug is significantly affected, that is if it is very much susceptible to degradation by lower enzymes then it is going to be less effective to the onslaught by, during the first pass effect, Ok.

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- Drugs that are administered in a different fashion (e.g. injection or inhalation) avoid the first pass effect and are distributed around the body before reaching the liver.
- Indeed, a certain proportion of the drug may not pass through the liver at all, but may be taken up in other tissues and organs en route.

So drug administered in a different fashion, for example through injection or inhalation they get directly into the blood stream and they avoid the first pass effect,

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- Drugs that are administered in a different fashion (e.g. injection or inhalation) avoid the first pass effect and are distributed around the body before reaching the liver.
- Indeed, a certain proportion of the drug may not pass through the liver at all, but may be taken up in other tissues and organs en route.

Ok. So they are distributed around the body before reaching the liver.

Of course a certain proportion of the drug may not pass through the liver at all in certain cases but may be taken up in other tissues or organs which are on route, Ok.

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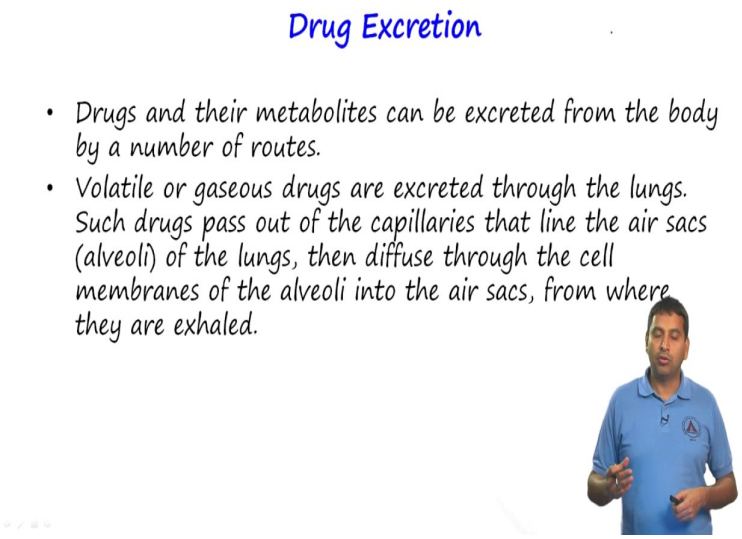

Now coming to excretion we have already looked at extensively about how there are number of processes that happen, that convert the drug into a more soluble form.

And one of the effects of increasing the solubility is to be able to get rid of it, right. So there are number of routes through which the drug and their metabolites are excreted.

So for example when you have volatile or gaseous drug that are getting in the system through the lung these go over to the capillaries that line the air sacs which are called as alveoli and then diffuse through the cell membranes into the air sacs from which they are exhaled, Ok.

Now the concentration of the, let us say you administer a gaseous drug and then there is a high level of the drug in the lungs which then gets into the blood supply.

And the reverse can happen wherein they are going to diffuse through the cell membrane back into the air sacs from which they are exhaled.

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- Gaseous general anaesthetics are excreted in this way and move down a concentration gradient from the blood supply into the lungs.
- They are also administered through the lungs, in which case the concentration gradient is in the opposite direction and the gas moves from the lungs to the blood supply.

Generally speaking, gaseous general anaesthetics are excreted in this way. And there is a concentration gradient from the blood supply to the lungs, Ok.

So typically when you are looking at the lungs, there is partial pressure of oxygen or of air and the oxygen moves from higher partial pressure to lower partial pressure.

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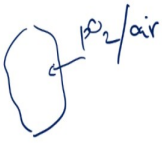

So when you have deoxygenated blood, from the air the oxygen is getting into the blood, right.

So imagine a similar situation wherein the general anesthetic is now coming into the lung. It is going to get in to the blood supply because the partial pressure of the anaesthetic is lower in the blood.

But imagine when the anaesthetic is removed then you have a higher partial pressure of the anaesthetic in the blood and so it gets exhaled through this route. So the concentration gradient is now in the opposite direction and so it moves from the lungs to the blood supply

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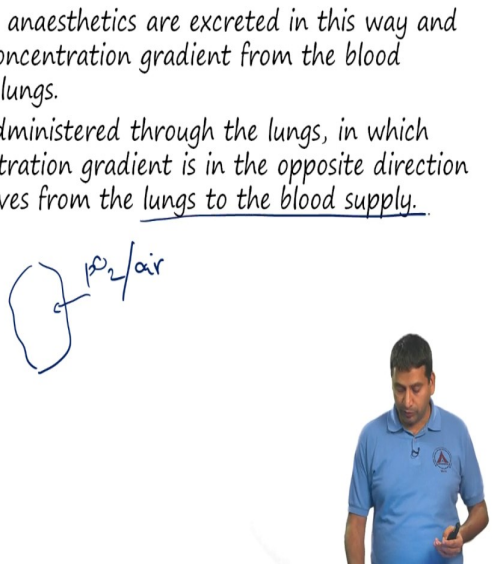

or vice versa.

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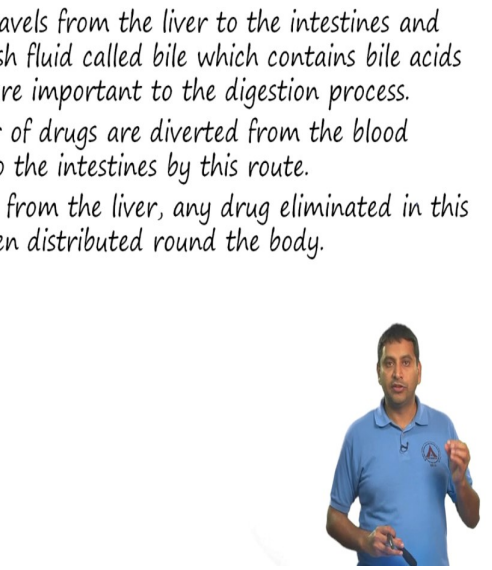

Similarly there is a bile duct which travels from the liver to the intestines. And it carries a greenish fluid called the bile, Ok. So this bile contains bile acids

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- The bile duct travels from the liver to the intestines and carries a greenish fluid called bile which contains bile acids and salts that are important to the digestion process.
- A small number of drugs are diverted from the blood supply back into the intestines by this route.
- As this happens from the liver, any drug eliminated in this way has not been distributed round the body.

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digestion process. A small number of drugs are diverted from the blood supply back to the intestine by this route, Ok.

So as this happens from the liver, any drug eliminated in this way has not been distributed in the body and so this is the way

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- The bile duct travels from the liver to the intestines and carries a greenish fluid called bile which contains bile acids and salts that are important to the digestion process.
- A small number of drugs are diverted from the blood supply back into the intestines by this route.
- As this happens from the liver, any drug eliminated in this way has not been distributed round the body.

in which the drug is actually going to prevent distribution across the body in a very consistent manner.

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- Therefore, the amount of drug distributed is less than that absorbed.
- However, once the drug has entered the intestine, it can be reabsorbed, so it has another chance.

So the drug is now distributed to a less extent and therefore it is less absorbed, Ok. So however once the drug has entered the intestine it can be reabsorbed and so it has another chance to be, to get to the target.

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- It is possible for as much as 10–15% of a drug to be lost through the skin in sweat. Drugs can also be excreted through saliva and breast milk, but these are minor excretion routes compared with the kidneys.
- There are concerns, however, that mothers may be passing on drugs such as nicotine to their baby through breast milk.

Now it is possible for as much as about 10 to 15 percent of the drug to be lost through the skin in the form of sweat, Ok.

Drugs are also excreted through saliva and in the case of lactating mothers, through the breast milk. However these are quite minor when compared to how much of the drug is lost through the kidneys.

So by the way in the case of mothers who are feeding the babies there are drugs such as nicotine that gets through the breast milk to the babies. So one needs to be careful while they are feeding.

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- The kidneys are the principal route by which drugs and their metabolites are excreted
- The kidneys filter the blood of waste chemicals and these chemicals are subsequently removed in the urine.
- Drugs and their metabolites are excreted by the same mechanism.

Now kidneys are the principal route by which the drugs and the metabolites are excreted. So the kidneys act as a filter and they filter the blood of waste chemicals and these chemicals are subsequently removed in the urine, Ok. So kidney plays a very important role in excretion.

Let us now

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- Blood enters the kidneys by means of the renal artery.
- This divides into a large number of capillaries, each one of which forms a knotted structure called a glomerulus that fits into the opening of a duct called a nephron

look at how the kidneys function. The blood enters the kidneys by means of the renal artery,

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Ok and what happens in this renal artery is that; it then divides it into a number of capillaries, each of which forms a knotted structure called as the glomerulus.

So you have the glomerulus which has the structure like this,

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- Blood enters the kidneys by means of the renal artery.
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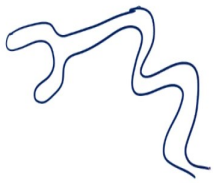

right. And you have here the artery which is supplying blood and here once the artery is getting in, it forms a number of small capillaries and then it goes out this way.

And

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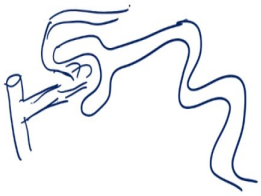
- Blood enters the kidneys by means of the renal artery.
- This divides into a large number of capillaries, each one of which forms a knotted structure called a glomerulus that fits into the opening of a duct called a nephron



this here is the nephron,

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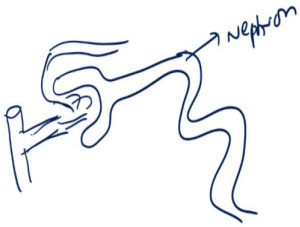
- Blood enters the kidneys by means of the renal artery.
- This divides into a large number of capillaries, each one of which forms a knotted structure called a glomerulus that fits into the opening of a duct called a nephron



this is the artery and here this is the renal artery

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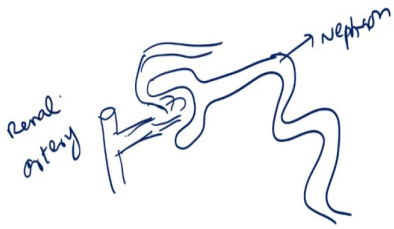
- Blood enters the kidneys by means of the renal artery.
- This divides into a large number of capillaries, each one of which forms a knotted structure called a glomerulus that fits into the opening of a duct called a nephron



and here is the, these small things here are called arterioles,

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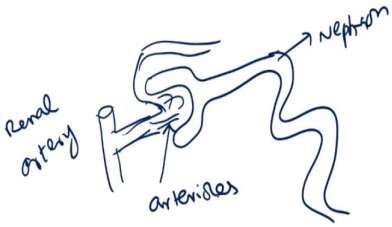
- Blood enters the kidneys by means of the renal artery.
- This divides into a large number of capillaries, each one of which forms a knotted structure called a glomerulus that fits into the opening of a duct called a nephron



Ok and they go back and they surround themselves and come back here and they form the renal vein, Ok.

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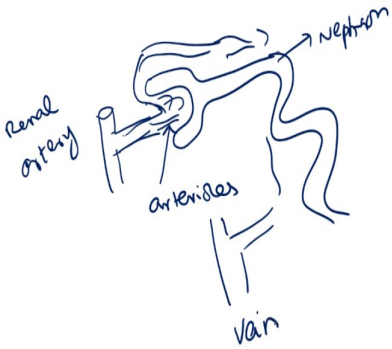
- Blood enters the kidneys by means of the renal artery.
- This divides into a large number of capillaries, each one of which forms a knotted structure called a glomerulus that fits into the opening of a duct called a nephron



So this is a cartoon representation of how the glomerulus and the nephron looks like. This is the glomerulus.

Here is the,

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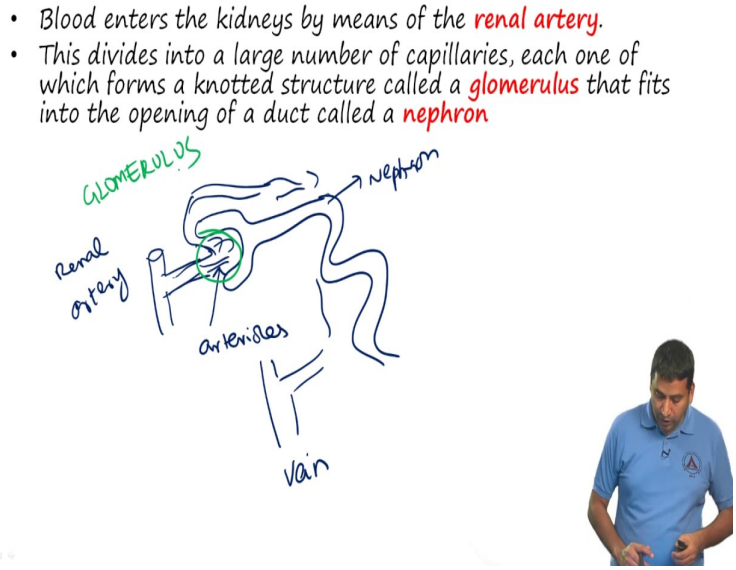

Ok so essentially what happens here is that the renal artery makes smaller and smaller capillaries and these capillaries form a knotted structure called the glomerulus that fits into the opening of a duct which is called a nephron, Ok. So this is where the activity of the kidney occurs.

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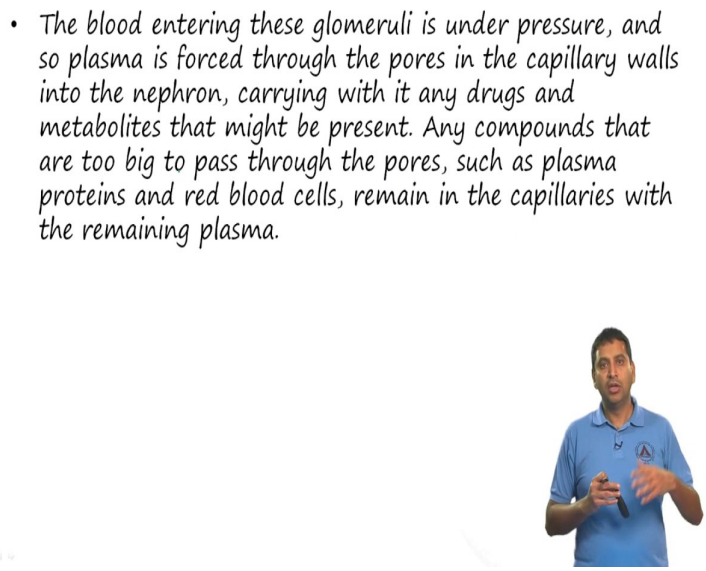

Now the blood entering the glomeruli is under pressure, right. So the plasma is forced through the pores in the capillary walls into the nephron, Ok.

So through the glomerulus the particles are forced through these pores

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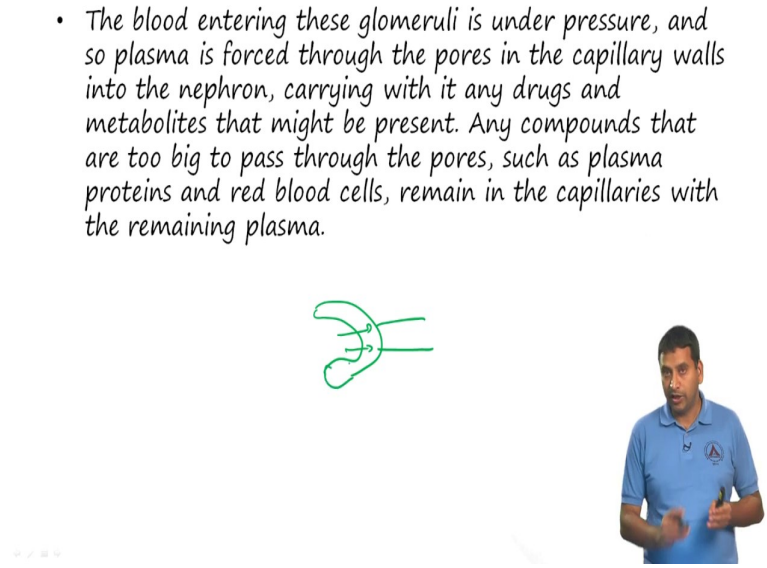

into the nephron. Into the nephron there are any drugs or metabolites that might be present also trapped, Ok.

Any compound that is too big to pass through these pores such as plasma proteins and red blood cells, they remain in the capillary. So the capillaries that are here,

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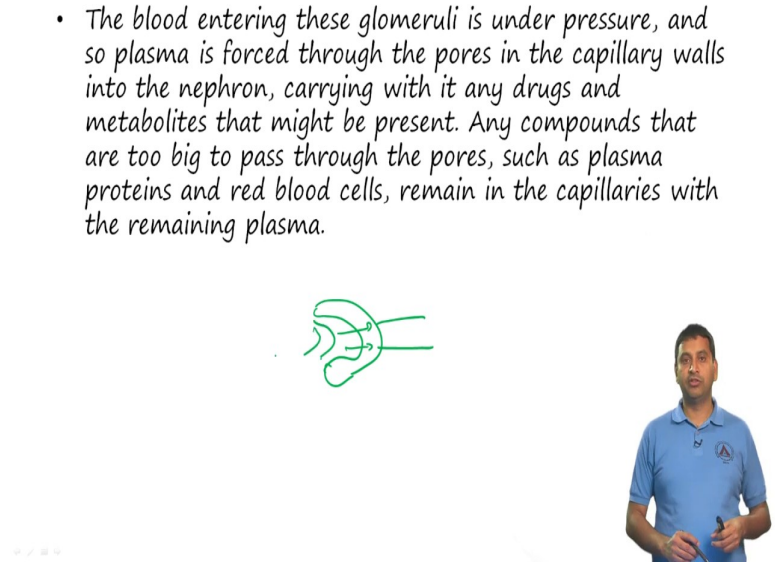

the proteins remain in the capillaries.

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- Note that this is a filtration process, so it does not matter whether the drug is polar or hydrophobic: all drugs and drug metabolites will be passed equally efficiently into the nephron.
- However, this does not mean that every compound will be excreted equally efficiently, because there is more to the process than simple filtration.

Now this is a filtration process. So it does not matter whether the drug is polar or hydrophobic. All that matters here at this point is how large the particle is. So if a particle is extremely large like a protein it is not going to get across.

But if it is a small molecule which is majority of the drugs or metabolites then these are going to be passed through quite efficiently into the nephron.

However this does not mean that every compound will be excreted with the same efficiency, Ok. Because this process is more than

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- Note that this is a filtration process, so it does not matter whether the drug is polar or hydrophobic: all drugs and drug metabolites will be passed equally efficiently into the nephron.
- However, this does not mean that every compound will be excreted equally efficiently, because there is more to the process than simple filtration.

just a simple filtration as we shall see.

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- The filtered plasma and chemicals now pass through the nephron on their route to the bladder.
- However, only a small proportion of what starts that journey actually finishes it.

So the filtered plasma and chemicals now pass through the nephron. We have already looked at the structure of the nephron. Nephron is something like this, right.

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- The filtered plasma and chemicals now pass through the nephron on their route to the bladder.
- However, only a small proportion of what starts that journey actually finishes it.

And here, this is where the second process of purification occurs. So only a small proportion of what starts this journey actually finishes it,

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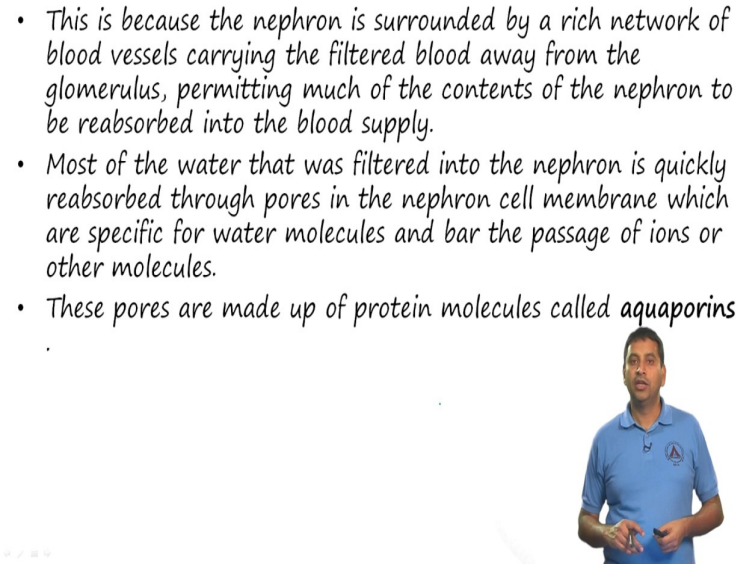

right.

This is because the nephron is surrounded by a rich network of blood vessels carrying the filtered blood away from the glomerulus, Ok. So this permits the content of the nephron to be reabsorbed into the blood supply.

So if you imagine that the nephron structure is like this, so this is

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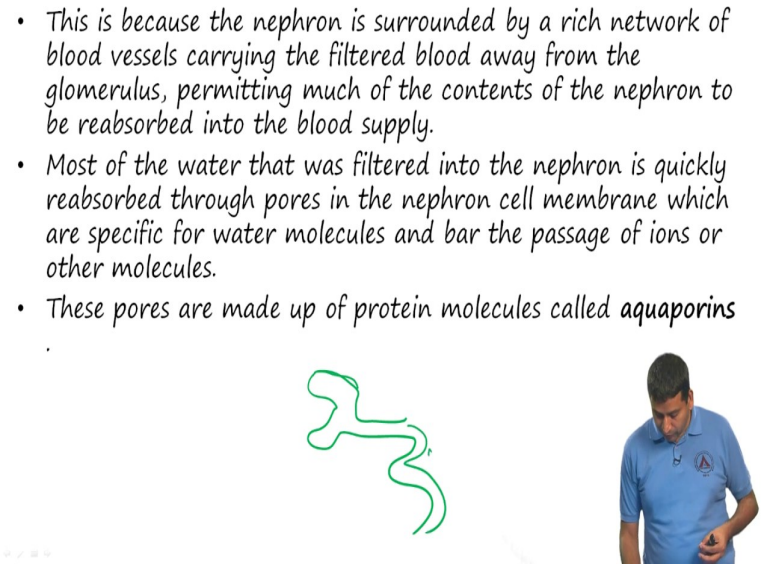

surrounded by blood vessels. And so through here the drugs and, or whatever metabolites are going

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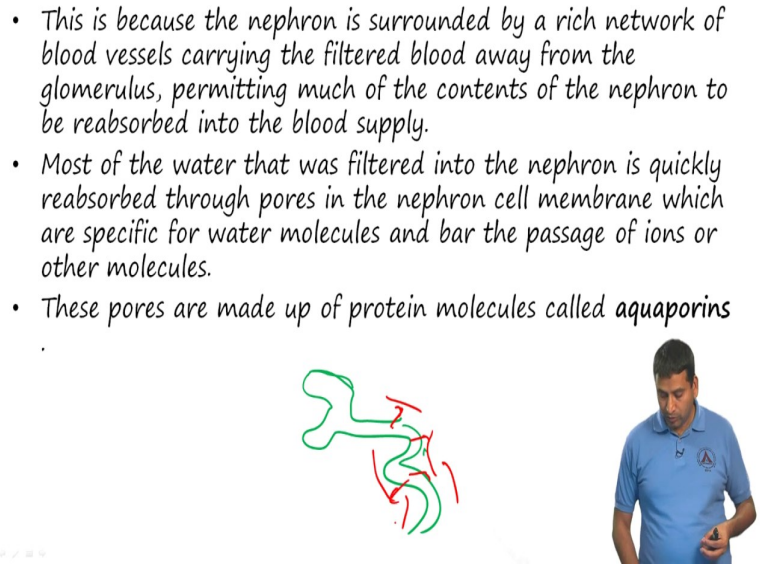

to pass across the nephron back into the blood supply, Ok. This is a process of reabsorption.

So most of the water that was filtered into the nephron is quickly reabsorbed through these pores in the nephron cell membrane and these are very specific for water molecules and they prevent the passage of ions or other molecules. And these pores are called as aquaporins.

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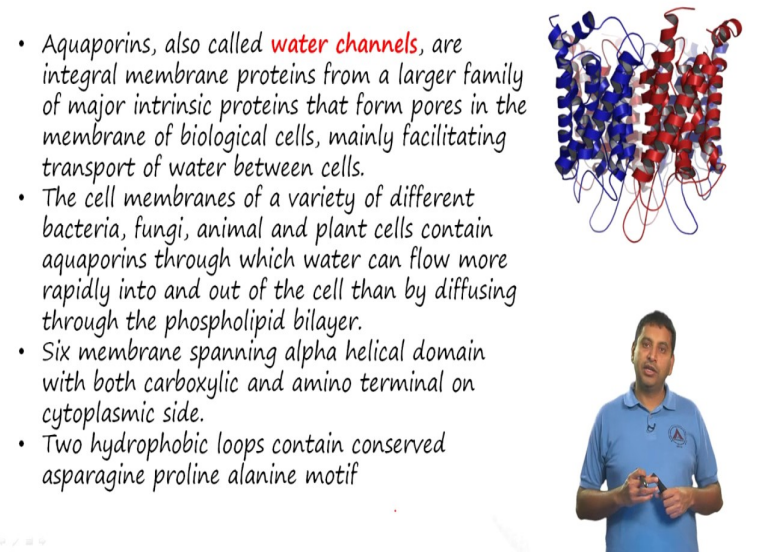

Let us understand a little bit about these aquaporins. Here is a structure of aquaporins; that is the crystal structure that is reported. Aquaporins are also called as water channels and these are integral membrane proteins from a larger family of a major intrinsic proteins that form pores, Ok.

And these mainly facilitate the transport of water between cells. So the cell membranes of a variety of different bacteria, fungi, animal and plant cells contain aquaporins through which water can flow.

And this structure contains 6 membrane spanning alpha helical

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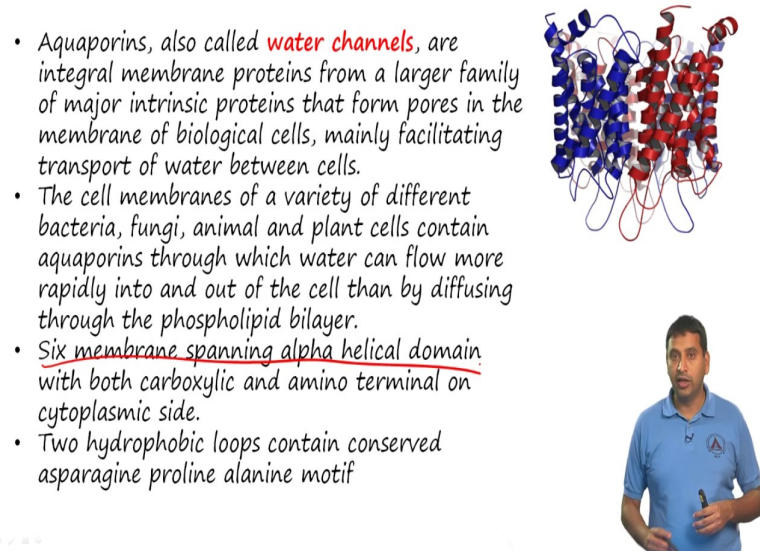

domains with both carboxylic and amino terminal on the cytoplasmic side. So this is on the inner, inner side is both the C terminal and the N terminal. And there are two hydrophobic loops containing conserved asparagine, proline and alanine motif,

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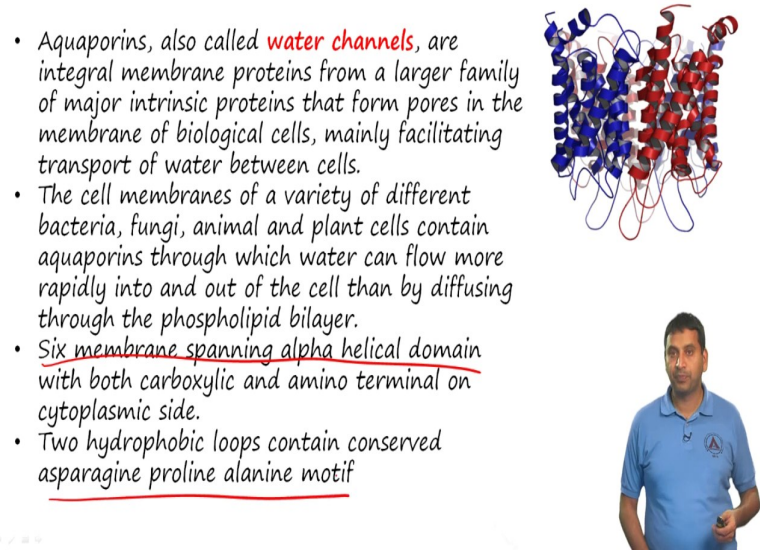

Ok.

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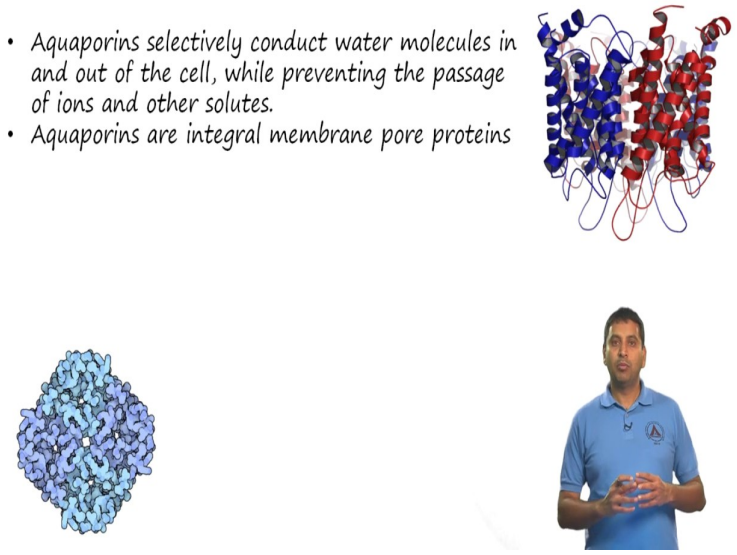

Aquaporins selectively conduct water molecules in and out of the cell and they prevent passing of other solutes, Ok. So here is the pore that you can

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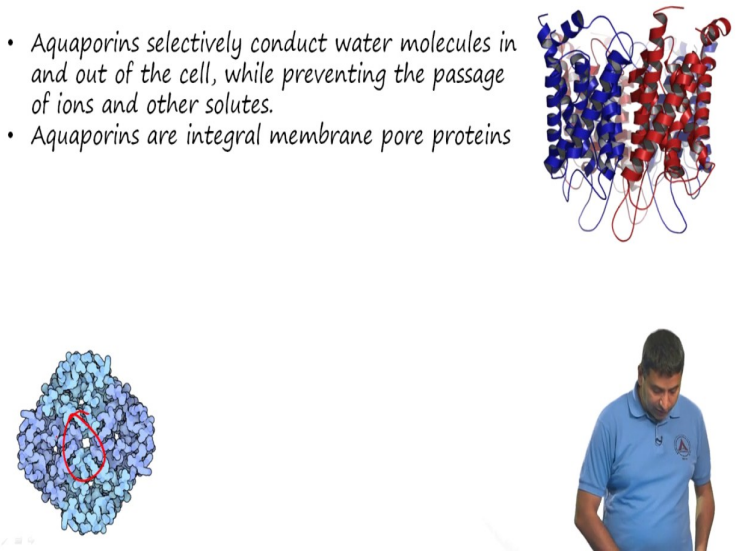

see that is created through which water is going to be transported.

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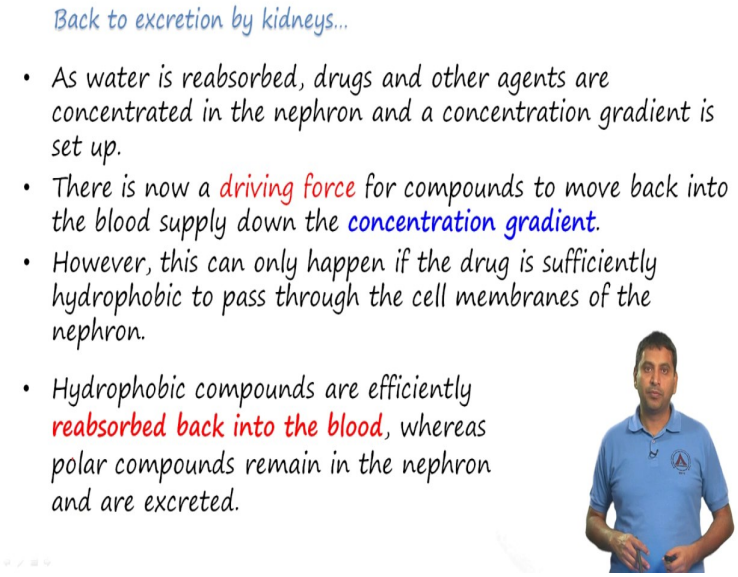

Now let us get back to the excretion by kidneys.

So as water is reabsorbed drugs or other agents are concentrated in the nephron and a concentration gradient is then set up, Ok. So now this becomes a driving force for compounds to move back into the blood supply down the concentration gradient.

However this can happen only if the drug is sufficiently hydrophobic to pass through the cell membranes of the nephron. So here is where the difference comes.

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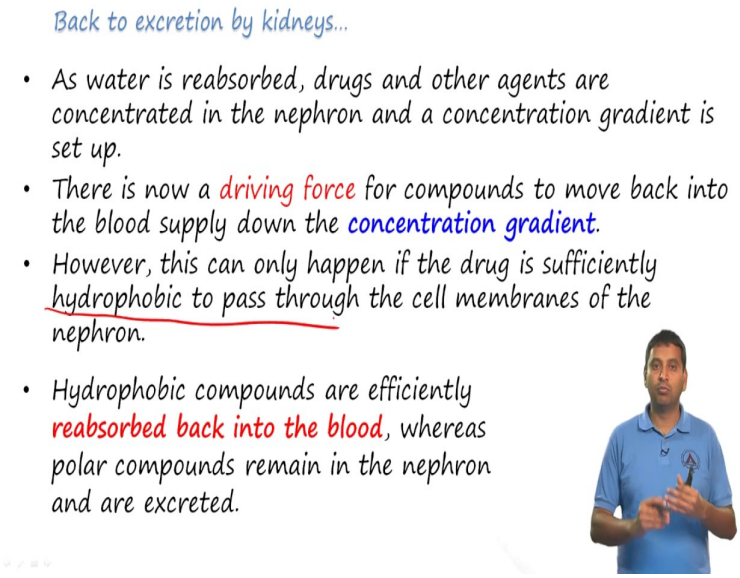

So the more hydrophobic the compound is, the better it is reabsorbed into the blood, OK and whereas polar compounds are unable to cross this membrane and therefore they are excreted.

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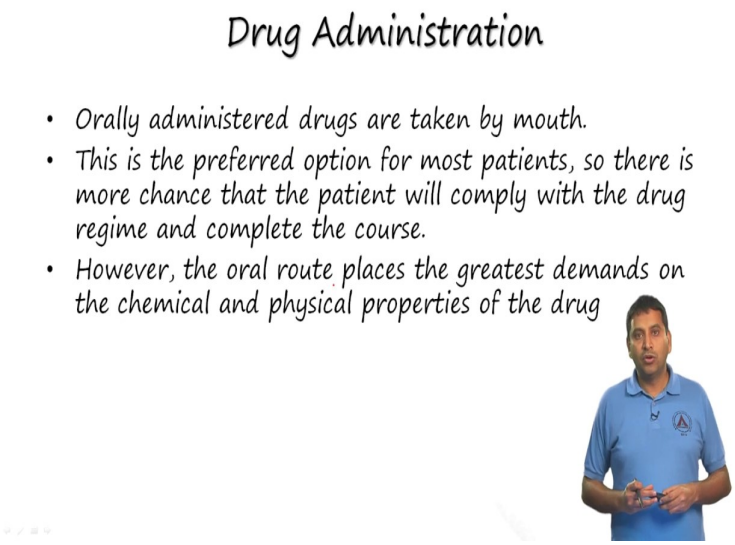

So that completes our discussion on how, what are the various ways in which the drug is going to be metabolized and absorbed and so on. And we also looked at the main route of excretion which is through the kidneys.

So now let us look at in detail what are the ways in which drug is administered, Ok. So of course orally administered drugs are taken by the mouth.

And this is the most preferred option because there is a higher chance that the patient will complain because there is no injection or pain that is induced during administration. But as we have looked at earlier, the oral route places the greatest demands on the chemical and physical properties of the drug.

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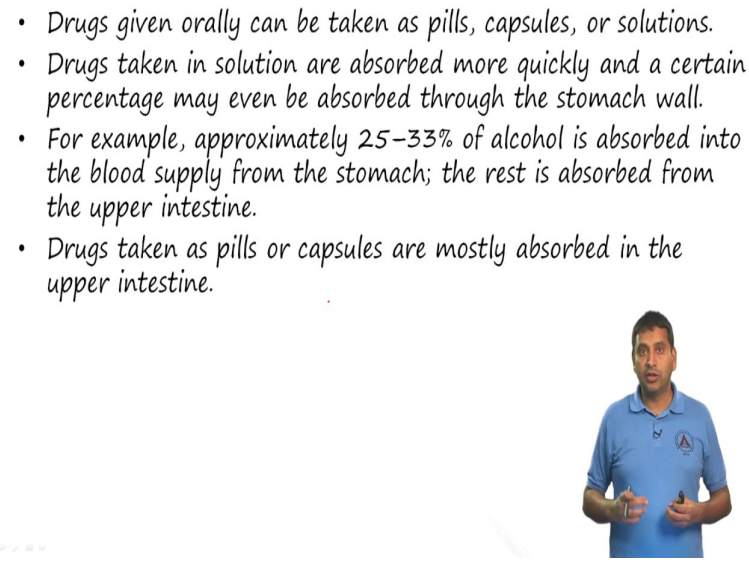

So drugs given orally can be taken as pills or capsules or solutions. We look at some of these later in the lecture. Drugs taken in solution are absorbed more quickly and a certain percentage may even be absorbed through the stomach wall, Ok.

So an example is alcohol. About

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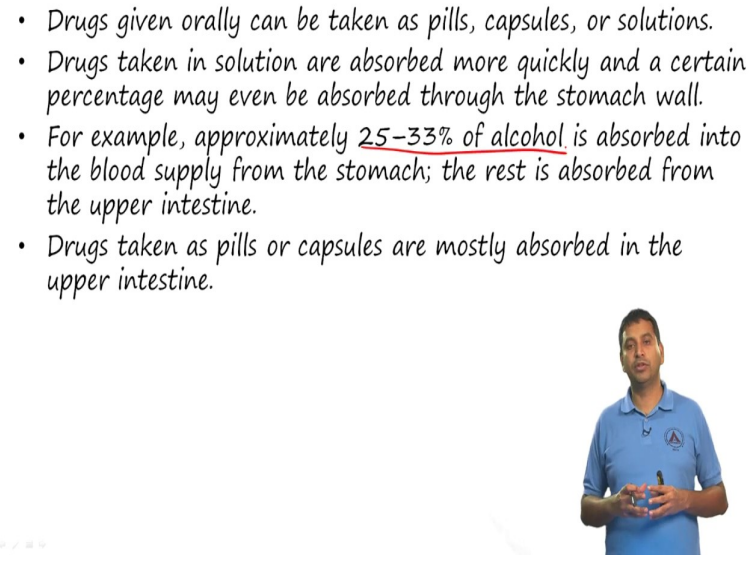

25 to 33 percent of alcohol is absorbed into the blood supply from the stomach. The rest is absorbed from the upper intestine. So drugs taken as pills or capsule are absorbed mainly in the upper intestine.

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- The rate of absorption is partly determined by the rate at which the pills and capsules dissolve.
- In turn, this depends on such factors as particle size and crystal form. In general, about 75% of an orally administered drug is absorbed into the body within 1–3 hours.

The rate of absorption is partly determined by the rate at which the pills or capsules dissolve. So the pills and capsules are made in such a manner that they contain the drug in it. And they have to dissolve or break down for it to be absorbed.

In turn this also depends on factors such as particle size and crystal form. So as a general rule, about 75 percent of an orally administered drug is absorbed in the body within

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- The rate of absorption is partly determined by the rate at which the pills and capsules dissolve.
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1 to 3 hours.

So if you see some of the drugs that are administered are given every 4 to 6 hours, that is because they are absorbed in about 1 to 3 hours and therefore you need the second dose shortly thereafter.

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- Specially designed pills and capsules can remain intact in the stomach to help protect acidlabile drugs from stomach acids.
- The containers then degrade once they reach the intestine.

Of course there are specially designed pills and capsules that can remain intact in the stomach to help acid labile drugs from stomach acids, Ok.

So we have already looked at previously that the stomach acids contain a very strong acid such as hydrochloric acid and so these are going to start degrading some of the drugs. And so you can design a capsule which is stable to low pH.

So these containers then degrade once they are in the intestine.

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- Care has to be taken if drugs interact with food. For example, **tetracycline** binds strongly to calcium ions, which inhibits absorption, so foods such as milk should be avoided.
- Some drugs bind other drugs and prevent absorption.

So there is also care has to be taken if the drug interacts with food, Ok. So for example the antibiotic tetracycline binds strongly to calcium ions which inhibits the absorption.

So foods such as milk should be avoided while

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- Care has to be taken if drugs interact with food. For example, **tetracycline** binds strongly to calcium ions, which inhibits absorption, so foods such as milk should be avoided.
- Some drugs bind other drugs and prevent absorption.

taking this tetracycline drug. Some drugs also bind to other drugs and prevent absorption.

We have also looked at previously certain problems with drug-drug interaction. So this becomes another issue that one needs to consider when we are taking multiple drugs.

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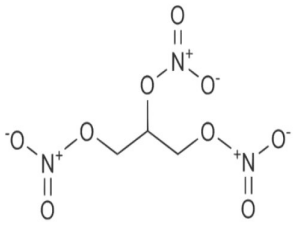
- Some drugs can be absorbed through the mucous membranes of the mouth or nose, thus avoiding the digestive and metabolic enzymes encountered during oral administration.
- For example, heart patients take **glyceryl trinitrate** by placing it under the tongue (sublingual administration).



Some drugs can be absorbed through the mucous membrane of the mouth or nose and they can avoid the digestive and metabolic enzymes.

This is especially relevant when you are looking at heart patients that take glyceryl trinitrate and they place it under the tongue which is called the sublingual administration.

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- Some drugs can be absorbed through the mucous membranes of the mouth or nose, thus avoiding the digestive and metabolic enzymes encountered during oral administration.
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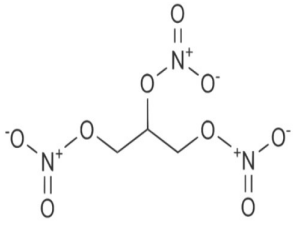

The structure of GTN is shown here.

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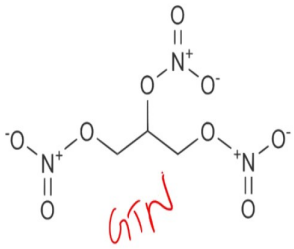

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- Nasal decongestants are absorbed through the mucous membranes of the nose.
- Cocaine powder is absorbed in this way when it is sniffed, as is nicotine in the form of snuff.
- Nasal sprays have been used to administer analogues of peptide hormones, such as antidiuretic hormone .
- These drugs would be degraded quickly if taken orally.

Nasal decongestants are absorbed through the mucous membrane of the nose, Ok and so you would give the nasal decongestant through the nose, Ok.

The highly addictive cocaine is absorbed in this way and which is why it is sniffed, right. And so is nicotine. You can also have nicotine in the form of snuff powder. And there are number of nasal sprays that are being used to administer certain peptide hormones such as anti-diuretic hormones.

So these drugs will be very quickly degraded if they are taken orally. So they are therefore made into a formulation and given as a powder or which can be something that can be administered through the nose.

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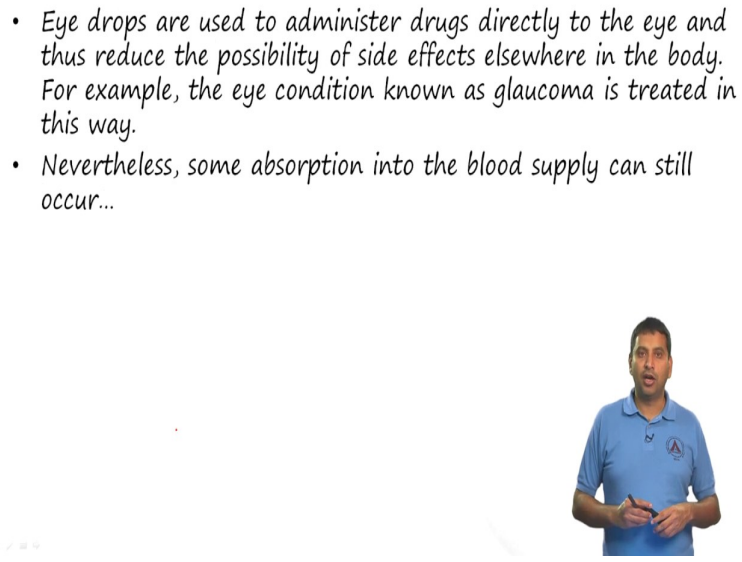

Of course there are number of eye-related diseases in which there are eye drops that are prepared. And so the eye drops are used to administer drugs directly into the eye. And this will reduce the possibility of side effects in the other parts of the body, Ok.

So for example

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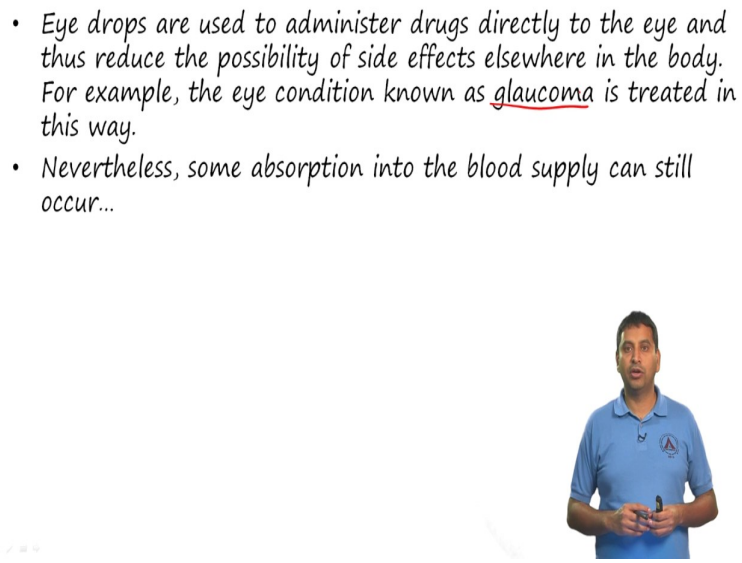

the disease called as glaucoma is treated this way, right. Of course some part of the eye drops will end up in the blood supply and that is something that one needs to consider while dosing with eye drops.

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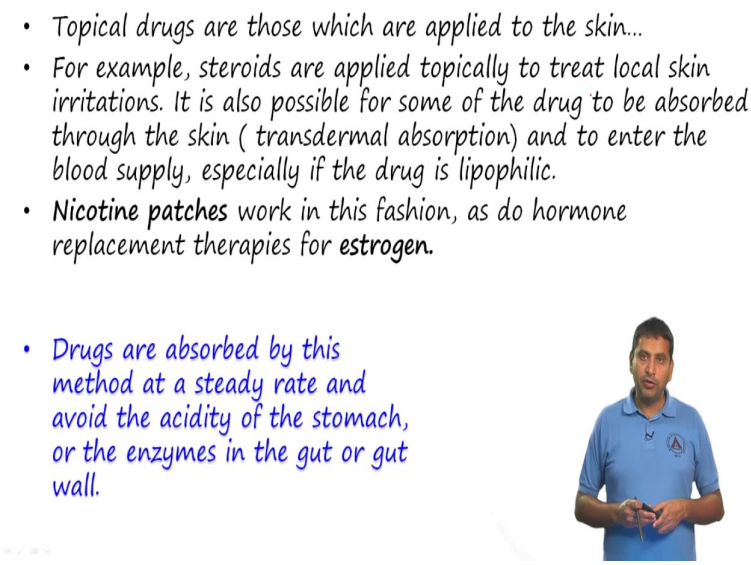

The other way to administer a drug is through the skin, Ok so you can apply drugs through the skin. For example steroids are applied topically to treat local skin irritations.

And of course there is, it is possible for some of the drug to be absorbed through the skin and to enter the blood supply especially if the drug is quite lipophilic.

You may be aware of these nicotine patches which are given to people who are trying to stop smoking. And these act in the same manner. And there are also hormone replacement therapies for estrogen, Ok.

So the advantage of, of transdermal absorption or transdermal way of delivering is that the drugs are absorbed in a very steady rate and they avoid the acidity of the stomach or the enzymes in the gut or the gut wall. So therefore this makes it a preferred route for certain kinds of drugs.

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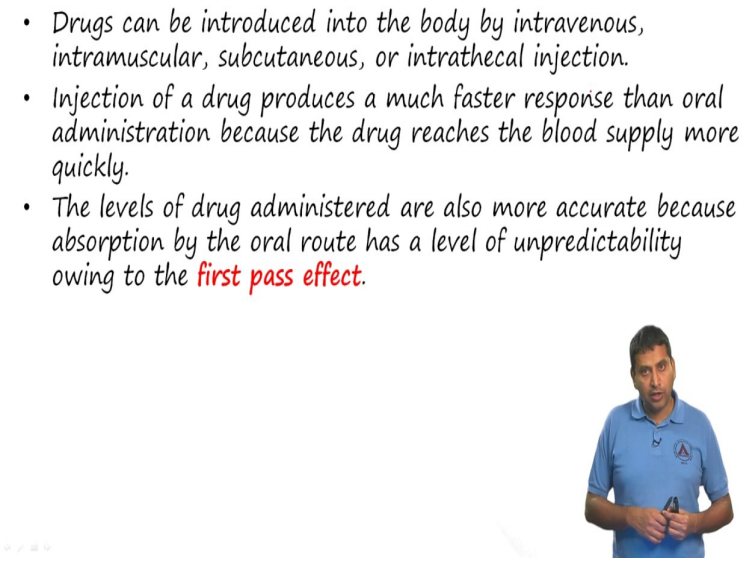

Drugs can also be introduced into the body by intravenous, intramuscular, subcutaneous, or intrathecal injections. So injection of a drug produces a much faster response than the oral administration.

So in certain cases where there is an emergency, for example that needs to be treated the injection is preferred over oral administration, right. So this, it is a huge advantage of using injections.

The levels of the drug administered are also more accurate because the absorption by oral route has a level of unpredictability. Because we just looked at the first pass effect where it is going to get into the liver and how well it is metabolized in the liver is, can vary from person to person.

So if you want immediate effect to occur, it is preferred to send it through the injection route.

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- Injecting a drug, however, is potentially more hazardous.
- For example, some patients may have an unexpected reaction to a drug and there is little that can be done to reduce the levels once the drug has been injected.
- Such side effects would be more gradual and treatable if the drug was given orally.

But there is also a problem with injection because as soon as you inject it the drug is entering into the bloodstream and so, because of that if there is an unexpected reaction to the drug, now treating that also becomes difficult.

So for example if you give this, the same drug orally and the side effect presents itself, it is going to be more gradual and perhaps treatable.

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- Injecting a drug, however, is potentially more hazardous.
- For example, some patients may have an unexpected reaction to a drug and there is little that can be done to reduce the levels once the drug has been injected.
- Such side effects would be more gradual and treatable if the drug was given orally.

But in the case of an injection, because you are giving it through directly through the blood it may be difficult to respond immediately to some drastic side effects.

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- Sterile techniques are essential when giving injections to avoid the risks of bacterial infection and is not always available in developing countries
- Risk of transmitting hepatitis or AIDS from a previous patient...
- Receiving an overdose when injecting a drug is also quite possible.

Of course there are sterile techniques that are needed and sometimes that creates a problem especially in developing countries. And this would create the risk of bacterial infection.

That is something that is always a serious problem. And you also have the problem of hepatitis or AIDS that can be transported through the needle, perhaps from a previous patient.

The other major problems with injection are receiving an overdose, because sometimes it is difficult to calculate the dose especially in certain cases, it is possible that giving an overdose through the injection is a major risk.

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- The **intravenous** route involves injecting a solution of the drug directly into a vein.
- Not particularly popular with patients, but it is a highly eff ective method of administering drugs in accurate doses and it is the fastest of the injection methods.
- As its effects are rapid, the onset of any serious side eff ects or allergies is also rapid.... the drug is given as slowly as possible.
- Intravenous drip is used...

So intravenous route involves injecting a solution of the drug directly into the vein, Ok. This is not particularly popular with patient but it is a highly effective method of administering drugs and especially in accurate doses. And of course this is one of the fastest of the injection methods.

As its effects are rapid, the onset of any serious effect or allergy is also rapid. And so the drug is typically given as slowly as possible. So you may have seen that in hospitals they use what is known as the intravenous drip and so this allows the drug to be administered at a very slow rate.

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- The **intramuscular** route involves injecting drugs directly into muscle, usually in the arm, thigh, or buttocks.
- Drugs administered in this way do not pass round the body as rapidly as they would if given by intravenous injection, but they are still absorbed faster than by oral administration.
- The rate of absorption depends on various factors, such as the diffusion of the drug, blood supply to the muscle, the solubility of the drug, and the volume of the injection.

The intramuscular route involves injecting it directly into the muscle, usually in the arm, thigh or buttocks and this way the drug does not pass around the body as rapidly as should it be through intravenous injection but they are still absorbed faster than that by oral administration.

So of course the rate of absorption depends on various factors such as the diffusion of the drug, the blood supply to the muscle, the solubility of the drug and the volume of injection, Ok.

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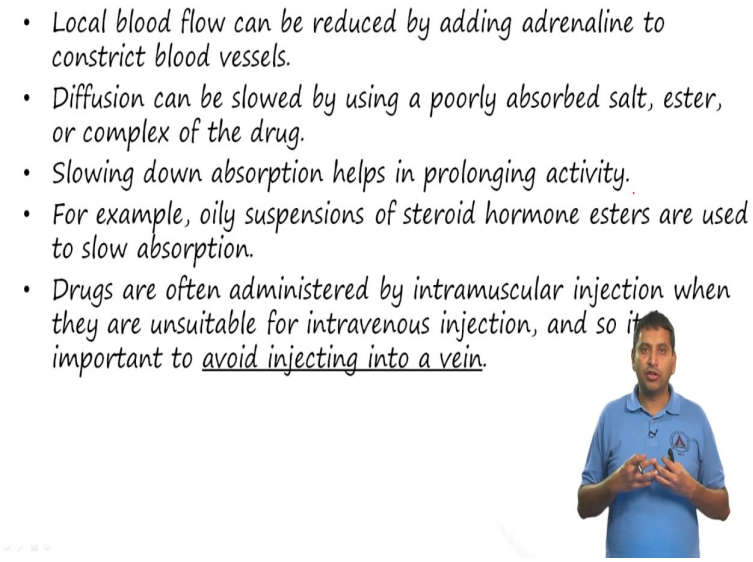

So sometimes the local blood flow can be reduced by adding adrenaline to constrict the blood vessels, Ok. So this will slow down the release of the drug into the blood supply, Ok.

So diffusion can be slowed using a poorly absorbed salt ester or complex of the drug, Ok. So what will happen is that the drug will sit there and then it has to get hydrolyzed and then it has to be absorbed and so on.

So slowing down this absorption is very useful because then you can prolong the activity, right. So it gives us the advantage of avoiding the first pass effect and also the advantage of slowing down the release of the drug.

So sometimes oily suspensions of steroid hormone esters are used to slow down absorption, Okay now drugs are often administered by intramuscular injection when they are unsuitable for intravenous injection, Okay so therefore it is very important to avoid injecting such intramuscular drugs directly into vein this can be sometimes fatal.

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- **Subcutaneous injection** involves injecting the drug under the surface of the skin.
- Absorption depends on factors such as how fast the drug diff uses, the level of blood supply to the skin, and the ability of the drug to enter the blood vessels.
- Absorption can be slowed by the same methods described for intramuscular injection.

The other way of doing an injection is through inject under the surface of the skin. This is known as subcutaneous injection. And here the absorption depends on how fast the drug diffuses and the level of blood supply and so on and of course the ability of the drug to enter the blood vessels.

Absorption can be slowed down by the same methods described for intramuscular injection. So you can just give it along with adrenaline or by as a salt or a ester.

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- **Intrathecal injection** means that the drug is injected into the spinal cord. Antibacterial agents that do not normally cross the blood–brain barrier are often administered in this way. Intrathecal injections are also used to administer methotrexate in the treatment of childhood leukaemia in order to prevent relapse in the CNS.

The last form is the intrathecal injection which is basically the injection into the spinal cord. Now it is very frequently used in situations where you have a bacterial infection in the brain

and administering an antibacterial drug is not very useful because it does not cross the blood brain barrier.

So you give this intrathecal injection so that you can avoid crossing the blood brain barrier. Intrathecal injection is also used for administering this anti-cancer drug

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methotrexate for the treatment of childhood leukaemia and in order to prevent relapse in the central nervous system.

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- Intraperitoneal injection involves injecting drugs directly into the abdominal cavity.
- This is very rarely used in medicine, but it is a method of injecting drugs into animals during preclinical tests.

Intraperitonial injection involves injecting directly into the abdominal cavity and this is very rarely used in the medicine but it is very commonly used in animals

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