Medicinal Chemistry
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Lecture No. 34
Drug Metabolism Part I

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Welcome back. In today's lecture we are going to look at drug metabolism. So this aspect of, of medicinal chemistry is very important and because we will, we will very soon see that even after we discover a drug and develop it there are number of things that can actually go wrong in, during metabolism that can make a drug ineffective.

It is also possible that a drug which is very effective in certain animal models may completely fail in humans because the metabolism is very different in animals versus humans.

So therefore understanding drug metabolism is a very important component of modern drug discovery. And if we have a good understanding of it and if we can build good models, then it is quite possible that we may be able to avoid certain problems that commonly people face during advanced stages of drug discovery, Ok.

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- Pharmacodynamics is the study of how drugs interact with a molecular target to produce a pharmacological effect, whereas pharmacokinetics is the study of how a drug reaches its target in the body and how it is affected on that journey.
- The four main issues in pharmacokinetics are: absorption, distribution, metabolism, and excretion.

So just to sort of, recap we have looked at what pharmacodynamics is. Pharmacodynamics is nothing but the study of how drugs interact with a molecular target, Ok. So for example we have looked at, on the cell surface there is a receptor, Ok so and to this receptor your drug is going to come and interact.

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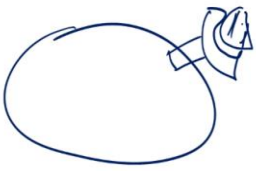
- The four main issues in pharmacokinetics are: absorption, distribution, metabolism, and excretion.



So how this drug interacts with the receptor to produce the desired signal

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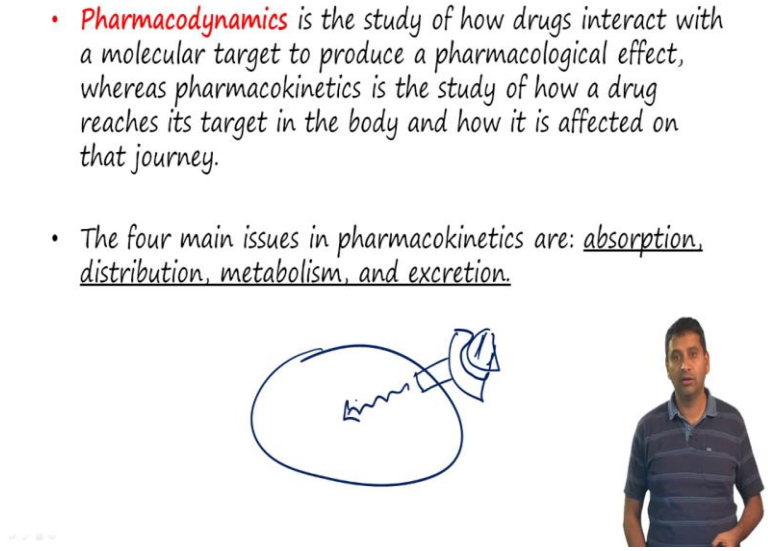

or to inhibit

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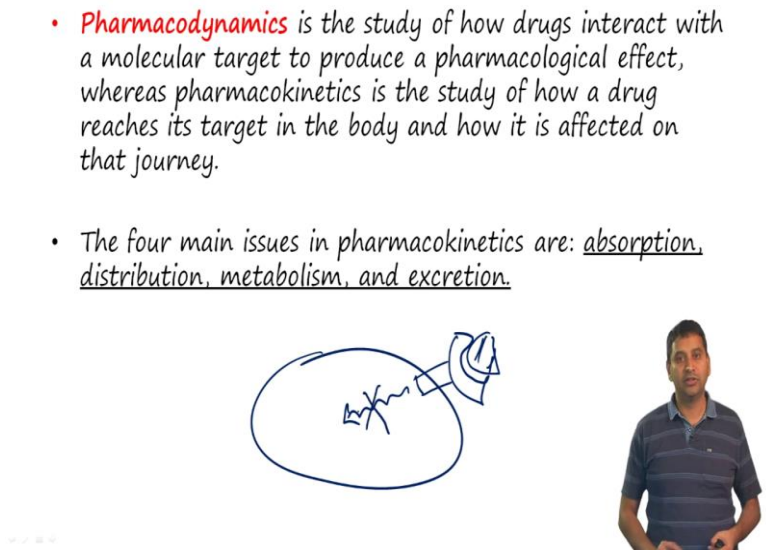

the signal is something that pharmacodynamics deals with, Ok. While pharmacokinetics is another field on its own,

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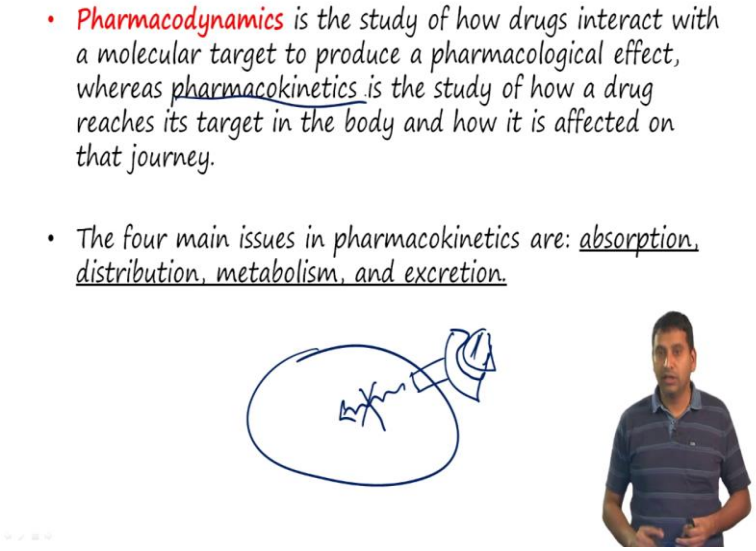

is the study of how a drug reaches its target in the body, Ok.

So as you can very well imagine that, you know just taking a drug orally, does not ensure that it gets into where we wanted to go and where we wanted to hit. So pharmacokinetics is the, is the detailed study of how this happens, Ok and whether the drug reaches the target in the body and how much of the drug reaches the body and so on, right.

So the main issues in pharmacokinetics that we are going to deal with. There are four of them. The first one is absorption. The second one is distribution. The third one is metabolism and the fourth one is excretion, Ok.

So this is also called as ADME,

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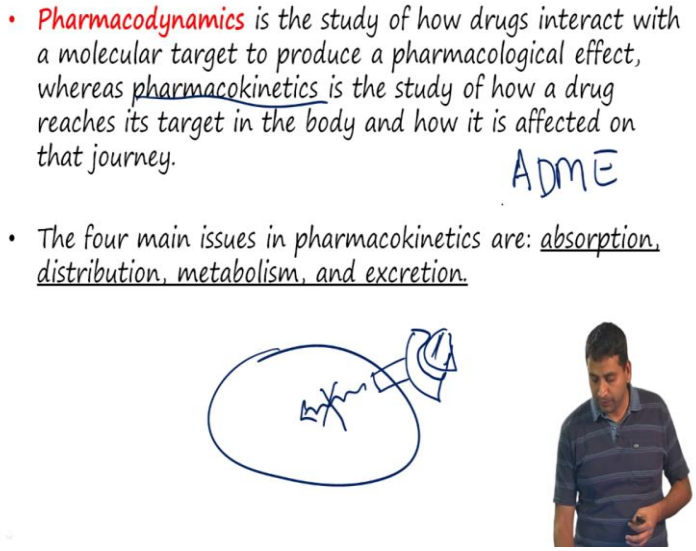

Ok. So ADME is a very important component of trying to understand how a drug or a drug like molecule functions after advanced stages of drug discovery,

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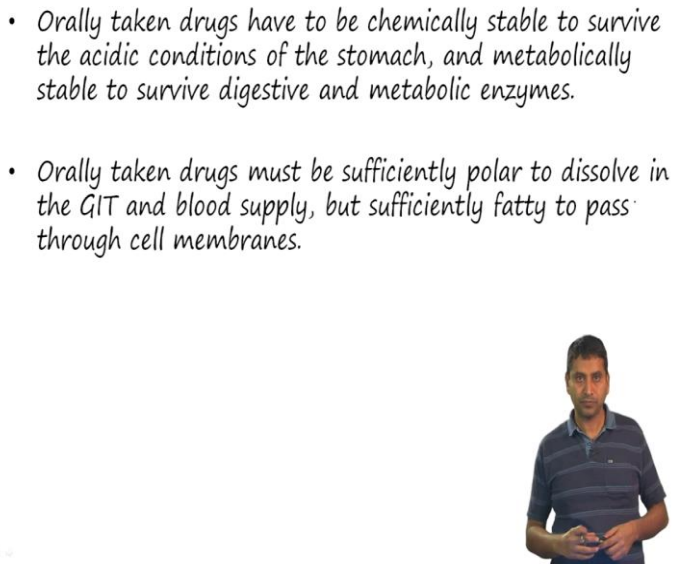

Ok.

So orally taken drugs, for example we have looked at in the previous lecture that orally taken drugs have to be extremely stable, right to survive the acidic conditions in the stomach and also quite stable to survive the digestive and metabolic enzymes.

So we have already looked at the various

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- Orally taken drugs have to be chemically stable to survive the acidic conditions of the stomach, and metabolically stable to survive digestive and metabolic enzymes.
- Orally taken drugs must be sufficiently polar to dissolve in the GIT and blood supply, but sufficiently fatty to pass through cell membranes.

conditions that the orally active or orally taken drugs are going to be encountering, Ok.

They should be sufficiently polar, so that they can dissolve in the gastrointestinal tract and get into the blood supply but they should also be sufficiently have enough lipids or sufficiently fatty to be able to pass through membranes. So both these criteria we have looked at the in the previous lecture.

So, at the end of it, it is for the drug to be orally active, it requires a lots of, it requires a number of parameters that need to be successful for it to be efficiently absorbed,

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- Most orally taken drugs obey Lipinski's rule of five...
- Highly polar drugs can be orally active if they are small enough to pass between the cells of the gut wall, are recognized by carrier proteins, or are taken across the gut wall by pinocytosis.

Ok.

So we also looked at that most orally drug, taken drugs follow the Rule of Five which was coined by Lipinski and highly polar drugs can be orally active if they are small enough to pass through the cells of the gut wall which are, and recognized by carrier proteins.

We have already seen the example of how this carrier protein can bind to the

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drug and take it across the gut wall.

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- Most orally taken drugs obey Lipinski's rule of five...
- Highly polar drugs can be orally active if they are small enough to pass between the cells of the gut wall, are recognized by carrier proteins, or are taken across the gut wall by pinocytosis.

Or it can also go through by pinocytosis. We have already looked

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- Most orally taken drugs obey Lipinski's rule of five...
- Highly polar drugs can be orally active if they are small enough to pass between the cells of the gut wall, are recognized by carrier proteins, or are taken across the gut wall by pinocytosis.

at the mechanism of pinocytosis wherein there is an invagination that occurs. There is an encapsulation and then it is passed through the gut wall. So these are the mechanisms by which highly polar drugs can be absorbed.

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- Distribution around the blood supply is rapid. Distribution to the interstitial fluid surrounding tissues and organs is rapid if the drug is not bound to plasma proteins.
- Some drugs have to enter cells in order to reach their target. A certain percentage of a drug may be absorbed into fatty tissue and/or bound to macromolecules. Drugs entering the CNS have to cross the blood–brain barrier.

And we also saw that distribution of the drug is quite rapid because rate of blood supply is very, very high. So within a few minutes after entering the blood, the drug is going to distribute itself across the body.

But the distribution is not even because there are certain areas where the drug would preferentially distribute to over other areas, Ok and another important component of it is whether the drug is

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bound to plasma proteins.

So we have already seen that plasma proteins can bind to a drug and this binding interaction can be, can be very strong sometimes and what happens is that a lot of drug is actually trapped in the plasma protein.

So we have also looked at a case where when you take another drug, this drug that is bound to this plasma protein actually dissociates. And, so one needs to keep this in mind while thinking about distribution.

Then some drugs we have already looked at have to enter the cell in order to reach the target. So the examples that we looked at are enzyme inhibitors. So if we design a drug

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ENZYME INHIBITORS

as an enzyme inhibitor then the drug has to enter the cell,

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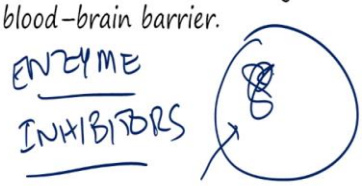

meet the enzyme of interest and then inhibit, inhibit its activity,

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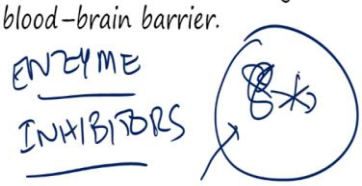

right, so for which this drug has to enter

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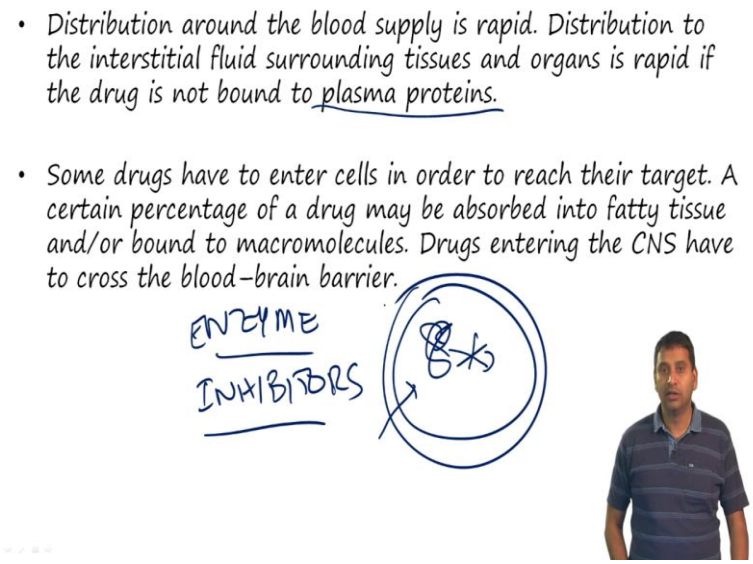

the target cell.

So therefore we have to keep this in mind when we are looking at how we are going to design the drug and whether it is going to reach the target and so on, right. So in order for the drug to cross the barrier, the cell membrane the drug has to have some level of lipophilicity and that is very crucial for it to enter the cell, right.

Now a certain percentage of the drug may also be absorbed into the fatty tissue that we looked at certain examples of that when you have, you know very lipophilic drugs it is possible that they are going to dissolve in the fatty tissue.

And we also looked at how the blood brain barrier forms a very, you know, very interesting situation where not all drugs are going to enter the, or going to be able to cross the blood brain barrier. So therefore if we are designing a drug that is going to hit the brain then we need to keep in mind that this, this molecule has to get across the blood brain barrier.

Or on the contrary, if you want a drug not to enter the brain then we need to be able to figure out the right structural parameters wherein it does not cross the blood brain barrier,

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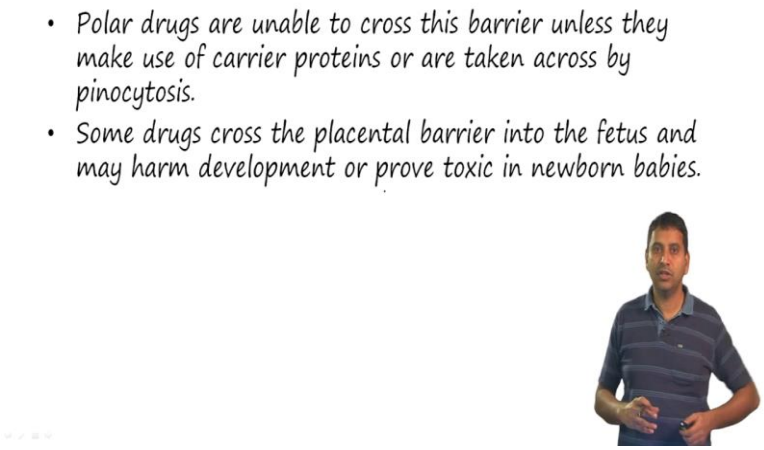

Ok.

So we have already seen that polar drugs are unable to cross the barrier unless they make use of carrier proteins or taken across by pinocytosis. And there is another interesting barrier which is called the placental barrier which is applicable to, to expecting mothers and so this placental barrier sort of protects the fetus from many harmful chemicals but the drugs can cross this placental barrier

And sometimes what happens is that this drug is, remains even after birth and it can prove toxic to new-born babies,

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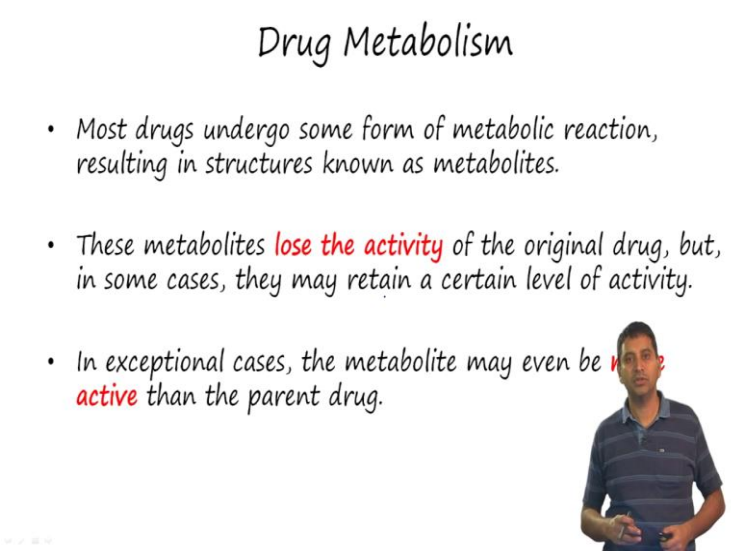

Ok. So with this background let us now look at drug metabolism. So most drugs undergo some form of metabolism inside the body, Ok. And these resulting structures are known as

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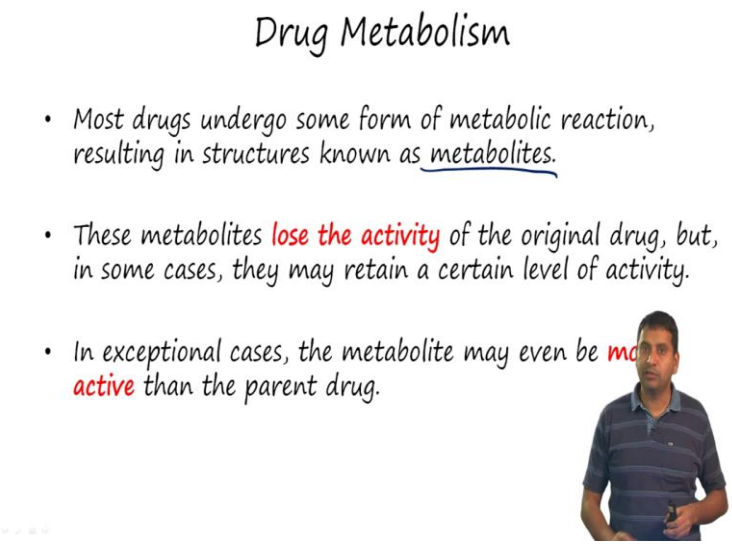

metabolites, right.

So these metabolites sometimes lose the activity of the original drug. So if the original drug, for example was designed to interact with the receptor surface, let us say there is a carboxylate on this surface

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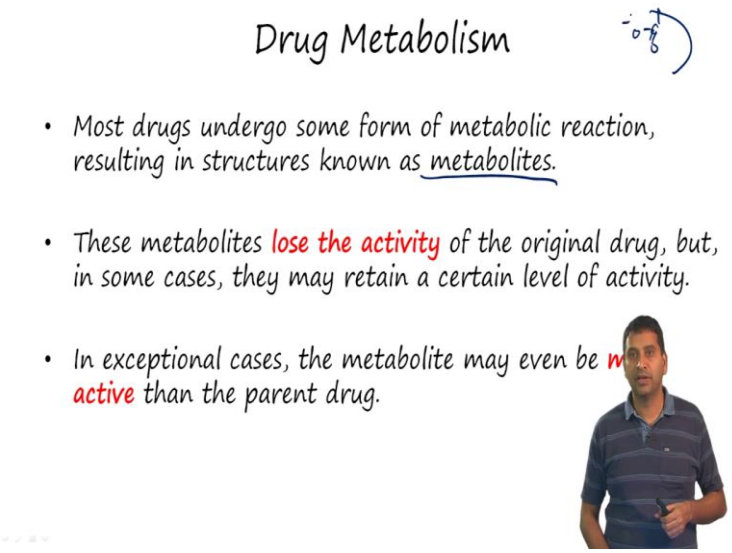

and if this, if the original drug was designed to have NH_3 plus,

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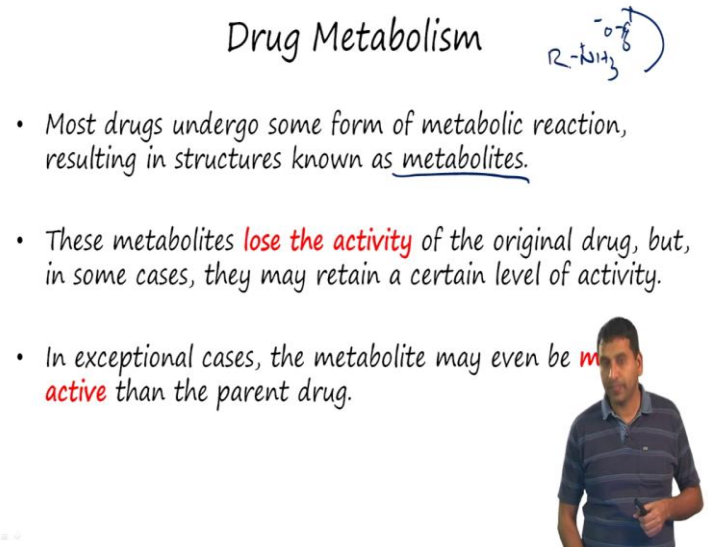

now if this NH_3 plus is actually metabolized to, let us say it gets oxidized to NO_2

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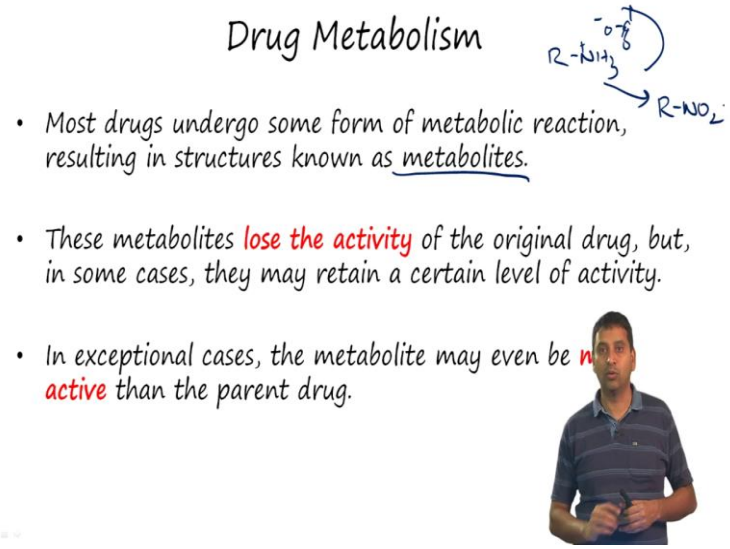

then that interaction is completely lost, Ok.

But it is also possible that some of these metabolites will retain some level of activity. So if the functional group change is not that drastic then it is possible that some of the activity can be retained. In some exceptional cases the metabolite may even be more active than the parent drug, Ok.

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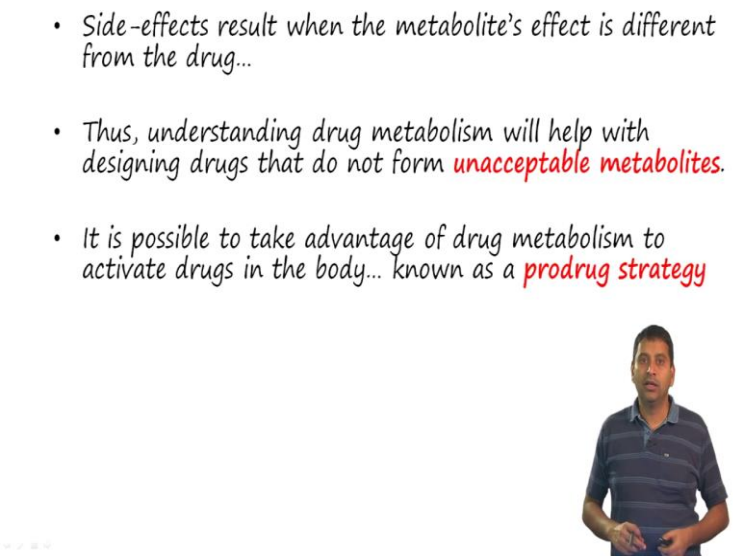

Now the reason why this metabolism is very important, one of the reasons is that a lot of side effects are actually associated with the metabolites and not actually with the drug.

So when the drug is tested through rigorous testing mechanism it is usually on a model system. And in the model system the actual drug may not be very toxic. But, or even in an animal system it may not be very toxic because the metabolism in animals is quite different sometimes from the metabolism in humans.

And so therefore once the drug is now administered to humans it is possible that certain side effects will result which are going to be deleterious.

So understanding drug metabolism will help with designing drugs that do not form unacceptable metabolites. So it is also possible to take advantage of drug metabolism to activate the drug in the body. So this strategy is known as the

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- Side-effects result when the metabolite's effect is different from the drug...
- Thus, understanding drug metabolism will help with designing drugs that do not form unacceptable metabolites.
- It is possible to take advantage of drug metabolism to activate drugs in the body... known as a prodrug strategy

prodrug strategy. We look at this in detail towards the later part of the course.

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Phase I and phase II metabolism

- The body treats drugs as foreign substances and has methods of getting rid of such chemical invaders.
- If the drug is polar, it will be quickly excreted by the kidneys...
- However, non-polar drugs are not easily excreted and the purpose of drug metabolism is to convert such compounds into more polar molecules that can be easily excreted.

So metabolism is divided into 2 parts. It is called phase I metabolism and phase II metabolism. So we look at both of these in some detail in this lecture. So as we can see, the body treats drugs as foreign substances because all, invariably all drugs are going to be, you know new to the, to the body and so it is going to treat it as the foreign substance.

Now in order to protect ourselves, our bodies have developed mechanisms to get rid of these foreign substances. So these are considered as chemical invaders

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and so the, sort of the, the metabolism takes care of these chemical invaders. Now the drug is very polar, Ok.

It is, let us say it is water soluble then it is quickly excreted by the

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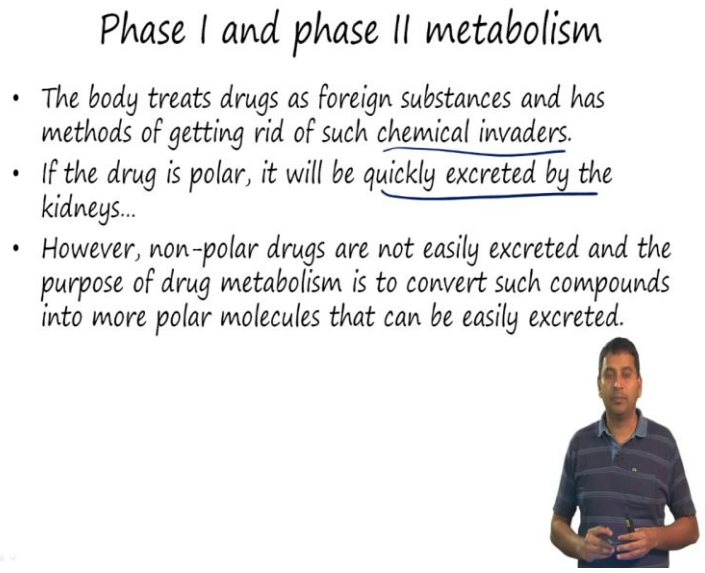

kidney. So that is one of the things that happens. So one of the mechanisms by which the drug is excreted is through the kidney if it is highly polar. But if it is not then it is not easily excreted through the kidney and it is here that drug metabolism occurs where the fundamental reactions that happen, invariably increase the polarity of the drug, Ok.

So the compound that is present inside

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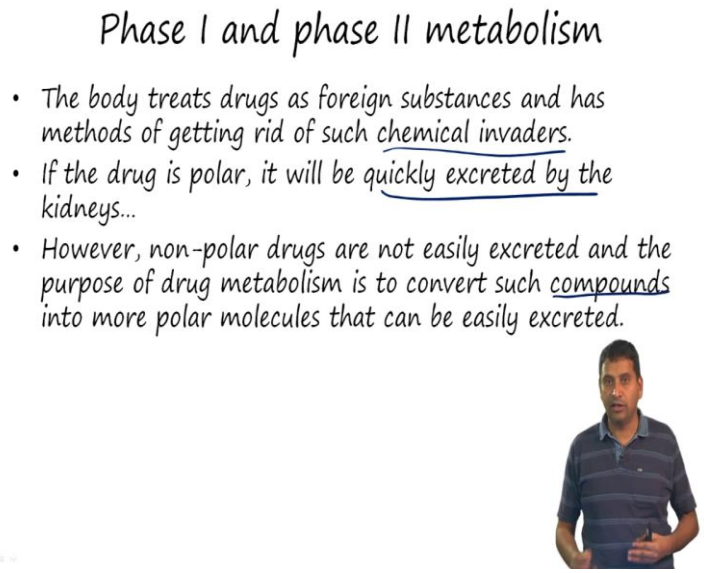

our body is made into

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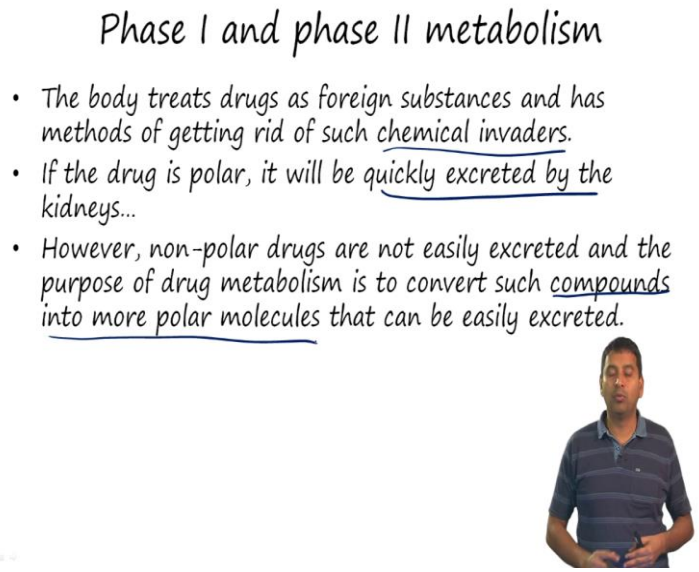

more polar molecules so that they can be easily excreted.

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- Non-specific enzymes (particularly cytochrome P450 enzymes in the liver) are able to add polar functional groups to a wide variety of drugs.
- Once the polar functional group has been added, the overall drug is more polar and water soluble, and is more likely to be excreted when it passes through the kidneys.

$$\text{Drug}-H + O_2 + NADPH + H^+ \xrightarrow{\text{Cytochrome P450 enzymes}} \text{Drug}-OH + NADP + H_2O$$

So one of the largest class of enzymes that do this are a very non-specific enzyme which is called as Cytochrome P450, and they are present in the liver, Ok. So one of the ways in which they act is to add a polar functional group. We shall look at it

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$$\text{Drug}-H + O_2 + NADPH + H^+ \xrightarrow{\text{Cytochrome P450 enzymes}} \text{Drug}-OH + NADP + H_2O$$

very shortly on a wide variety of drugs, Ok.

So then as we just saw that once you make the molecule more polar, it is then made water-soluble and it is excreted through the kidney. So now let us look at the reaction that Cytochrome P450 catalyses. So you have a drug, let us say with a hydrogen molecule and in the presence of oxygen NADPH which is a cofactor which we looked at earlier and you need a source of proton.

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$$Drug{-}H + O_2 + NADPH + H^+ \xrightarrow{\text{Cytochrome P450 enzymes}} Drug{-}OH + NADP + H_2O$$

So P450 acts

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$$Drug{-}H + O_2 + NADPH + H^+ \xrightarrow{\text{Cytochrome P450 enzymes}} Drug{-}OH + NADP + H_2O$$

on this and converts this to drug OH and the byproducts are NADP and water,

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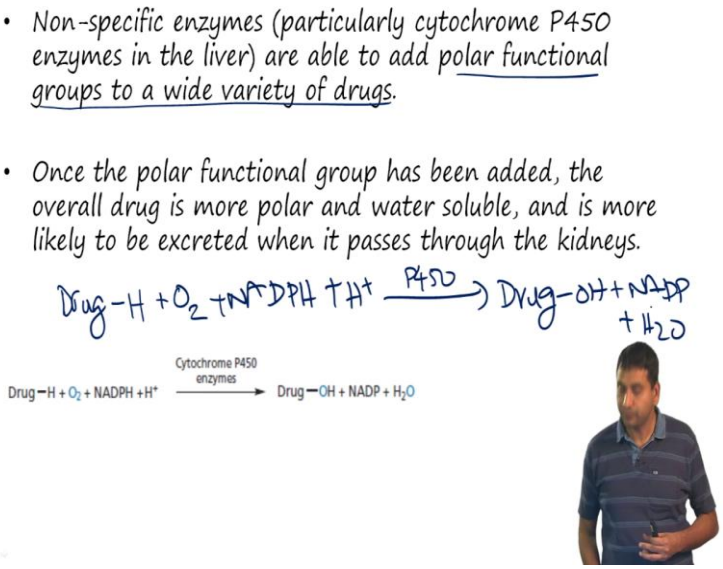

Ok. So in the process the drug has now been converted from, let us say an alkane to alcohol. So this improves the polarity substantially or increases the polarity substantially and helps our system to get rid of it through the kidneys.

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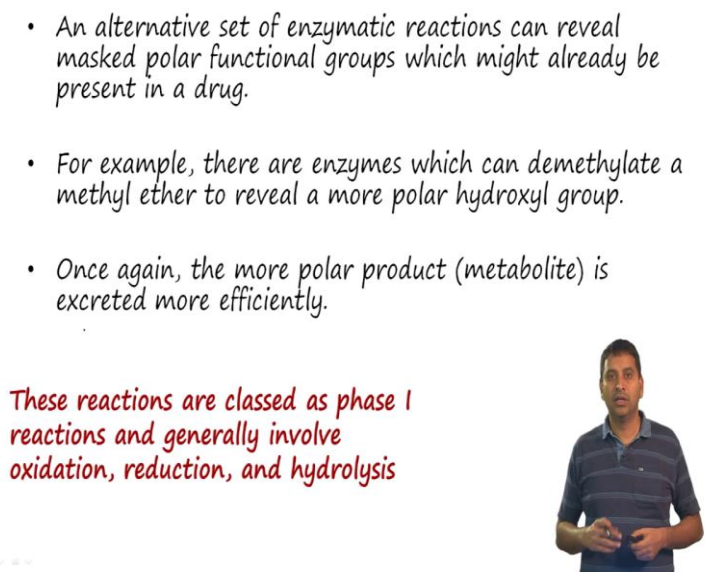

So an alternative set of enzyme reactions can also reveal masked polar groups, Ok. So let us say there is a molecule which has a ester in it, right. So now if you do a demethylation

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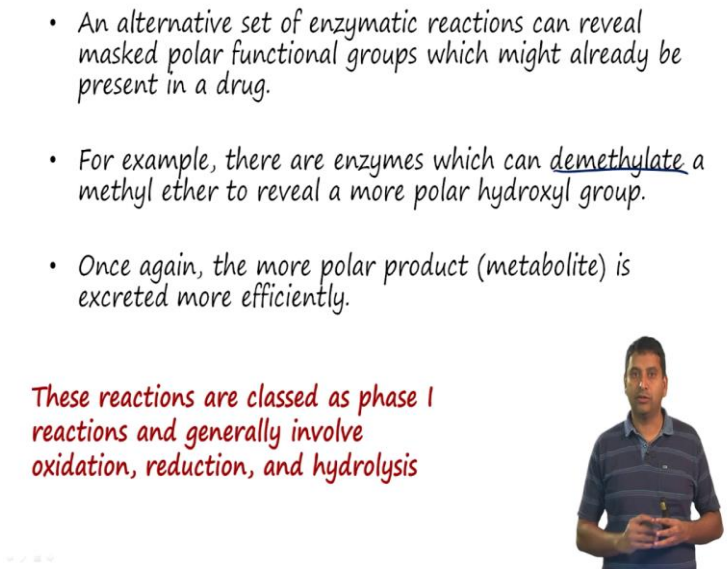

of the ester then the ester is going to get converted to a carboxylic acid.

So the reaction that we are looking at is RCOOMe getting converted to RCOOH.

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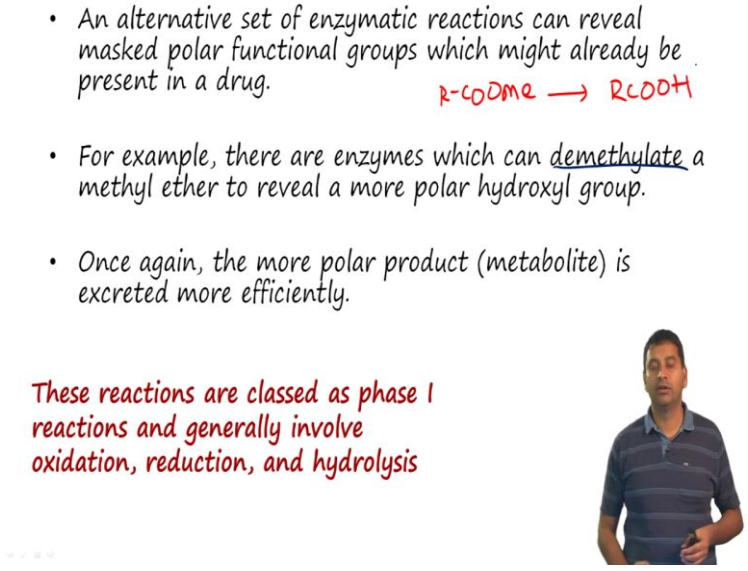

So this kind of a transformation is going to make the molecule more water soluble, Ok. And again once you make it more polar then it is excreted more efficiently.

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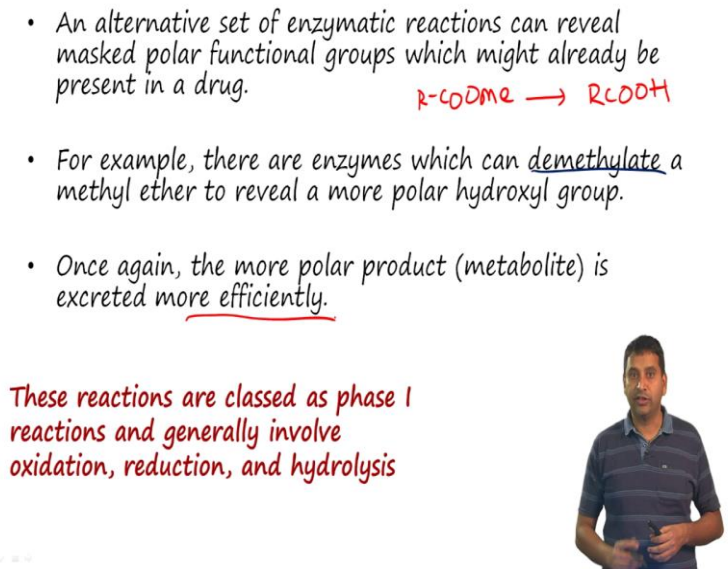

So these reactions are classed into one phase of reactions and they are called phase I reactions. And they generally involve oxidation, reduction and hydrolysis.

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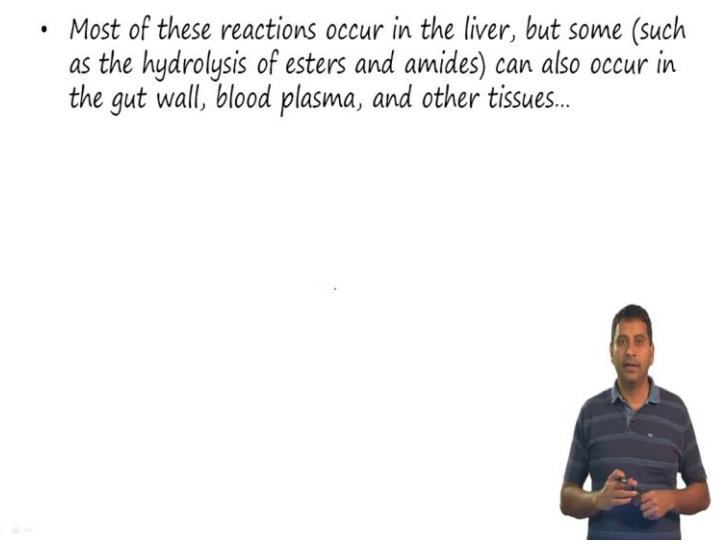

So most of these reactions occur in the liver but some processes such as ester hydrolysis or amide hydrolysis can also occur in the gut wall or in the blood plasma and other tissues.

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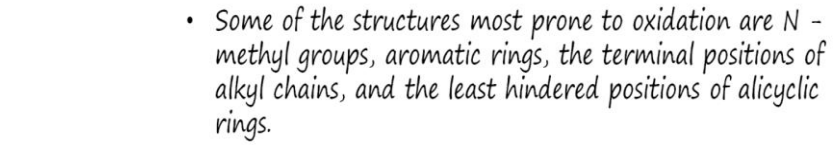

Now some of the structures in drugs are most prone to oxidation and these structures are N-methyl groups, Ok so basically you have NCH_3, Ok aromatic rings let us say, you have a benzene

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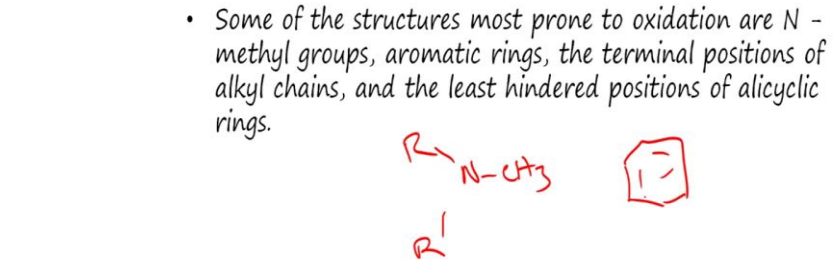

ring, Ok and terminal positions of alkyl chains.

So let us say you have a long alkyl chain and you have a CH_3 in the end, then this position

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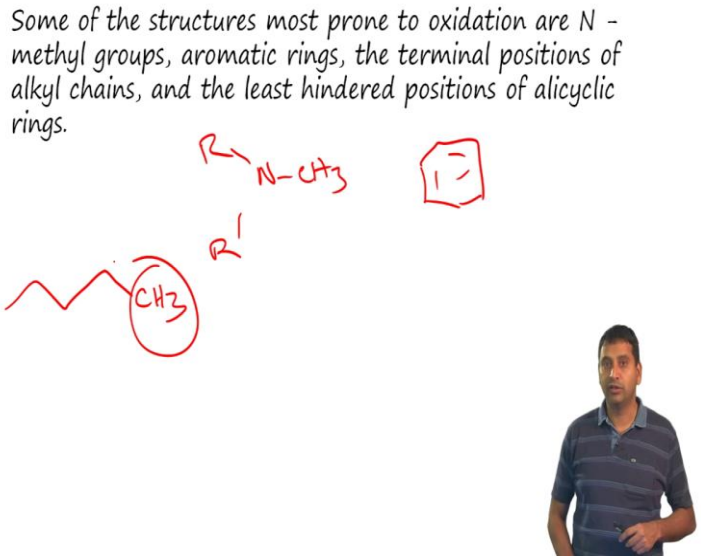

is more susceptible to oxidation compared to the internal position. So these are three examples of three functional groups that are pretty much more susceptible to oxidation.

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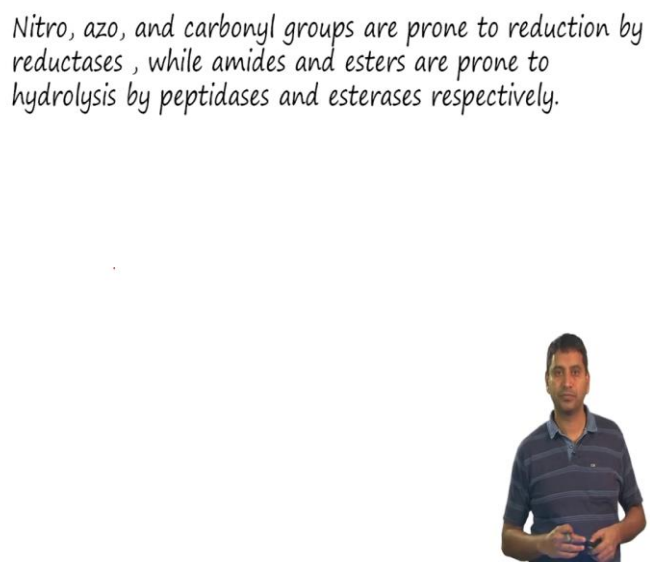

Other groups such as nitro group which is basically N double bond O O minus, nitro group,

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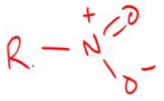
- Nitro, azo, and carbonyl groups are prone to reduction by reductases , while amides and esters are prone to hydrolysis by peptidases and esterases respectively.



the azo group, azo group is N double bond N,

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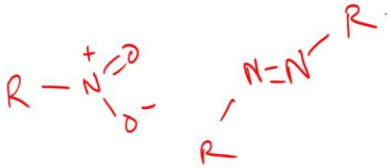
- Nitro, azo, and carbonyl groups are prone to reduction by reductases , while amides and esters are prone to hydrolysis by peptidases and esterases respectively.



right and carbonyls which is C double bond O, these are more prone

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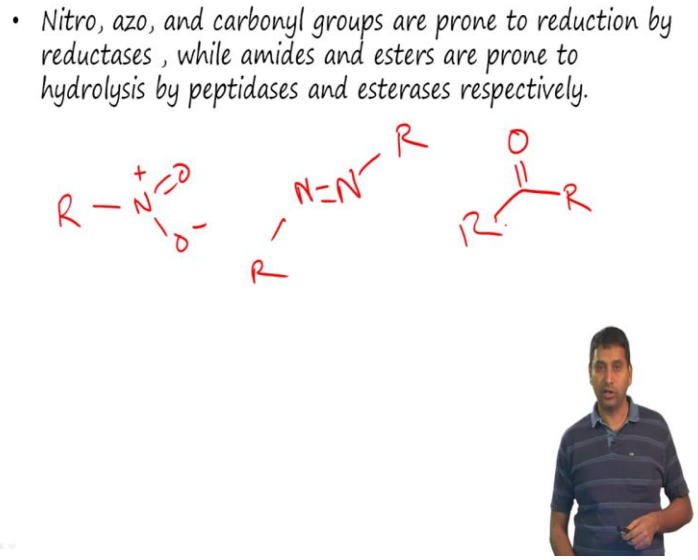

to reduction, Ok.

So when the nitro group undergoes reduction it is going to form RNHOH which in turn is going to get convert to RNH_2

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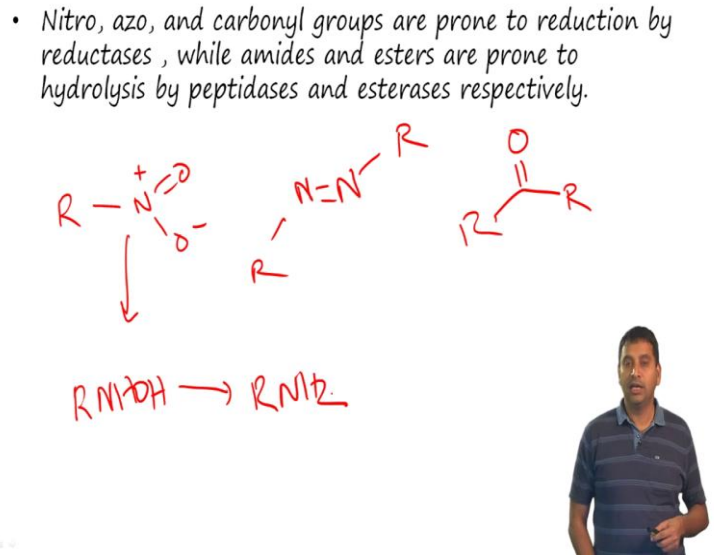

and this can break down eventually by reduction to form RNH_2 and

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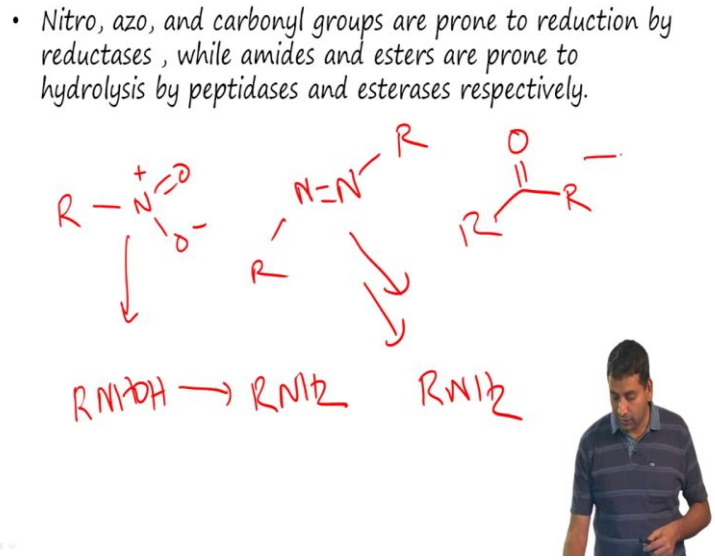

a ketone can get converted to R

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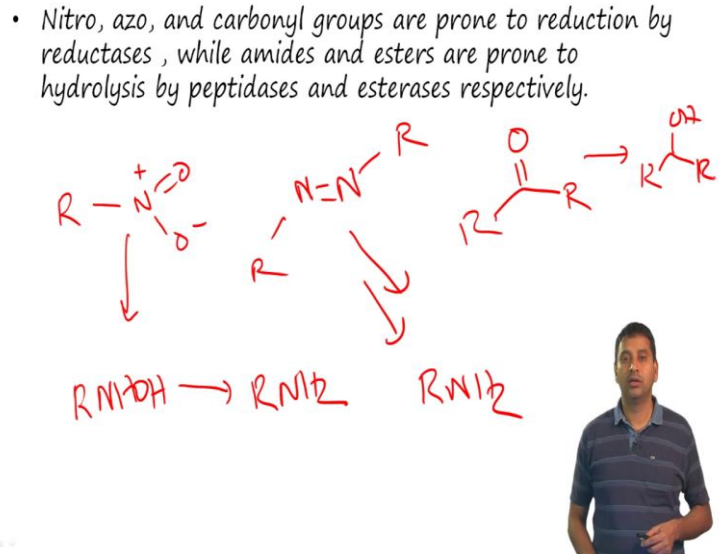

and alcohol, Ok. So these are some of the reactions that can occur and of course amides and esters as we discussed earlier are susceptible to hydrolysis

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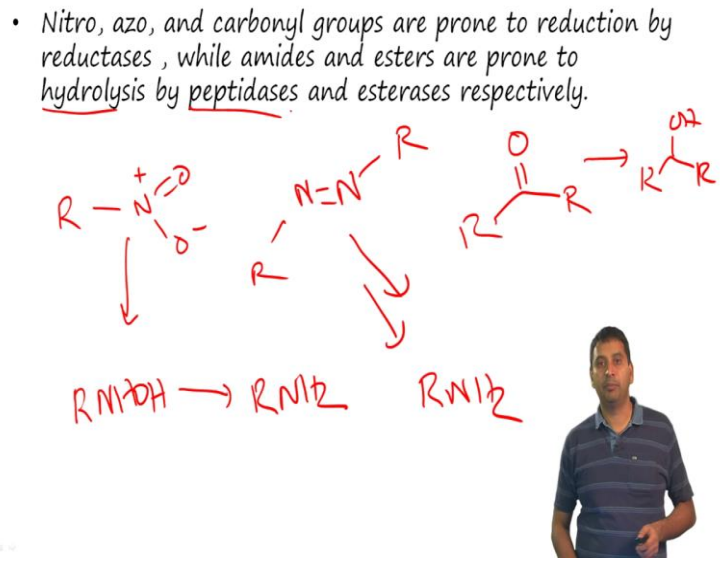

by peptidases and esterases.

So we have looked at this, these cases previously in detail so I am not going to repeat this.

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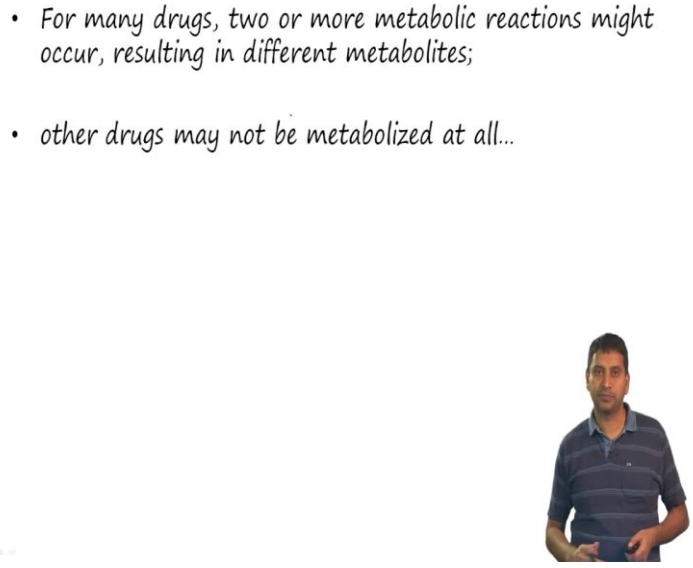

For many drugs it is also possible that two or more metabolic reactions might occur. So you can have ester hydrolysis followed by oxidation of a different functional group or you can have amide bond cleavage followed by reduction and so on and so forth, Ok.

And of course there are also drugs which may not

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- For many drugs, two or more metabolic reactions might occur, resulting in different metabolites;
- other drugs may not be metabolized at all...

be metabolized at all. So you have certain times functional groups which do not really react with some of the enzymes and so they may not get metabolized at all.

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- Knowledge of the metabolic reactions that are possible for different functional groups allows the medicinal chemist to predict the likely metabolic products for any given drug, but only drug metabolism studies will establish whether these metabolites are really formed.

So knowledge of the metabolic reactions that are possible for different functional groups allows us as medicinal chemists to be able to predict the likely metabolic product.

So for example, if I have a nitro group in my drug then I can somewhat predict that it is going to undergo reduction. Or if I have a ketone then I can also suggest that it might get reduced to the alcohol, right. So therefore it is very important that we recognize this and understand how these processes occur.

But this predictive value is also not that great and it is possible that some of the metabolism that we may predict may not occur. So only way to find this out is actually to do drug metabolism studies which will establish whether these metabolites are really formed or not,

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- Drug metabolism has important implications when it comes to using chiral drugs, especially if the drug is to be used as a racemate.
- The enzymes involved in catalysing metabolic reactions will often distinguish between the two enantiomers of a chiral drug, such that one enantiomer undergoes different metabolic reactions from the other.

Ok.

Drug metabolism is also very important when you are looking at chiral drugs, Ok. We have spent quite a bit of time with examples on, on what chiral drugs are and how they can differentially interact with receptors.

So for example a chiral molecule may interact with a receptor site in a particular way and the, the opposite enantiomer may interact with it in a very different way and so therefore one needs to be able to understand how this chiral drug interacts.

It is also possible that this chiral drug, this molecule with a chiral center is actually used as a racemate, right. So now if we use a molecule as a racemate then we need to be able to

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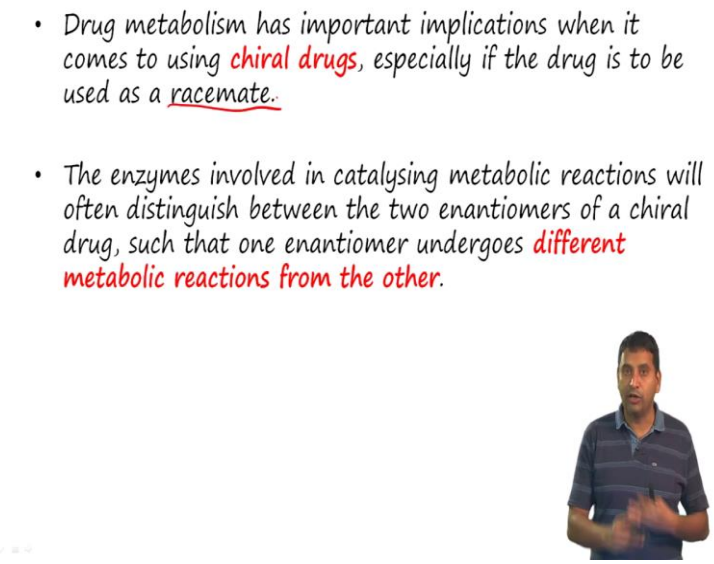

individually test each of the enantiomers and it is also possible that a chiral drug may racemize in the body. So the, the presence of the chiral center creates certain issues that we need to deal with in detail in drug metabolism.

So the enzymes involved in catalyzing metabolic reactions will also distinguish between these two enantiomers, right. So it is possible that one enantiomer interacts in a way that is very different from the other enantiomer and not just that, it may give you completely different metabolites as well, Ok.

So when we are dealing with chiral centers one needs to be sensitive to this situation and work accordingly,

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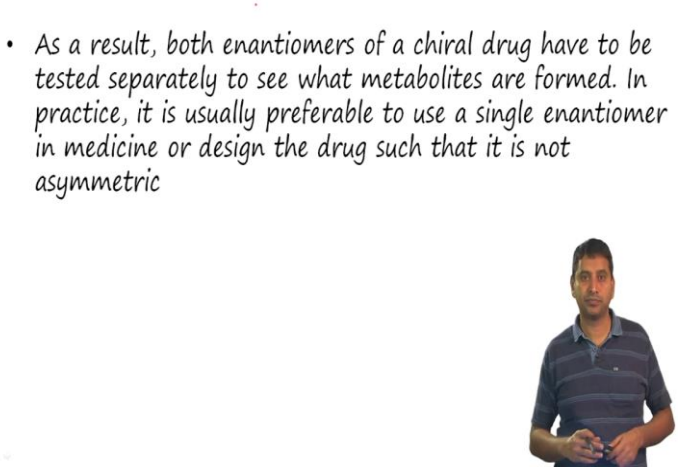

Ok. So what we need to do is we would take both enantiomers of the chiral drug and they have to be tested separately and to see what metabolites are formed, Ok.

Now in practice it is usually preferable to have a single enantiomer, right, so that is the role of

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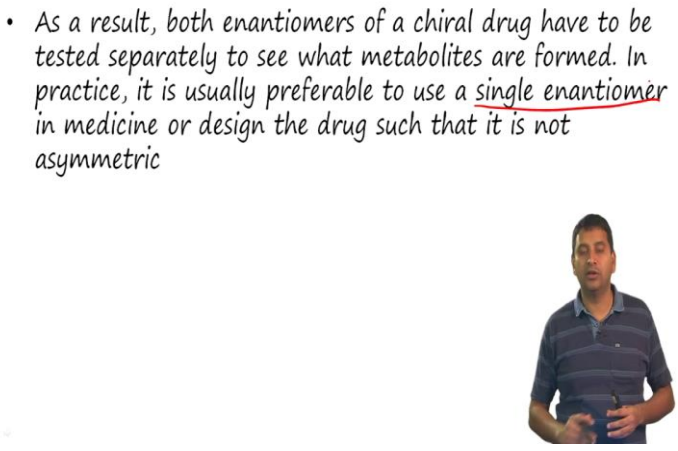

asymmetric synthesis, or even better is to design a drug that is not, that does not have an asymmetric center. Because, if we do have an asymmetric center then you are going to have these kinds of issues.

And so you can develop compounds which do not have an asymmetric center. That means you will make a compound which does not have a chiral center.

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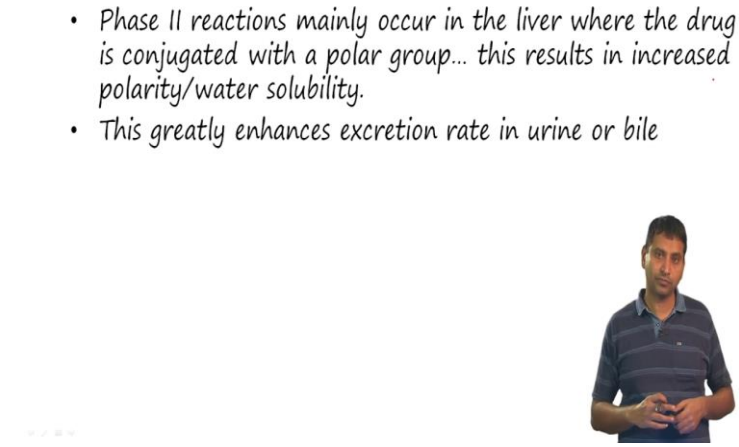

Phase II reactions mainly occur in the liver where the drug is actually conjugated with the polar group.

So the difference between a phase 1 and phase II process is that the phase II, you will have something coming and adding to the drug and making the entire molecule more polar, Ok.

So this results in increased polarity or water solubility, Ok. And again the same concepts apply as in phase I. And you would increase the excretion rate

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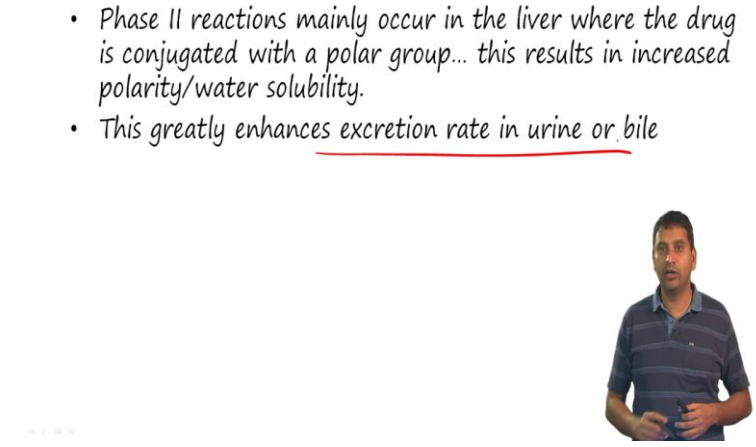

in urine or in bile, Ok. So as you might have figured out both phase I and phase II have very similar goals that is to convert the less polar molecule to a more polar molecule,

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- Both phase I and phase II reactions can be species specific, which has implications for in vivo metabolic studies.
- The metabolites formed in an experimental animal model may not necessarily be those formed in humans.

Ok.

Now phase I and phase II reactions can be quite species specific. That is something that undergoes metabolism in a particular way in a mouse model may be different from a primate model and in the primate model may, may actually be different from humans.

So experimental animal models are important but sometimes they are quite different from what actually happens in humans, right. And this has also led to certain opportunities because sometimes when a particular drug does not work in an animal model, we would still take it up to the next level because it is possible that the drug may actually work in humans,

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- Metabolic enzymes in different organisms can **distinguish** between identical functional groups or alkyl groups located at different parts of the molecule (regioselectivity), as well as between different stereoisomers of chiral molecules (stereoselectivity).

right.

So metabolic enzymes in different organisms can actually distinguish between identical functional groups or alkyl groups located at different parts of the molecule. So this is the concept of regioselectivity.

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- Metabolic enzymes in different organisms can **distinguish** between identical functional groups or alkyl groups located at different parts of the molecule (regioselectivity), as well as between different stereoisomers of chiral molecules (stereoselectivity).

So you can have a metabolic enzyme which is regioselective to a particular area of the molecule while the other metabolic enzyme can be regioselective in the other region, right.

But of course you can also have the stereoselectivity

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- Metabolic enzymes in different organisms can **distinguish** between identical functional groups or alkyl groups located at different parts of the molecule (regioselectivity), as well as between different stereoisomers of chiral molecules (stereoselectivity).

where you have different stereoisomers inside the, in the same molecule or a single stereoisomer where one metabolic enzyme recognizes one stereocenter while the other one does the other way in other case.