Medicinal Chemistry
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Lecture 37
Drug Metabolism – Part IV

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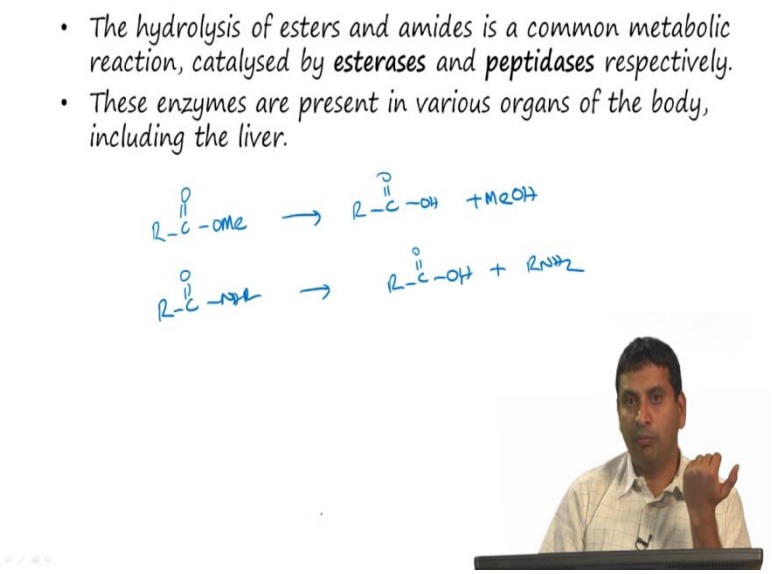

Another thing which we can expect to happen is if you are dealing with an ester or an amide that they can undergo hydrolysis by esterases or peptidases to produce the corresponding carboxylic acid. So you have R - C double bond O, let us say we have a methyl ester that is going to cleave and form a carboxylic acid and methanol okay. You can also have R - C double bond O - NHR which can be cleaved by peptidases to form R - C double bond OOH the carboxylic acid and an amine okay. So of course these enzymes are present in various organs in nearly all cells so therefore this is may not be restricted only to the liver okay.

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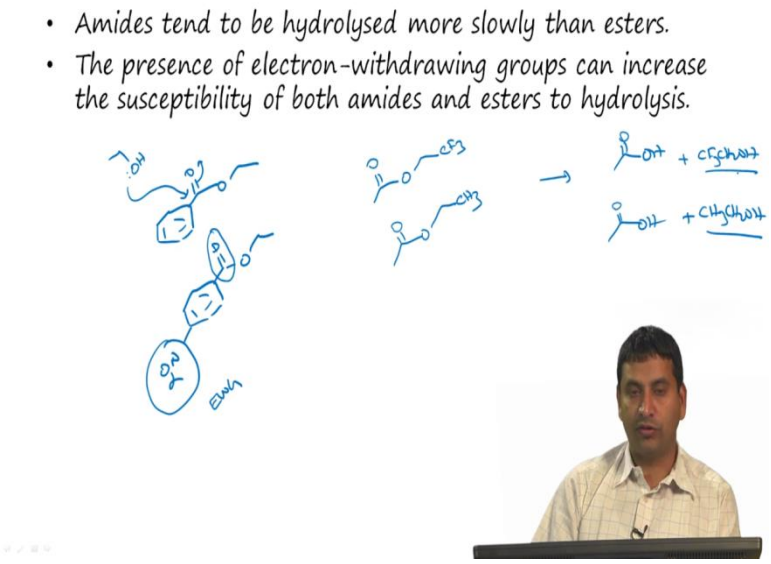

Now we all know that amides are tend to be hydrolyzed much slower compared to esters and typically the presence of electron-withdrawing group so for example, if we have an ester of benzoic acid versus an ester of *para*-nitro benzoic acid, the one with the electron withdrawing group is more susceptible to hydrolysis. This can be explained because you have usually a serine residue which is going to attack here. It is a nucleophilic addition reaction and so nucleophilic addition reaction the carbonyl which has an electron withdrawing group on it is more susceptible to attack because it has a greater concentration of partial positive charge that is given to it the electron withdrawing group, so one can imagine that this reaction is going to be faster.

On the other hand, you can also have an ester which has let us say a CF_3 group on it versus an ester which has CH_3. So between these two, the product of this reaction is C double bond OOH + CF_3CH_2OH and CH_3CH_2OH, so the stability of or the leaving group ability of this trifluoro-ethanol is much better than the leaving group ability of ethanol so these are more susceptible to hydrolysis.

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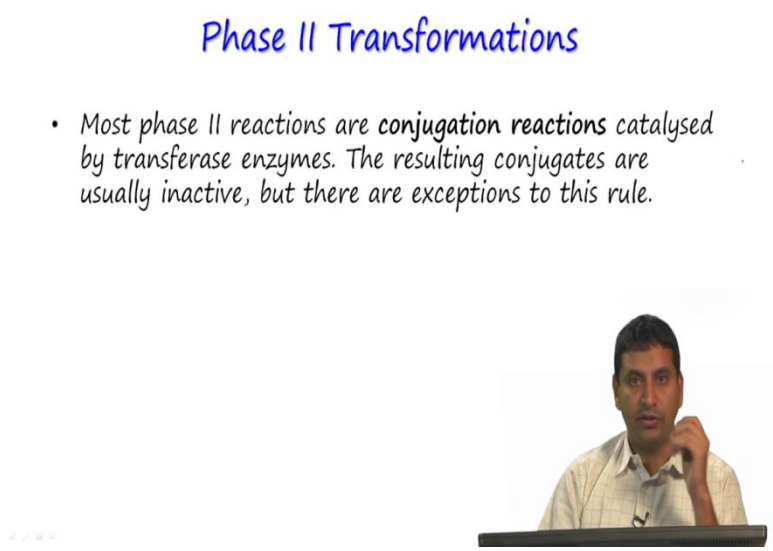

Now let us talk about some phase 2 transformations. Phase 2 transformations are basically conjugation reactions which means that you have 2 molecules which are going to react with each other and form a bio-conjugate and these are catalyzed by enzymes known as transferase okay. The resulting conjugates are usually inactive at of course there are exceptions to this rule okay.

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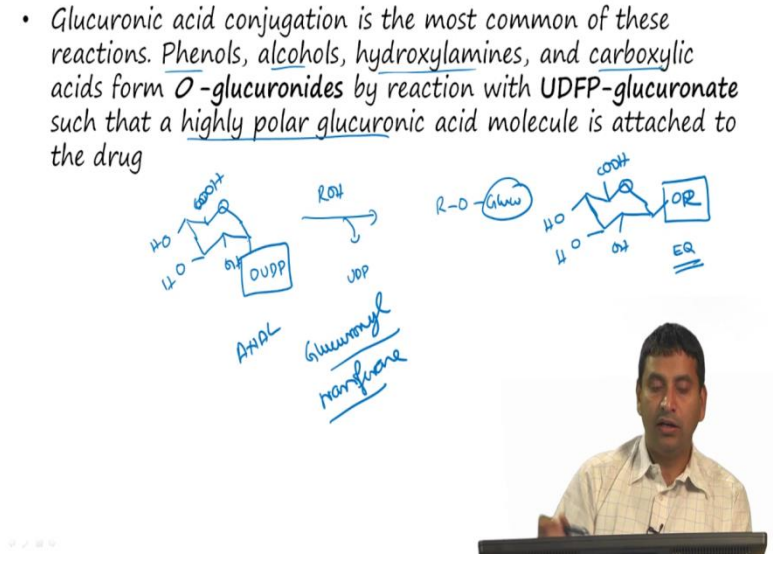

So the first class of conjugation reaction is addition of glucuronic acid or conjugation with glucuronic. So glucuronic acid is basically a sugar whose structure going to draw so it has an OH here as a COOH, OH, OH so it is basically sugar with carboxylic acid, there is a glycosidic bond and usually you have UDP as the living group okay that is unit in uridine

diphosphate. Once you this reacts with an alcohol and let us say what happens is that you kick out UDP which is the phosphate you kick out UDP and you form R - O with the glucuronic acid sugar. So let us draw out the structure of the sugar and we will find something very interesting about this, so the sugar is basically in the chair conformation.

You have O – R here, O, COOH is in the axial equatorial position, OH is in the equatorial position equatorial so on, right. But the important point here is that the UDP which was in the axial position has been kicked out and the new alcohol is in the equatorial position and so at the anomeric centre there is an inversion that occurs okay. So this is catalyzed by the enzymes glucuronyl transferase okay. So now one important point about both this enzymes or this process is that you are actually producing a highly polar glucoronic acid attached to a somewhat less polar alcohol okay. So again, as you can see the common theme here is that you conjugated with something that is highly polar so that you can facilitate excretion. And so this reaction can occur with phenol, alcohol, hydroxylamines and carboxylic acid so we look at some examples now.

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- The resulting conjugate is excreted in the urine, but may also be excreted in the bile if the molecular weight is over 300.

And the resulting conjugate is excreted in the urine, but it can also be excreted in the bile if the molecular weight is over 300, so with this let us look at some of the examples of glucoronidation. So variety of functional groups could be involved in this so you have R - C double bond O – NH_2 which is basically an amide which can form glucuronides which I am just going to call as Gluc, right. Similarly you can have hydroxylamine or hydroxylamino derivative forming R – N – O - Gluc so basically this is the OH that is going to substitute the and produce the sugar and they can also be examples of sulphonamides reacting so R – S -

double bond O – NH_2 can give you R – S - double bond O - NH glucuronides,. So these are again some examples of how nitrogen or oxygen based glucuronides can be formed.

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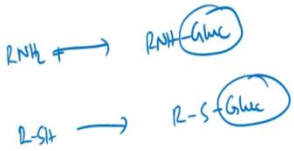

You can also have an amine reacting which give you RNH then you see other examples are thiols to give you R – S – Gluc and so on, right.

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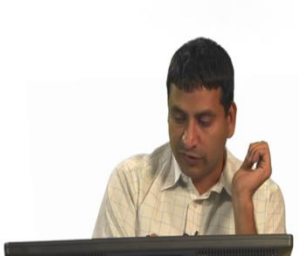
- Another form of conjugation is sulphate conjugation.
- This is less common than glucuronation and is restricted mainly to phenols, alcohols, arylamines, and *N* -hydroxy compounds.



Another common form of conjugation is called the sulphate conjugation. So here what happens is that a sulphate group is added and this is of course far less common compared to glucuronidation and it is mainly restricted to phenols, alcohols, amines and *N*-hydroxy compounds. So the transformation that we are talking about here is R – OH with a

sulphotransferases okay and the product that is given is R – O - S double bond O double bond O H okay. And this is actually catalyzed by a species known as 3 prime phosphoadenosine5 prime phosphorsulfate okay.

So if you look at the structure you see here that this is the phosphate, here is the sulphate so it looks exactly like an adenosine phosphate except that it has a sulphate group that can be transferred. So once this group is ready, the enzymes sulfotransferase uses this as a cofactor and transfer the sulphate group okay. Aromatic hydroxylamine and hydroxylamides also forms unstable sulphate conjugates that can be toxic okay.

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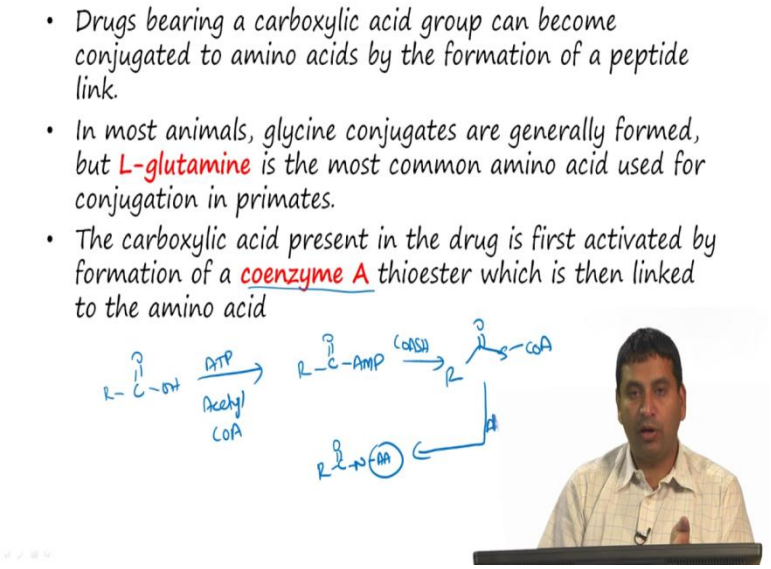

Now, drugs bearing a carboxylic acid group can become conjugated to amino acid by forming a peptide link okay. In most animals, glycine conjugates are generally formed but glutamine is the most common amino acid used for conjugation in primates. The carboxylic acid present in the drug is first activated to form a coenzyme A thioester which is then linked to the amino acid. So what happens is, you have R - C double bond O – OH, which then reacts with ATP and acetyl CoA to give you R - C double bond O - AMP, which then reacts with CoA SH to give you the corresponding S derivative okay, and this derivative is now active and it reacts with an amino acid to give you R - C double bond O - N amino acid okay. So this is how an amino acid can be linked to a carboxylic acid okay it is transferred by acetyl CoA okay.

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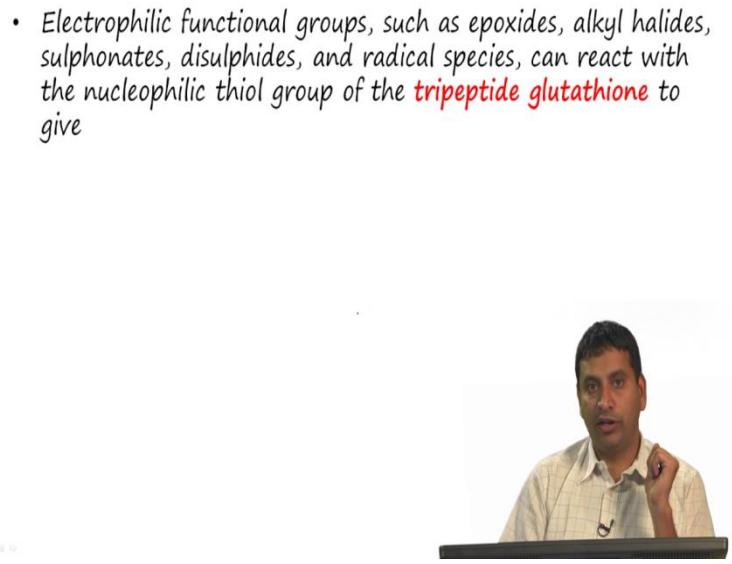

And there are other reactions conjugation reactions which can occur, which is basically the enzyme glutathione tranferase, which transfers the tri-peptide glutathione to produce glutathionylated adduct. , okay. There are number of electrophilic functional groups such as epoxides, alkyl halides, which are produced during epoxides are produced during cytochrome P450 mediated oxidation, you can have alkyl halides in many drugs. Sulphonates are again possible and of course disulphides and there are other radical pieces that can be produced okay, and these are all targets for this tripeptide known as glutathione okay.

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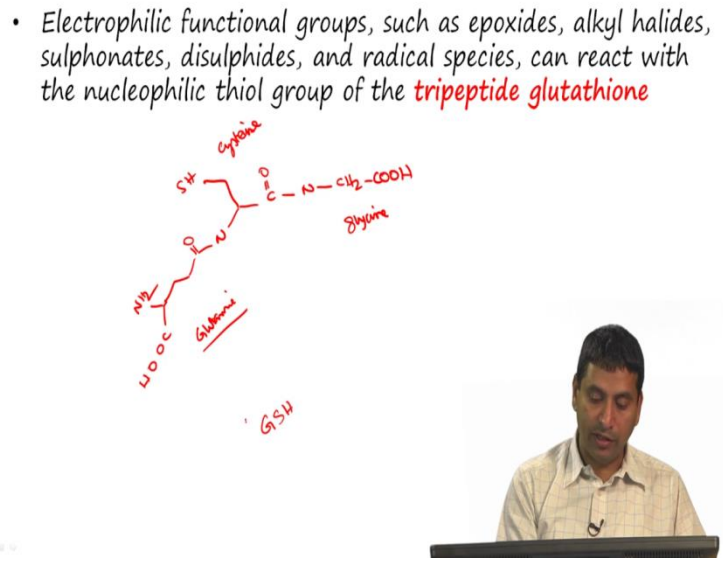

So the structure of glutathione is as follows so CH_2 – COOH – N - C double bond O – N and this is attached to the thiol residue which is from cysteine , this is glycine, cysteine right and the last amino acid here is glutamine okay.So this is glutamine right. So this is a tripeptide that is derived from cysteine and is very commonly used in the cell for protection from oxidative stress as well as in these conjugation reactions, so this glutathione is typically abbreviated as GSH okay.

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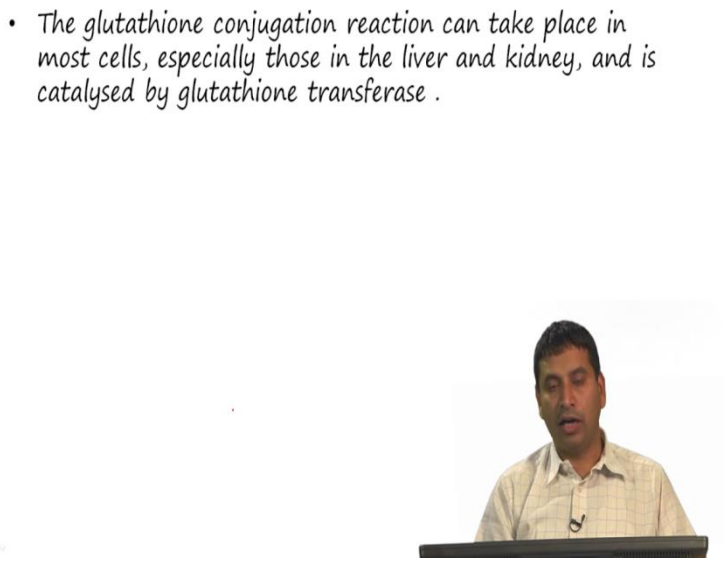

So glutathione conjugation can happen in nearly all cells and especially these occurs quite more frequently in the liver and kidney and it is catalyzed by the enzyme known as glutathione transferase.

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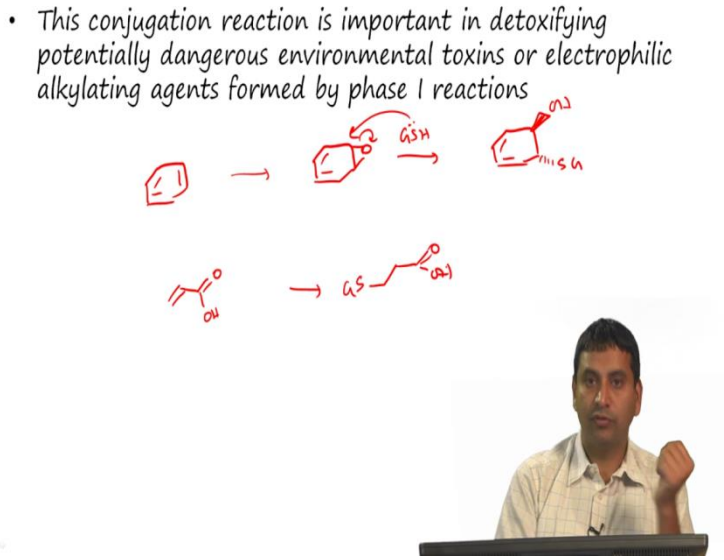

This conjugation reaction is important in detoxifying potentially dangerous and environmental toxins or electrophilic alkylating agents which are formed during phase 1 reactions. So for example, during the phase 1 reaction, when you are dealing with an aromatic system you end up forming an epoxide, right. And this epoxide can then be conjugated with glutathione to produce glutathione related conjugate such as shown here okay. And similarly you can have Michael acceptor which are formed which can then react with glutathione to produce these types of molecules okay.

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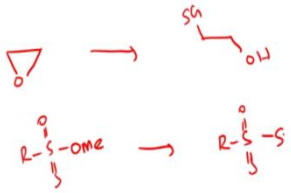

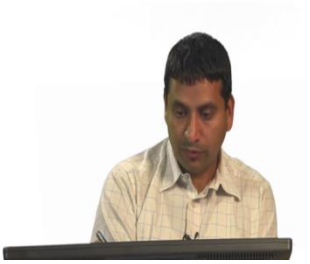

You can also have regular epoxides which can react with glutathione to produce the corresponding glutathionylated adducts or you can also have sulphates, which are excellent alkylating agents which can react with glutathione to produce this kind of intermediate okay.

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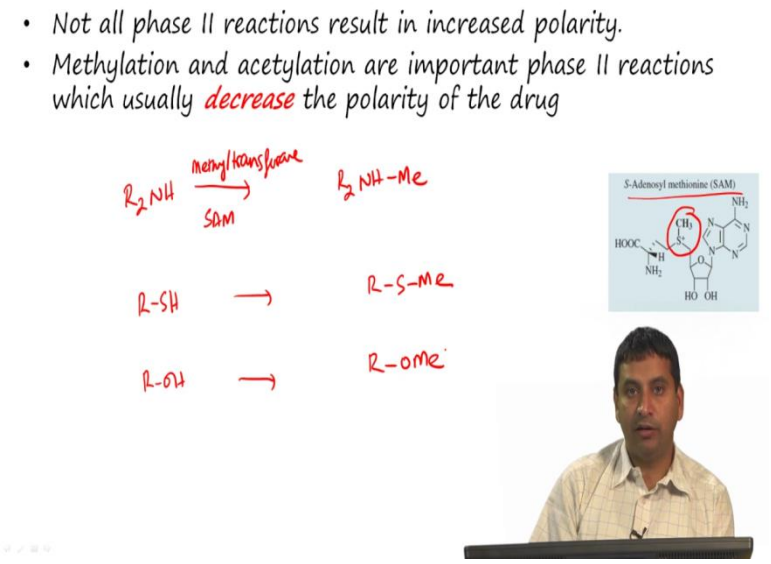

Now, not all phase 2 reactions result in increased polarity, there are some examples of methylation and acetylation which are important phase 2 reactions which can occur, but these usually result in decrease of polarity okay. Now let us look at methylation reactions, methylation reactions are catalyzed or mediated by the species called S-Adenosyl methionine. So example of reaction that we are looking at is R_2NH, so there is an enzyme called as methyl transferase in the presence of S Adenosyl methionine, so you see here that this is the active species of S adenosine methionine and it gives you R_2NHMe okay.

And similarly you can also have a thiol reacting under similar conditions to give you SMe or you can have an alcohol reacting to give you ROMe. So all these are methylation reactions that are mediated by SAM okay, so in order to look, let us spend a couple of minutes and look at how SAM functions.

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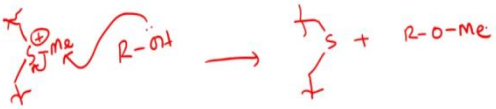

So you have the S-Adenosyl methionine who structure I am not going to draw completely but it has an important SMe group here. And now if you can imagine that there is an a nuclear file such as an alcohol ROH, it can attack here and this is being an excellent living group because it is a neutral thioether you can propose or one can imagine that this reaction can occur very easily and it will give you this thio ether ROMe okay. So it is a very important reaction, methylation is a very important reaction but keep in mind that once the functional group the molecule is methylated, the polarity of the molecule group actually decreases okay.

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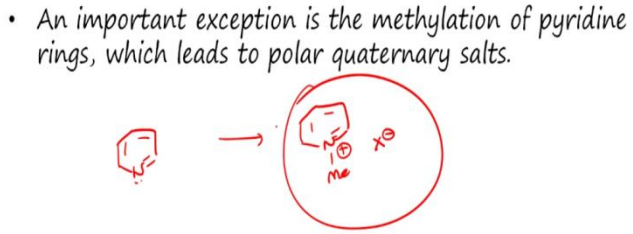

Now, one important exception is that in this case so we have this molecule called as pyridine whose structure is shown here, basically an aromatic ring with a nitrogen on it. So once this gets methylated, it forms a *N*-methyl pyridine which is actually as a full positive charge, so here upon methylation this molecule becomes more polar, right.

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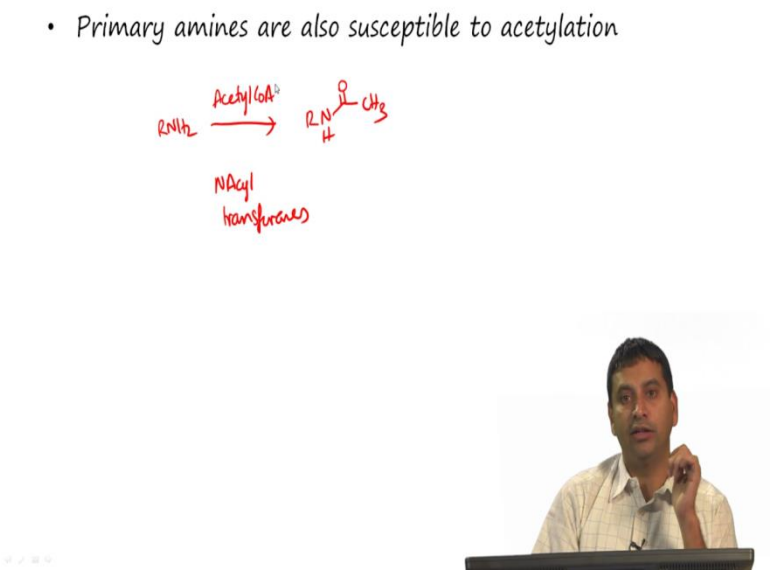

The other reactions that we looked at is acetylation, so primary amines such as RNH_2 can react with or can undergo acetylation reactions and form RNH C double bond O – CH_3 and these are mediated by *N*-Acyl transferase. So when you have a glutathione being transferred, you have glutathione transferase, when you have a methyl group being transferred you have a methyl transferase, and when you have a Acyl group being transferred here to an amine it is called *N*-Acyl transferase. And again this is mediated by acetyl CoA which we have already looked at in the previous slides okay.

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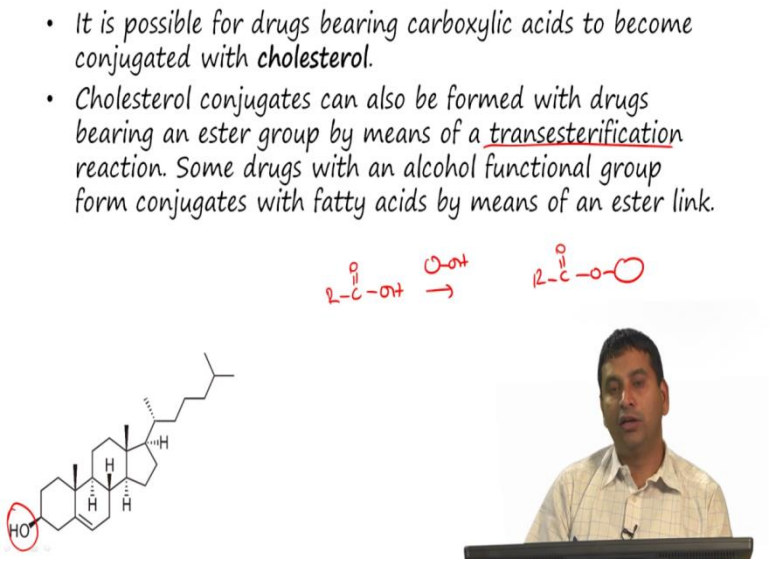

Lastly, it is also possible for drugs bearing carboxylic acids to be conjugated with cholesterol. So here is the structure of cholesterol and it has a free alcohol present here and so you can imagine carboxylic acid R C double bond OH can react with the cholesterol oxygen to give you R - C double bond O - O cholesterol, okay. So this a drug with an ester can do a transesterification reaction wherein cholesterol can be added okay. Sometimes an alcohol functional group can also form conjugates with other fatty acids to produce an ester functional group, but again all of these transformations are going to result in increase hydrophobicity or reduced polarity.

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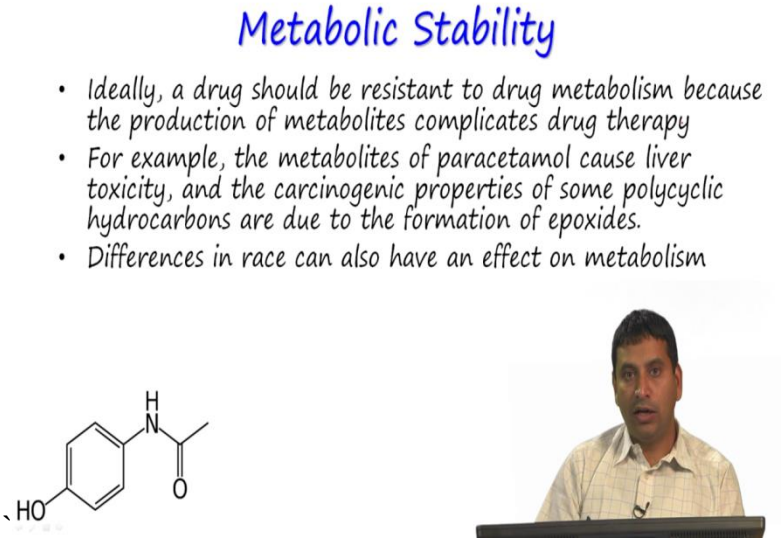

Lastly, we want to discuss about metabolic stability where ideally the drug that we are going to develop should be resistant to drugs metabolism because the production of metabolites usually complicates drug therapy so you have lots of side effects associated with this. So an example, wherein this metabolite is going to be problematic is in paracetamol which is very commonly consumed and what happens in this paracetamol is that it forms a metabolite which is actually quite toxic and it can cause it also cause, some of these can have carcinogenic properties. It is also important to recognize that among humans there are differences in the race of a human and this can also manifest itself in how a drug is metabolized.

So sometimes certain drugs act in a particular way or metabolized in a particular way in white and Caucasian people and it act in a very different way in Asian or in Chinese people and therefore this is also important factor in determining the metabolic stability.