Medicinal Chemistry
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Lecture No 03
Intermolecular Binding Forces

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Welcome back. We looked at, in the past couple of lectures, about how one can identify a lead. We looked at an overview of what medicinal chemistry is and it is actually drug discovery is basically trying to find the lead.

So in today's lecture we look at how a drug interacts with the target, Ok. So keep in mind, this interaction is nothing but there are forces that are operating between the drug and the target. So today we will look at some of the aspects of these.

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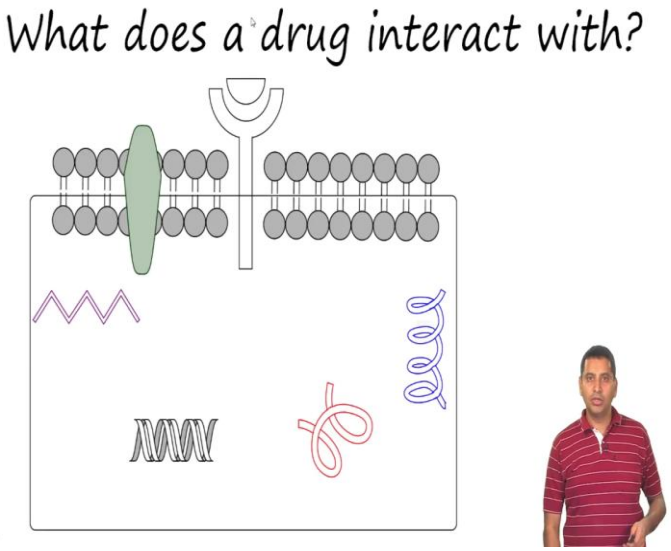

So before we do that, if you look at a picture of a cell, the cell consists of, of a lipid bilayer and typically there are

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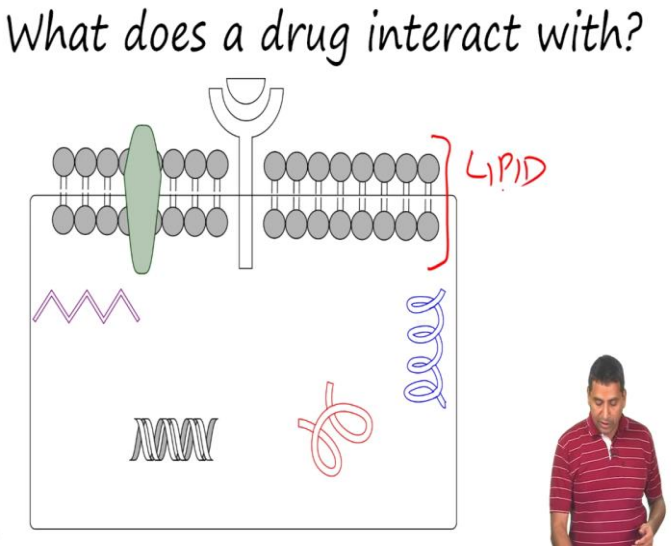

receptors on the surface which is marked here. And then there are also transport proteins which I have

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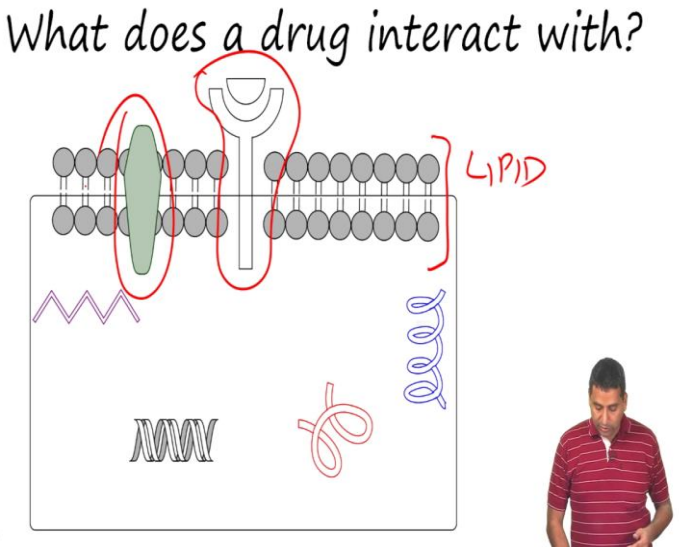

shown here. And these are some generic representations of different kinds of proteins which we will look at in detail.

And here is the

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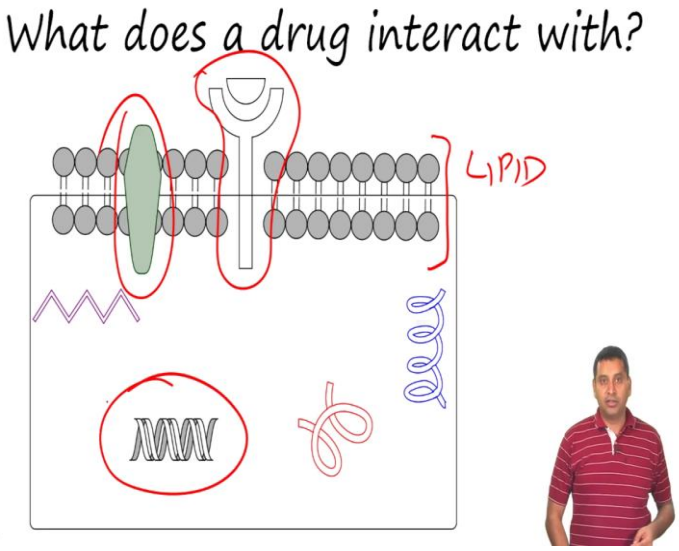

carrier of the genetic information which is DNA or RNA as the case may be, Ok. So these are the main targets that we will look at. In today's lecture we will look at how these, how the drug interacts with any of these targets,

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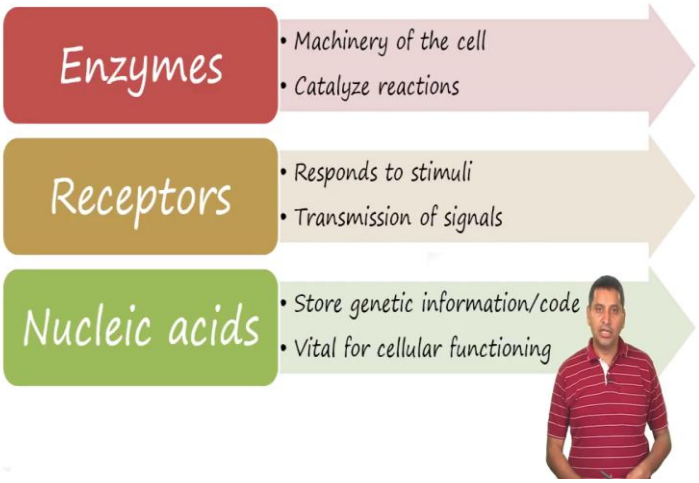

Ok.

So just to recap, enzymes are the main machinery of the cell. They catalyze several reactions

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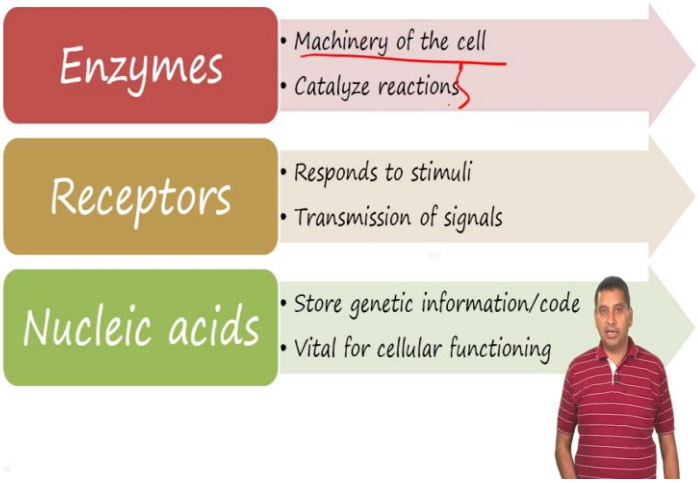

and we shall look into detail about how this, how this catalysis occurs. And receptors as I mentioned to you are basically the

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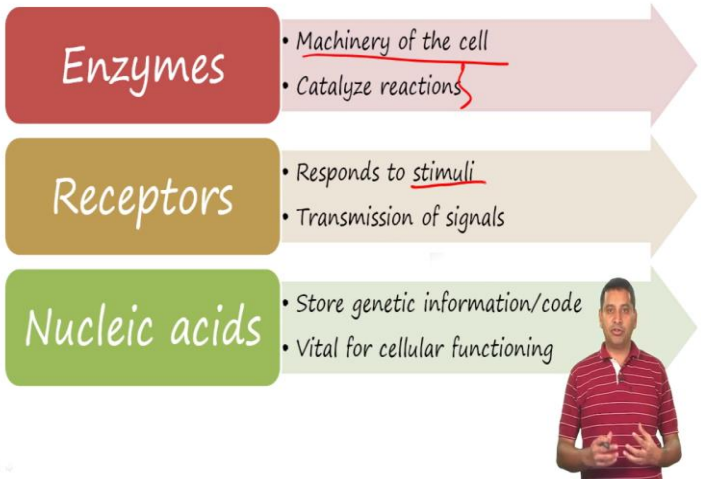

major components of signaling inside a cell.

So they are typically located on the cell surface and they respond to stimuli. And they are vital in transmission of signals. For example neuro-transmission is mediated by receptors for example.

Now the third most important target inside

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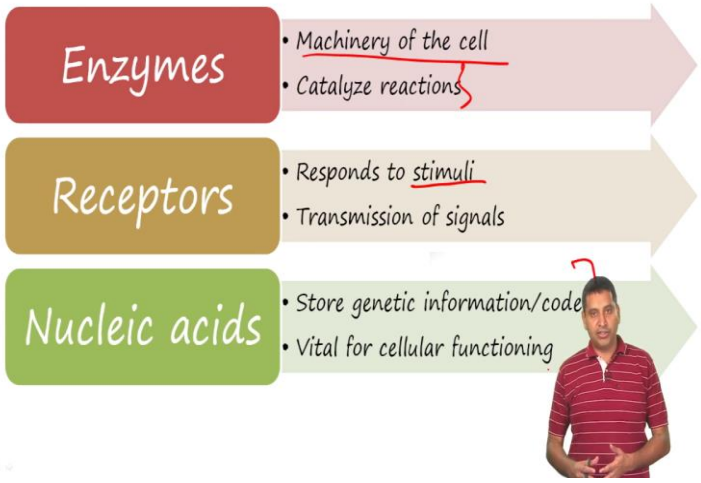

a cell, nucleic acids, these molecules hold the genetic information or genetic code and of course, without them the cell cannot function because they have the blueprint for the working

of the entire cell. So keeping these targets in mind, let us look at how drugs interact with each of these targets, Ok.

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- The vast majority of drugs used in medicine are targeted to proteins, such as receptors, enzymes, and transport proteins.
- Therefore, it is important to understand protein structure in order to understand drug action on proteins.

So the vast majority of drugs that are used today are targeted at proteins, Ok. So these proteins as I mentioned earlier are classified as receptors which are on the cell surface, enzymes which are typically present inside the cell and transport proteins which are in the membrane, Ok.

So it is important therefore for us to understand how, what protein structure is all about in order for us to understand how the drug acts on the protein. So let us look at some of the aspects of what determines the structure of a protein.

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- Proteins have four levels of structure: primary, secondary, tertiary, and quaternary.

Now proteins have 4 levels of structure. They are named in the ascending order of numbers which is primary, secondary, tertiary and quaternary, Ok.

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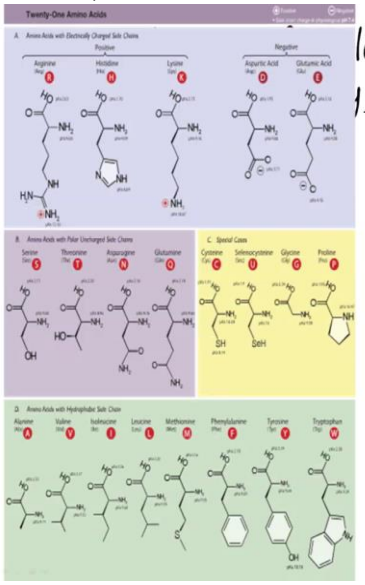

levels of structure:
, tertiary, and

So the primary structure is nothing but the sequence of amino acids and here is a box showing all the naturally occurring amino acids. We won't go into these in detail but this is an aspect of self-study that, that you can take up and so the sequence in which these amino acids are arranged is called the primary structure,

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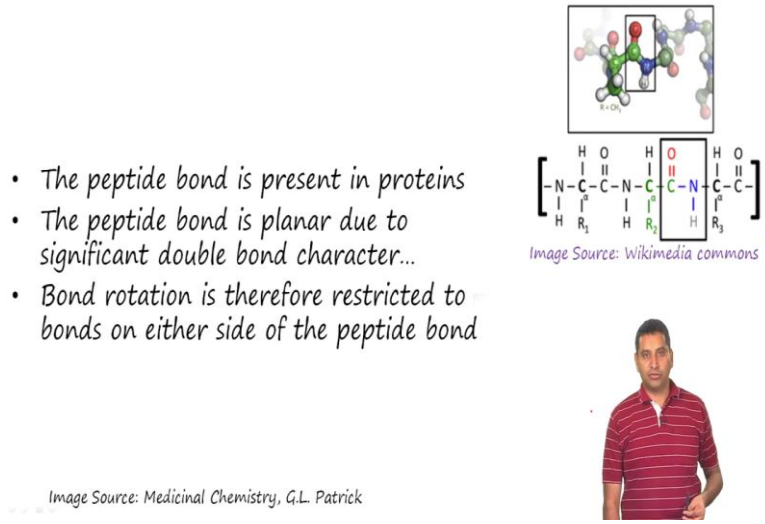

Ok.

And the bond that occurs within, among these is

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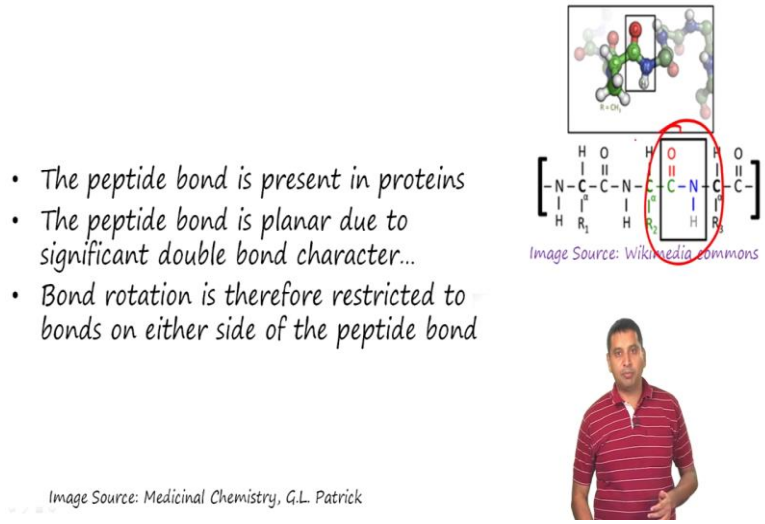

known as a peptide bond. It is nothing but an amide bond. And the peptide bond is planar because of significant double bond character.

So if you see here

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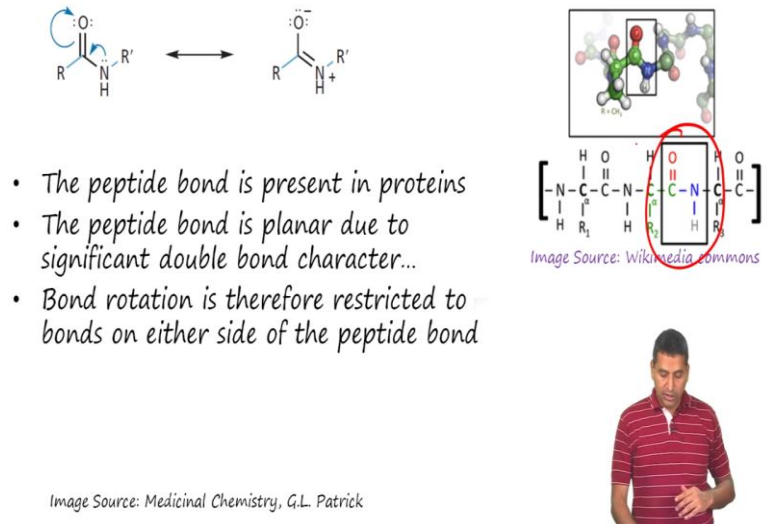

that there is a resonance form wherein the lone pair of nitrogen goes in to the amide and forms this kind of a resonance

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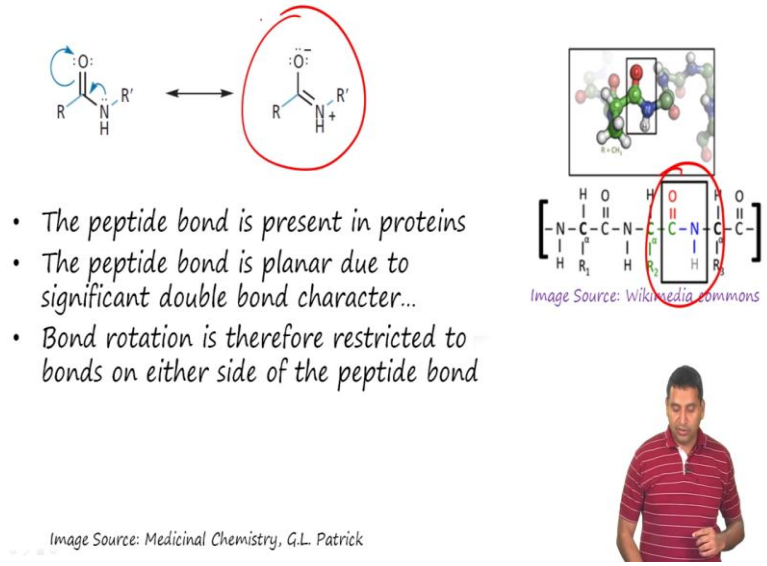

form. And therefore there is a significant double bond character between this carbon-nitrogen bond. As a result, the rotation across this carbon-nitrogen bond is also quite restricted, Ok.

So this is something

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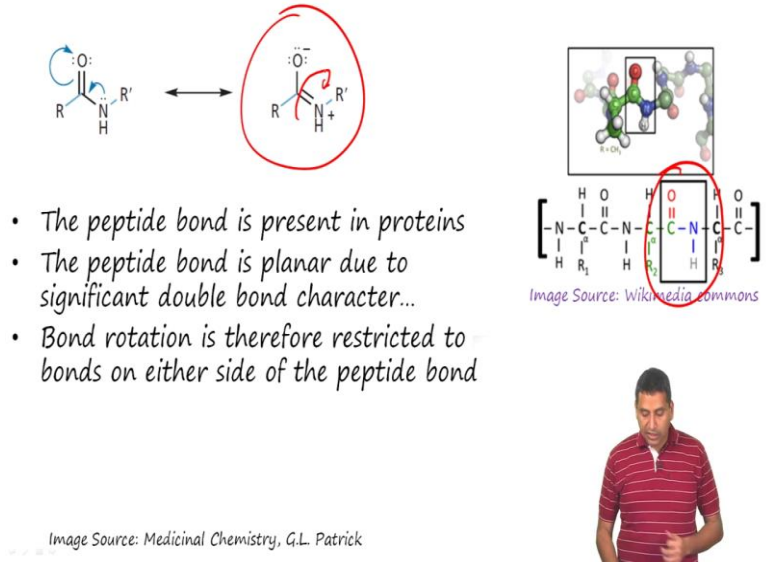

that offers a unique character to peptide bonds and so whatever bond rotation that happens has to happen on either side of the peptide. So it has to happen on this side, or on this side,

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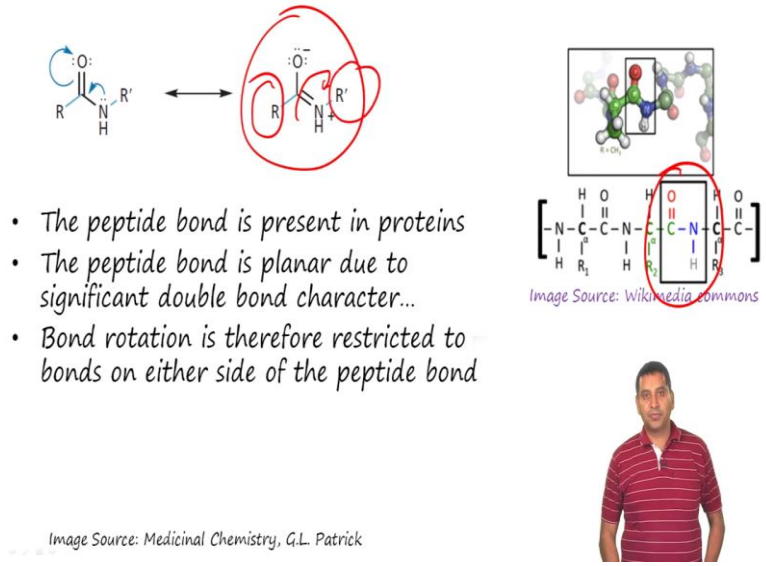

Ok. So let us keep that in mind when we are looking at the next to understand

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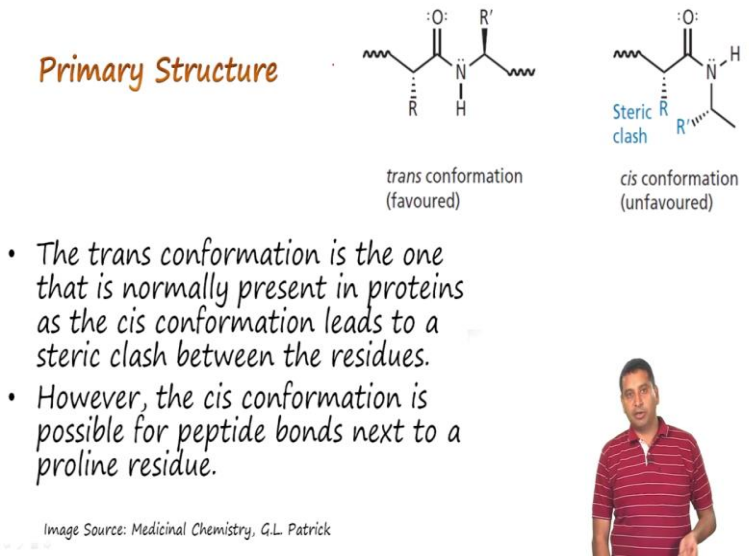

the primary structure, Ok.

Not only there is a double bond character in the amide bond but there is also a conformational restriction. So here in this cis conformation there is

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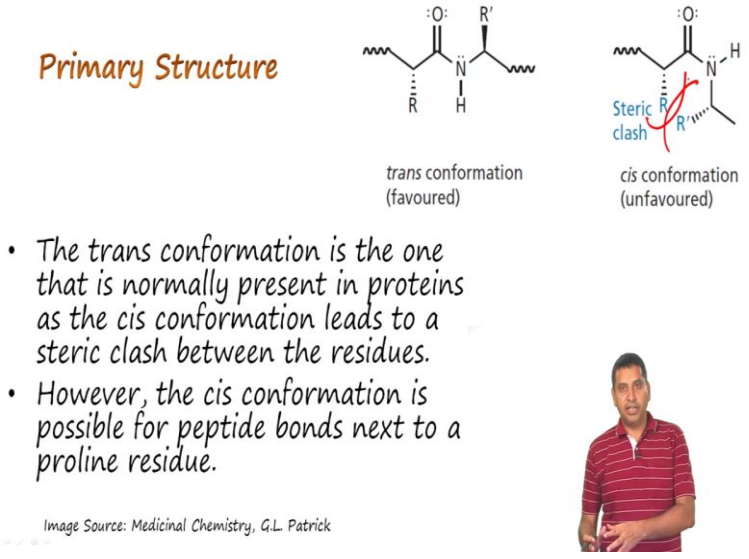

steric hindrance which can disfavor this conformation and, so therefore the trans conformation is more favoured.

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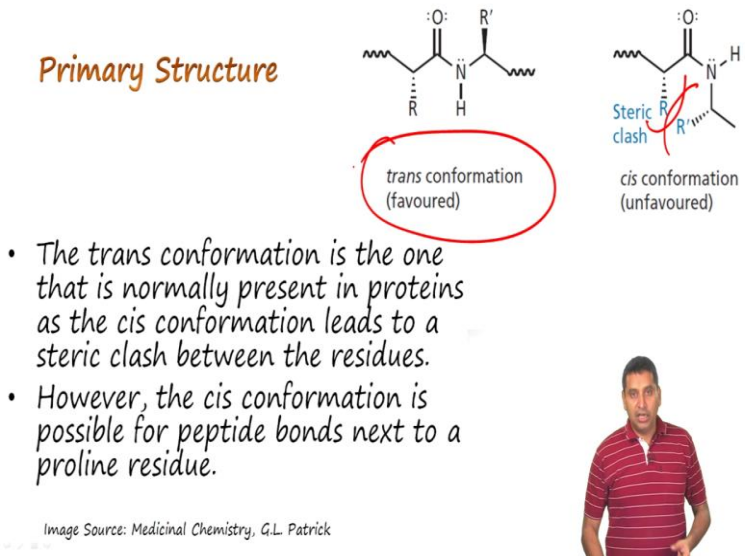

And, so not only the double bond plays an important role but the conformation of this also can play a role in way in which primary structure is present, Ok. So the cis conformation is of course possible when you have a proline residue.

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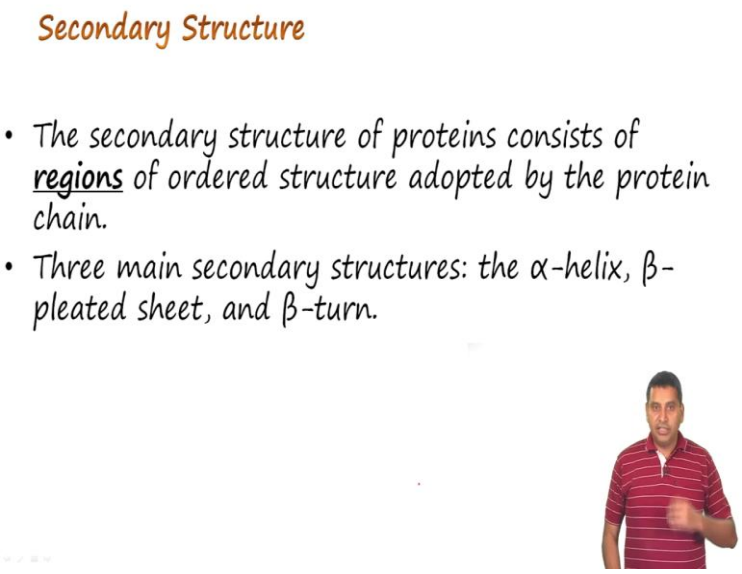

The secondary structure is nothing but how there are regions where there is order that is adopted by the protein chain, Ok. So here the main types of secondary structures are the alpha helix, the beta pleated sheet and the beta turn, Ok.

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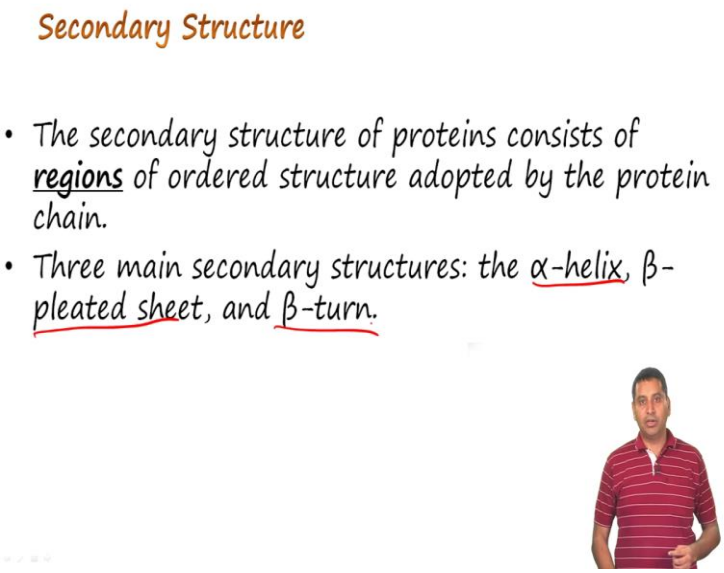

So we will look at some of these in a little bit of detail.

And, so here is the

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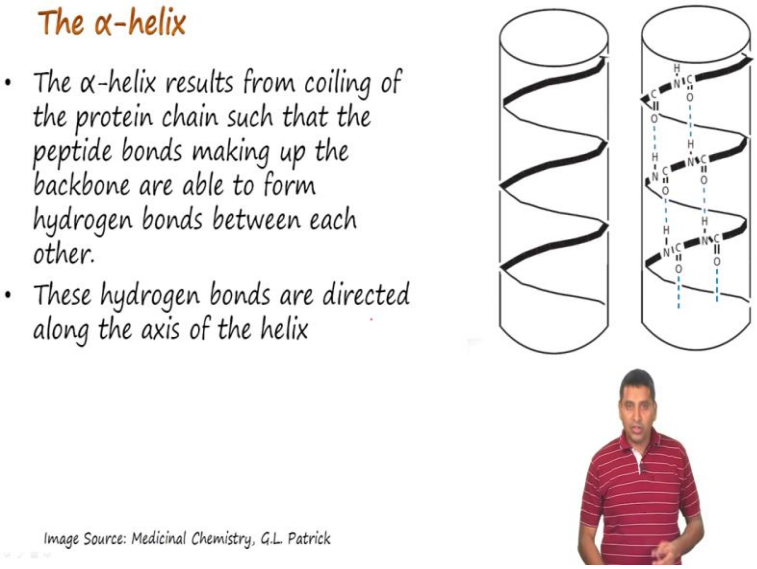

first secondary structure which is the alpha helix, Ok. So in the alpha helix what happens is that there are intra-molecular hydrogen bonds that are present which can play an important role in the way in which the residues

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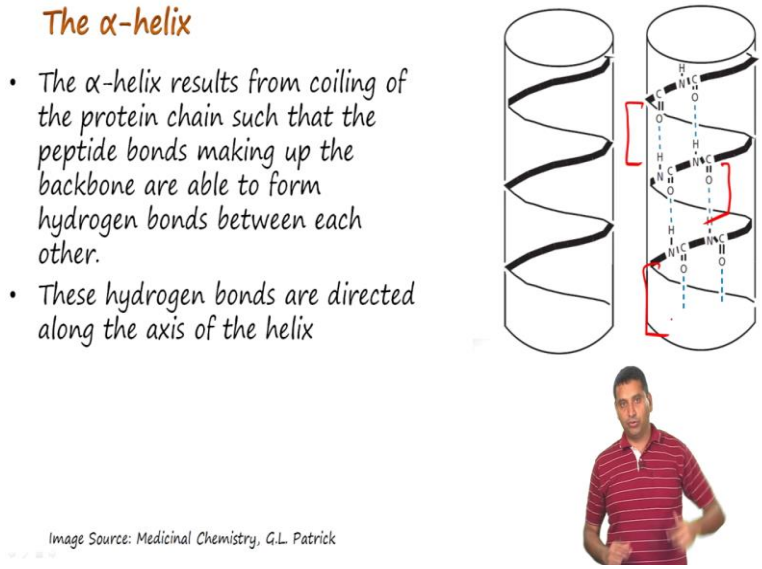

are arranged, Ok.

And these hydrogen bonds are arranged along the axis of the helix

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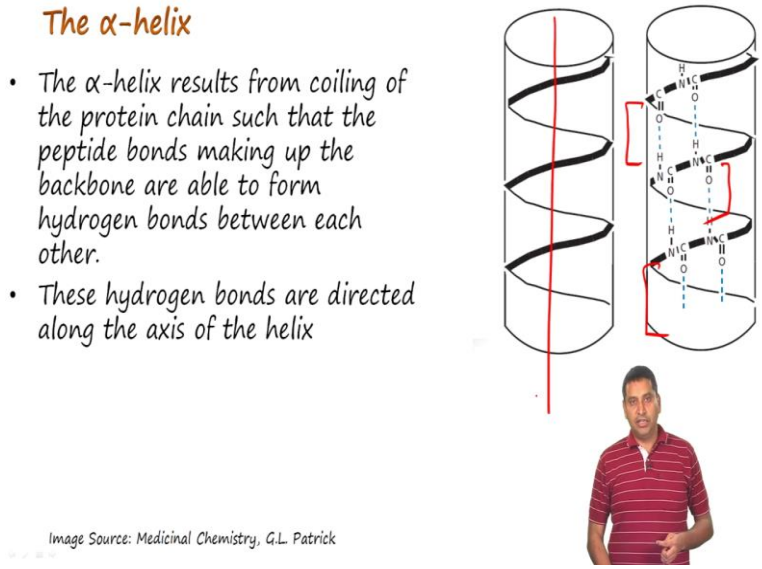

and it is a very important secondary structure and it is an important component of many proteins which is alpha helix, Ok.

So in the alpha helix there is a coiling of the protein such that the peptide bonds make up the backbone, Ok and there is a hydrogen bond that occurs between these, each of these coils. So this is an important structure, secondary structure that is present in a number of proteins, Ok.

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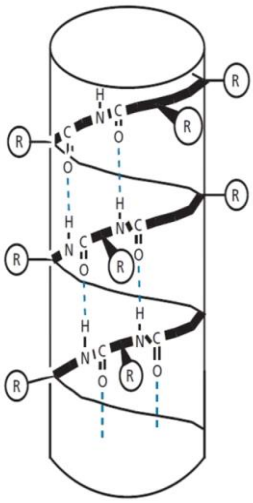

Position of side chains

- The position of the side chains is at right angles from the helix, thus minimizing steric interactions and further stabilizing the structure.

So here interestingly, what happens is that the R group which is the,

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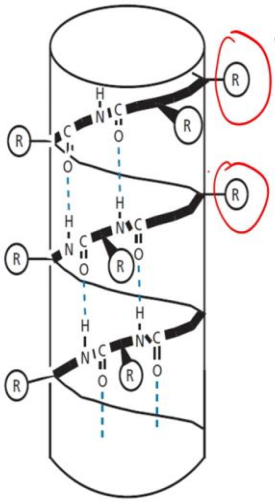

Position of side chains

- The position of the side chains is at right angles from the helix, thus minimizing steric interactions and further stabilizing the structure.

typically let us say it is a

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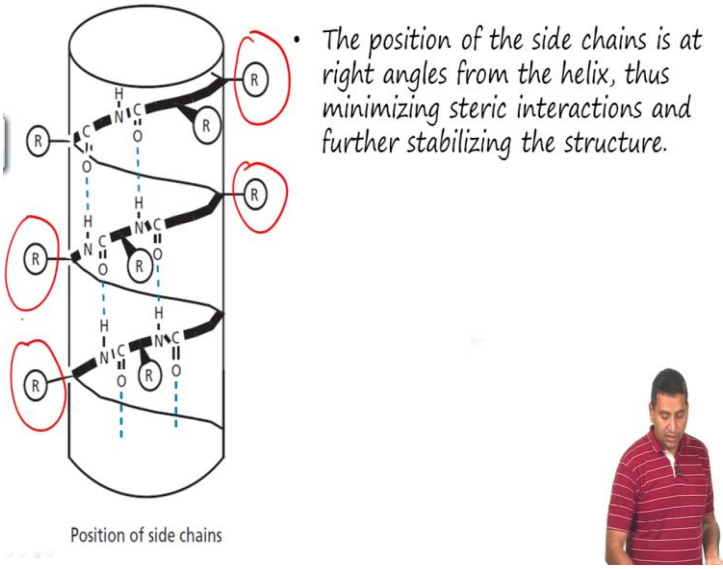

isolucine or lucine or any of the other amino acids, the R group ends up being outside the alpha helix, Ok. So this results in minimizing the steric interactions and stabilizing the structure, Ok.

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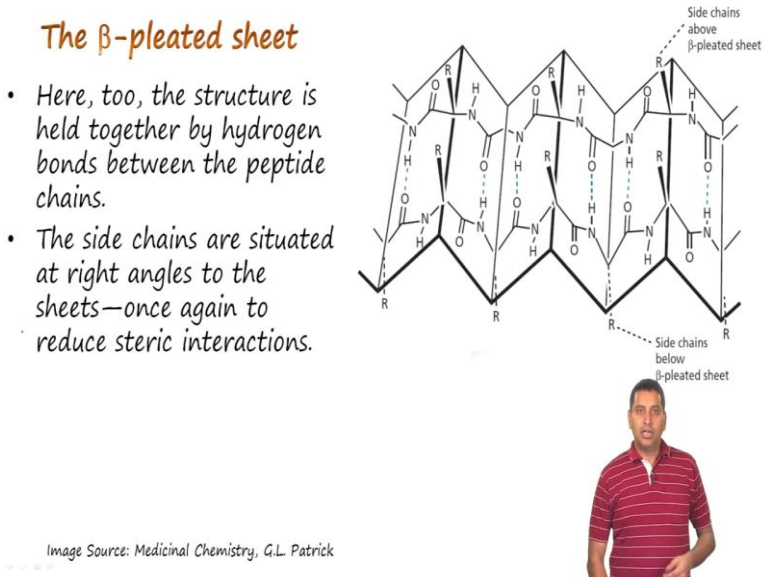

Now the next secondary structure is actually the beta pleated sheet. So here again the structure is held together by

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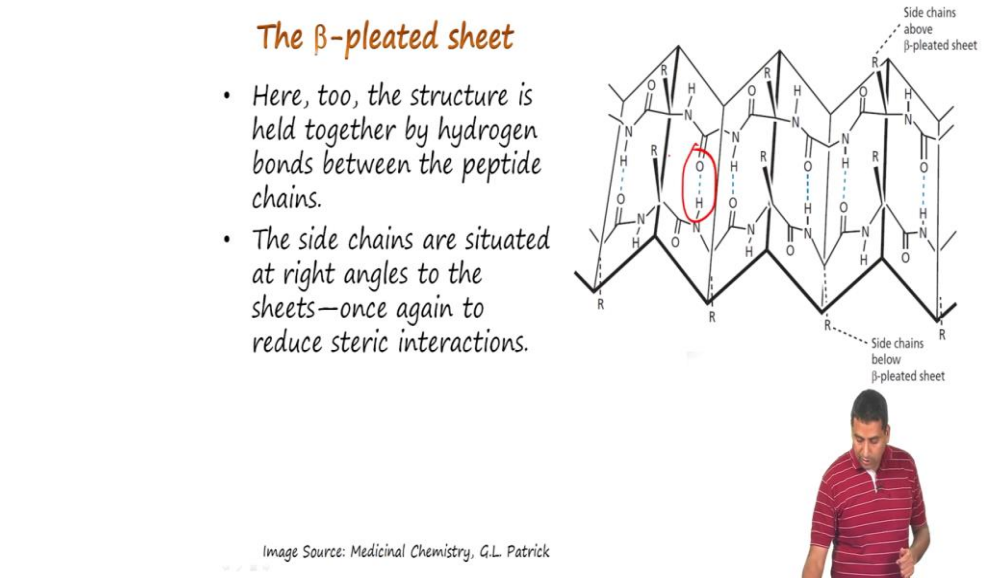

hydrogen bonds,

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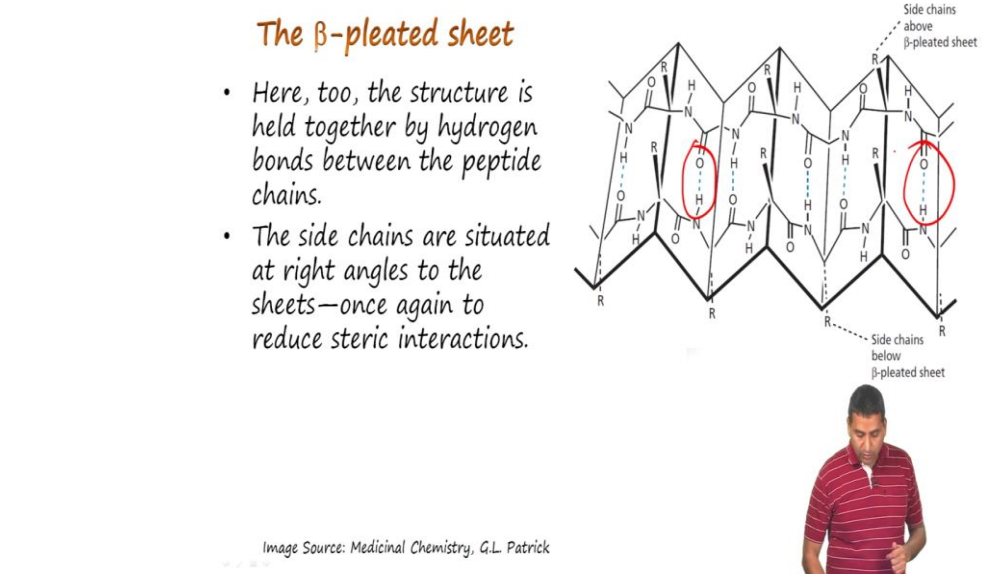

Ok. We look into in detail about the other, the nature of hydrogen bond shortly. But what happens is that, this undergoes the arrangement of the beta pleated sheet is, along this, is something like

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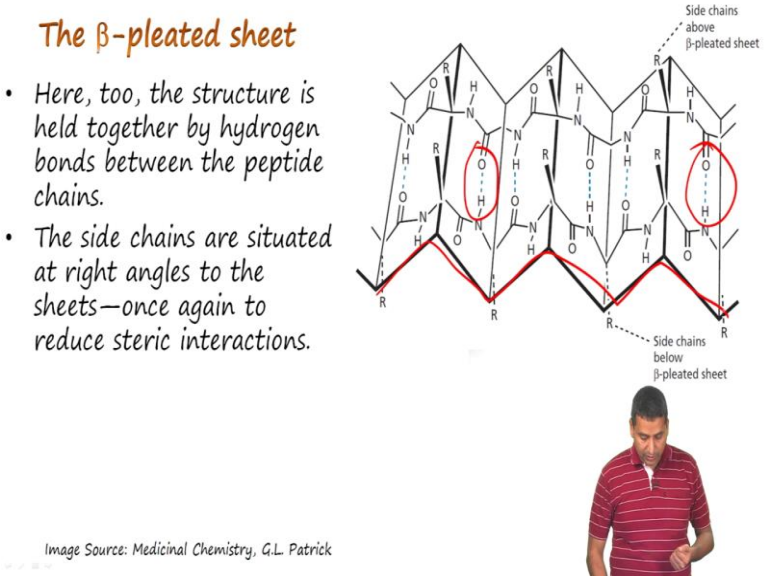

this, Ok.

Now what happens is that, the sidechains are situated again at right angles from the sheet to again

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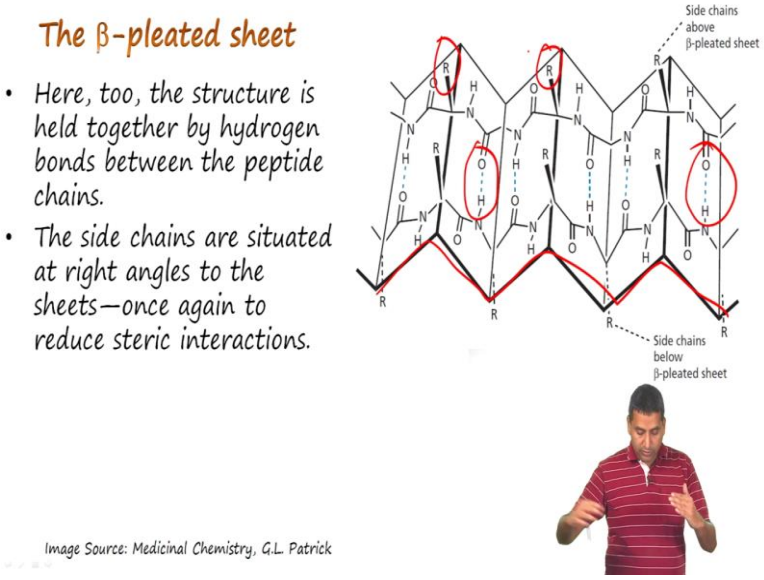

reduce the steric interaction, right. So these are two important structures, the alpha helix and the beta pleated sheet wherein the sidechain is actually protruding outside, Ok.

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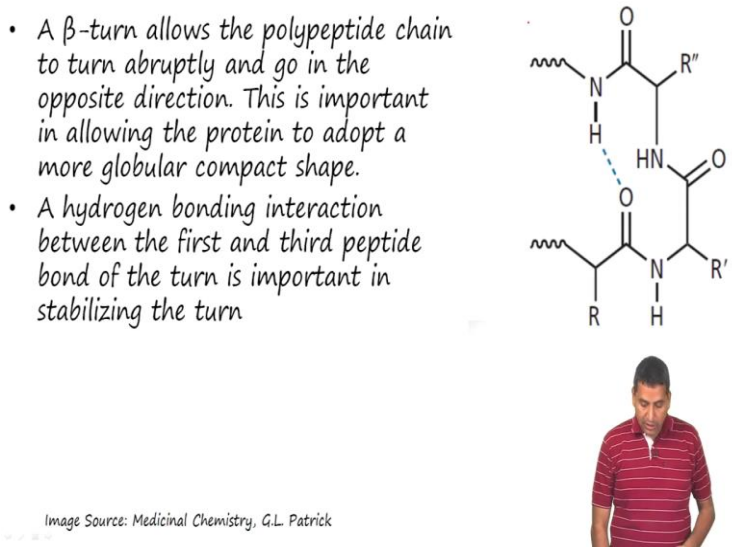

Now a beta turn is nothing but, it helps, it is another special case of intra-molecular interaction where it allows the polypeptide chain to abruptly change its direction and as a result it becomes more globular in nature, Ok.

So here is an example of

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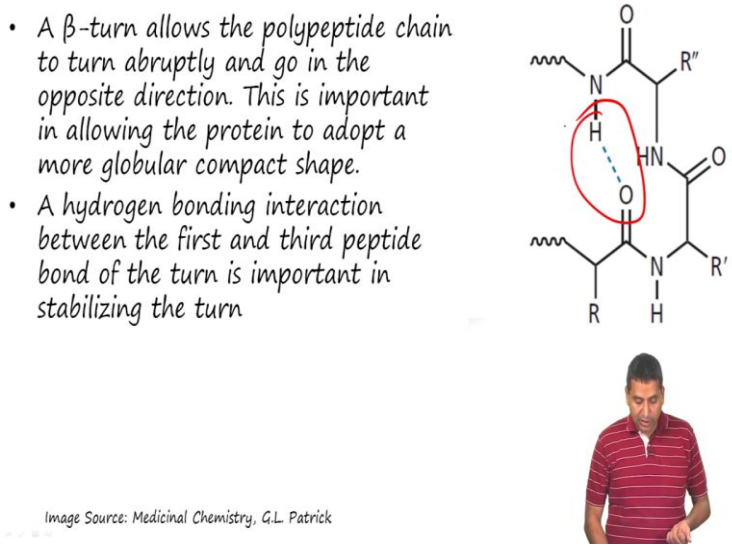

the beta turn. Here the hydrogen bonding interaction between the first and the third peptide residue occurs which stabilizes the turn, Ok. So we look in to detail a little bit later about the types of proteins but globular proteins are ones which allow the proteins to have a more compact shape, Ok.

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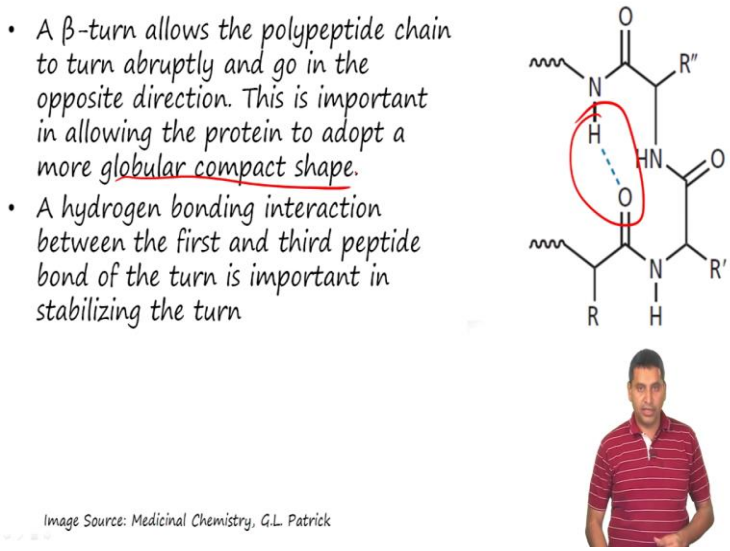

And shape again is, is one of the important criteria of how protein function is determined.

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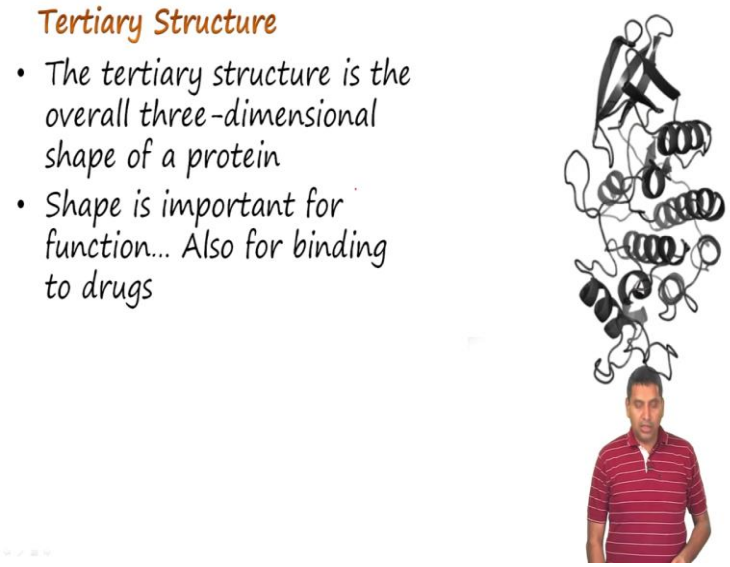

Now after we looked at the primary structure which is nothing but the sequence of amino acids and the secondary structure where there are regions of order in the protein.

Now let us look at the tertiary structure which is nothing but the overall three dimensional shape of a protein,

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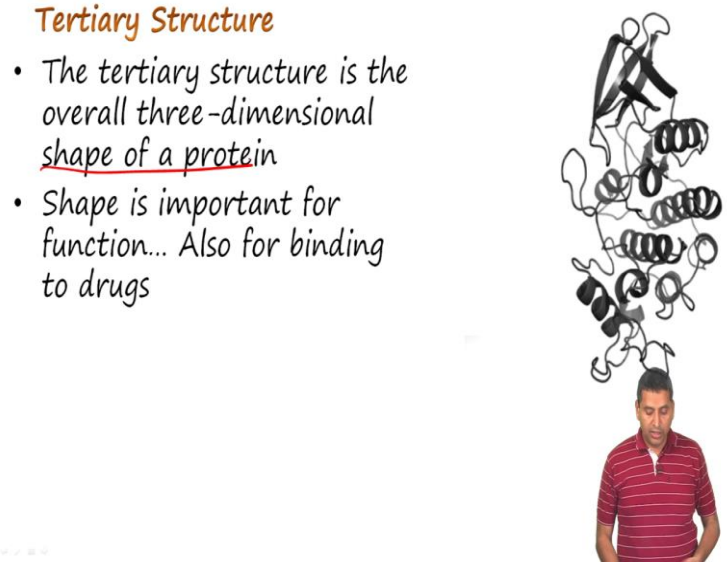

Ok. Now as I mentioned earlier, shape is very important for determining the function but it is also important for how a drug binds to a protein, Ok.

So in this case, so I can

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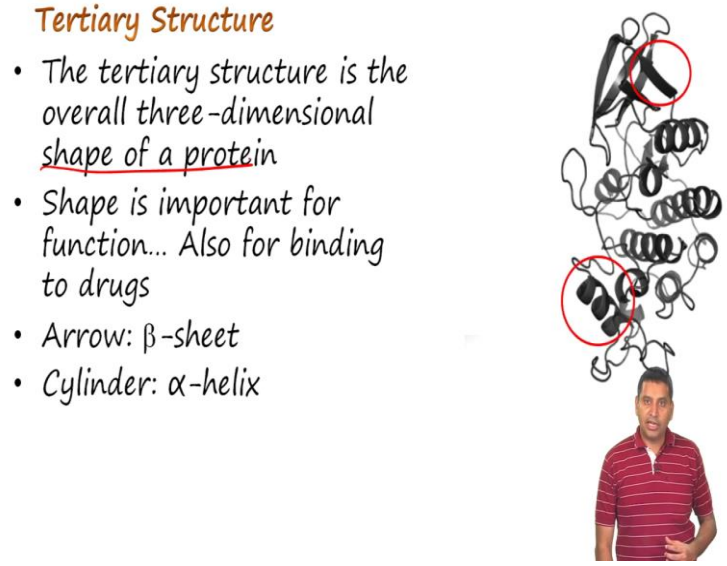

show you this is a representation of a protein. Now there are the alpha helix portions are represented here and the arrow which is showing here is, is nothing but the beta sheet, Ok.

Now if you take a string and place it on a table, let us say, you will rarely find that it actually folds up itself, right. But a polypeptide does not do that. If you put a polypeptide what happens is it starts to fold, Ok and it starts to assume these ordered structures.

So one of the ways in which we understand this folding is that because each of these amino acids which are constituents of a polypeptide have a functional group attached to it. These functional groups can interact, Ok and this interaction can actually be attractive or it can also be repulsive. And this helps the protein assume a shape which is thermodynamic minimum, Ok.

Of course there are large number of scientists who have, who work on this problem of protein folding and it is something that is still a lot needs to be understood but there is a fairly good understanding of how some of these processes occur and that is useful for us to, to understand how a drug can interact with a protein. But broadly these interactions can either be attractive or repulsive,

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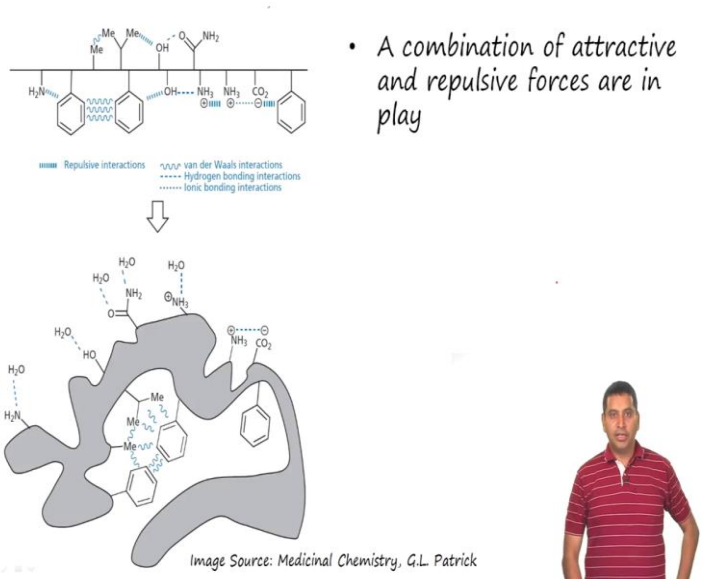

Ok.

So what happens is that, so when you have a long polypeptide

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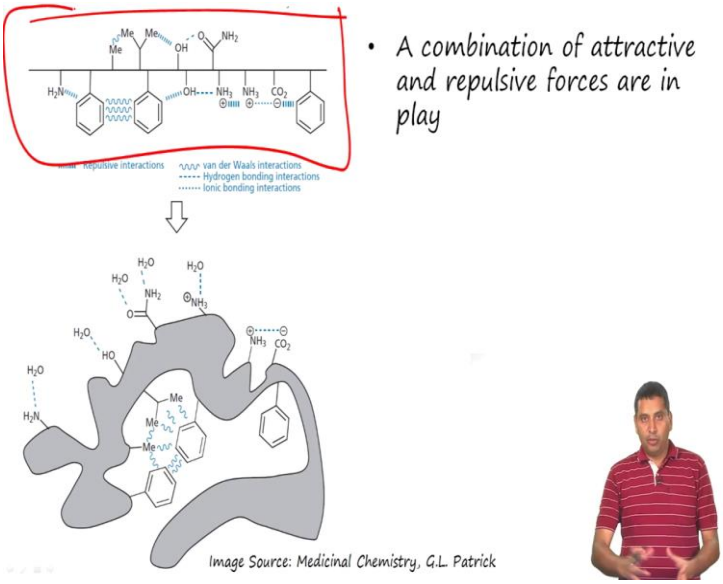

chain, typically what happens is the hydrophilic residues which are basically the amines and the carboxylates

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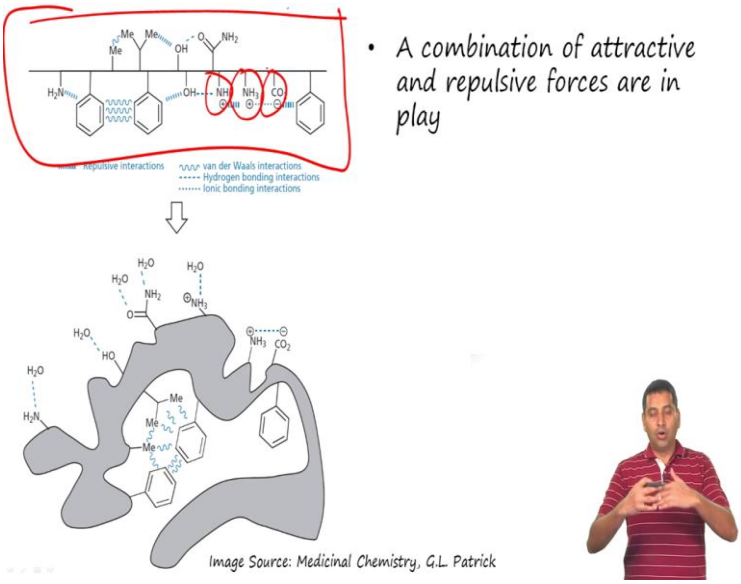

go out on the surface of the protein and this is because typically the protein folding occurs in aqueous media which is basically water and so there is lot of potential stabilization that occurs

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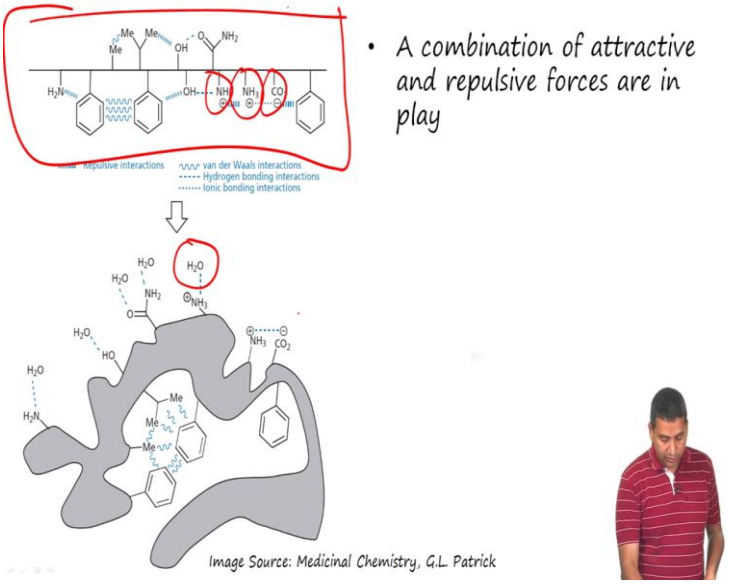

in water.

And the hydrophobic residues which are, for example represented by this start to go inward, Ok. So therefore there is a combination of attractive forces which is hydrogen bonding on the hydrophilic residues and, repulsive forces which is hydrophobic and that makes the protein take to a shape where the hydrophobic interactions actually start

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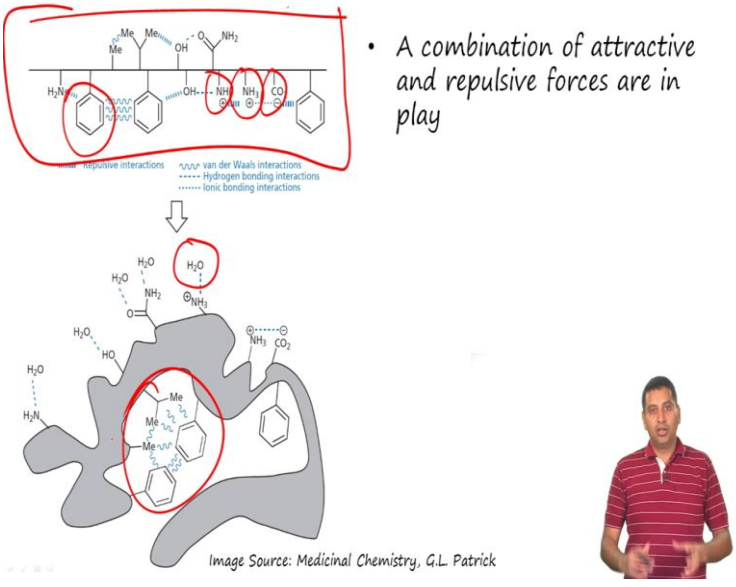

going along together,

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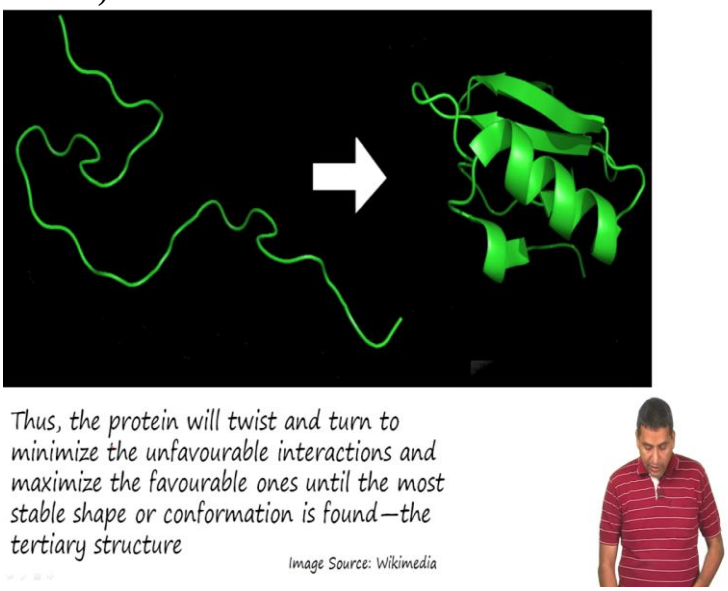

Ok.

So this is another representation of how this long polypeptide chain can actually fold and so here is, on the left is a long polypeptide chain and what happens is that it can actually go through favorable and unfavorable interactions and as a combination of this, it can assume this shape. And this is the tertiary structure of a protein,

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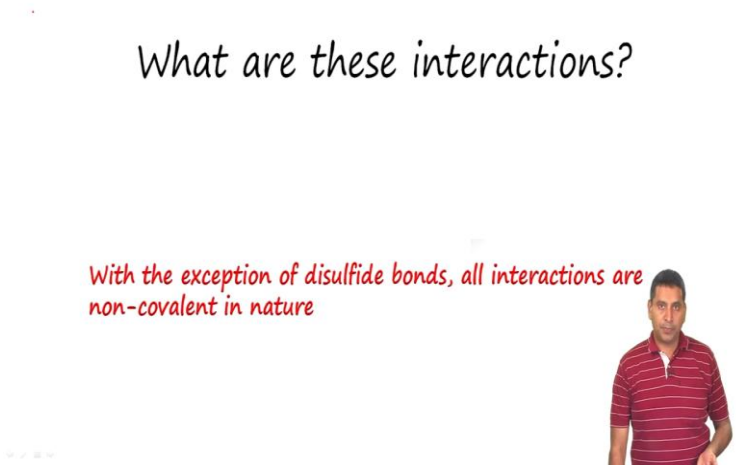

Ok.

Now in order for us to understand what, how a protein folds and how these interactions occur, we need to understand what these interactions are, Ok.

And there are disulfide bonds which are actually covalent in nature. Other than disulfide bonds all other interactions are non-covalent. But let us first look at what a disulfide

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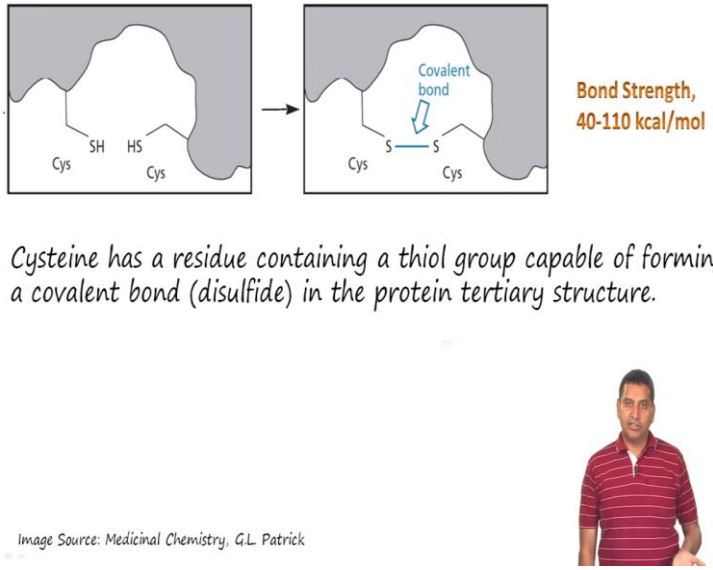

bond is.

A disulfide bond is nothing but a bond between two thiols

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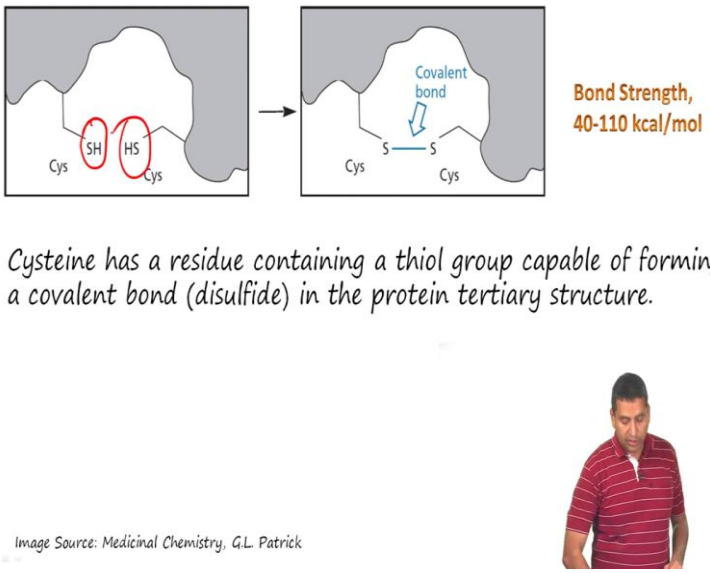

which are a part of cysteines and this is an oxidative modification where a new bond is formed between sulphur and sulphur,

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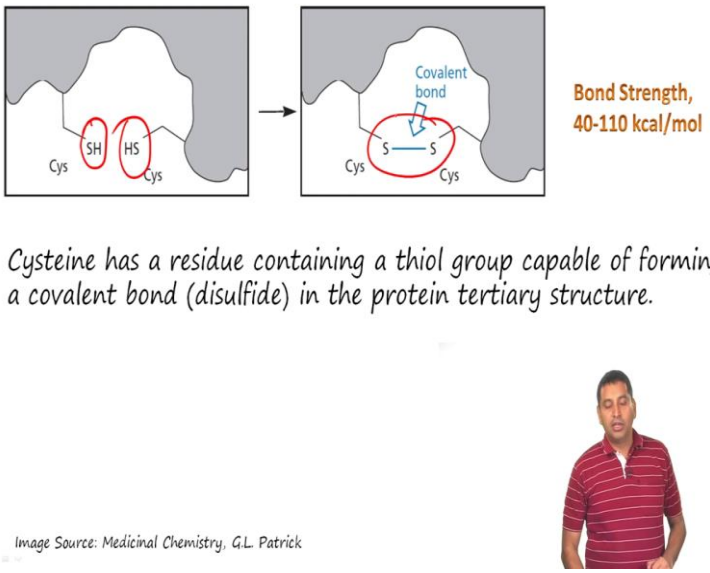

and this results, this is a covalent bond, Ok. And covalent bond, the typical bond strength varies from 40 to about 110 kilocalories per mole and it is a very, it is a fairly strong bond and it is difficult to break.

So during folding if there are two cysteine residues which are far away from each other, they can come together and by doing an oxidative modification they can actually form a disulfide bond which is sometimes referred to as a disulfide bridge and this helps the protein assume a particular structure, Ok.

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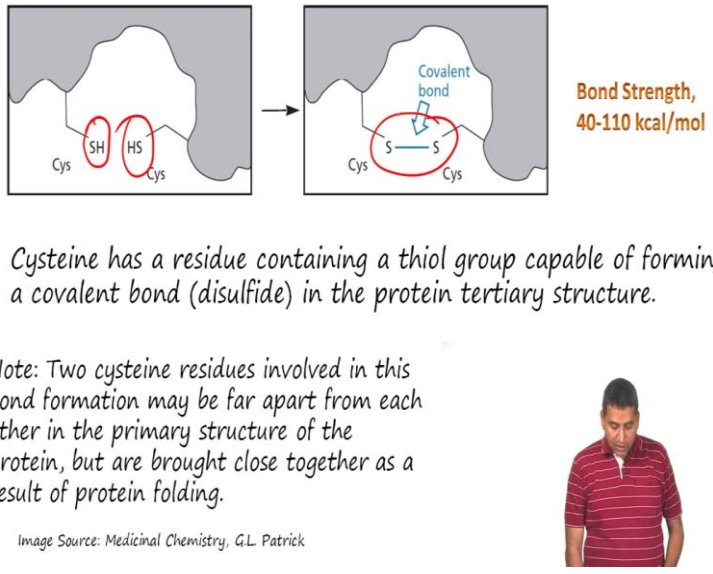

Now these two cysteine residues can actually be quite far from each other. They will have to be close to one another, right?

So the primary structure is therefore, there is very little information that one could get from the primary structure which will help us understand how it can fold, because you can have two cysteine residues which are quite far from each other which can form a disulfide bridge and push the folding in a particular direction,

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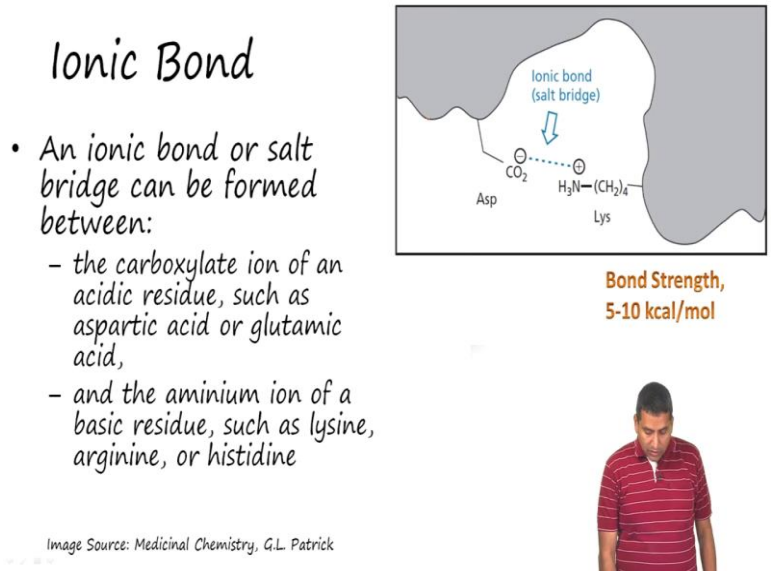

Ok.

The second important bond that is formed is actually an ionic bond, Ok. An ionic bond is nothing but an interaction between a positively charged species and a negatively charged species. This is also sometimes referred to as salt bridge and this occurs when, in neutral pH when you have a carboxylic acid, it usually exists as carboxylate,

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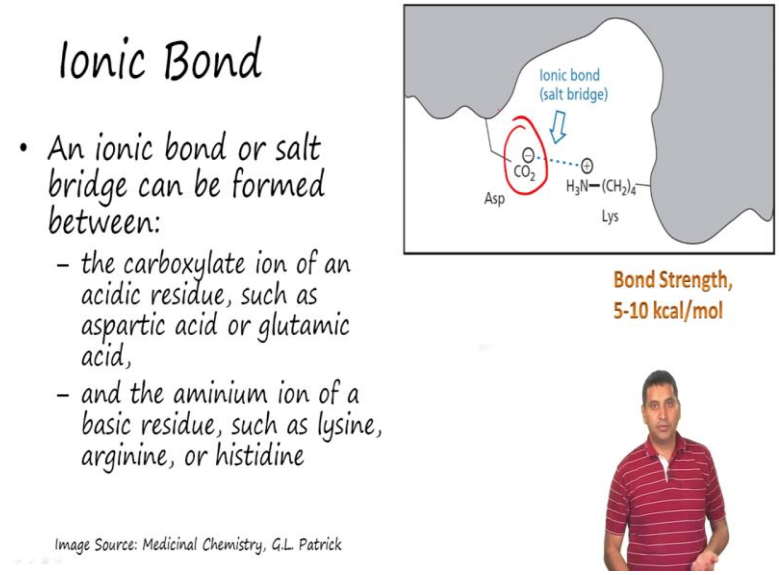

Ok. And if you have an amine, it exists as ammonium.

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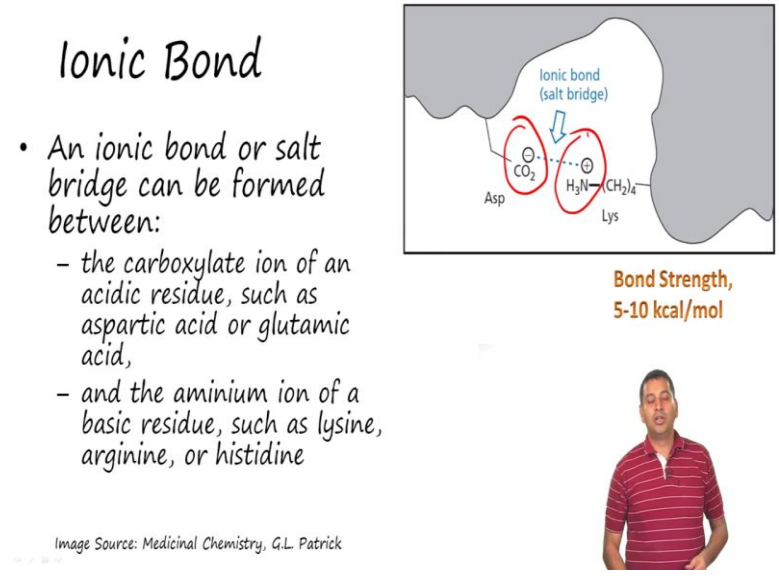

So now a positively charged ammonium species can interact favorably with a negatively charged carboxylate ion and this forms what is known as an ionic bond or a salt bridge. It is not a very strong bond.

The bond strength is somewhere

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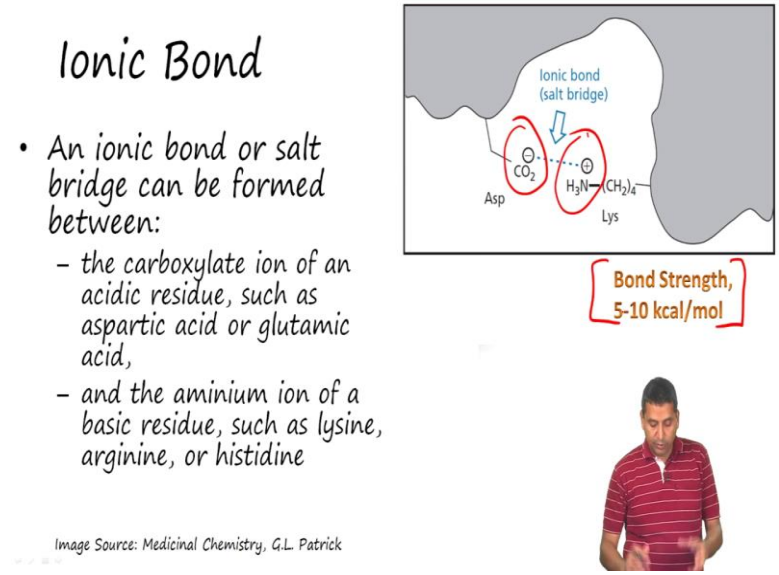

between 5 to 10 kilo calories per mole, and the amino acid residues that can interact in this are aspartic acid, glutamic acid which are,

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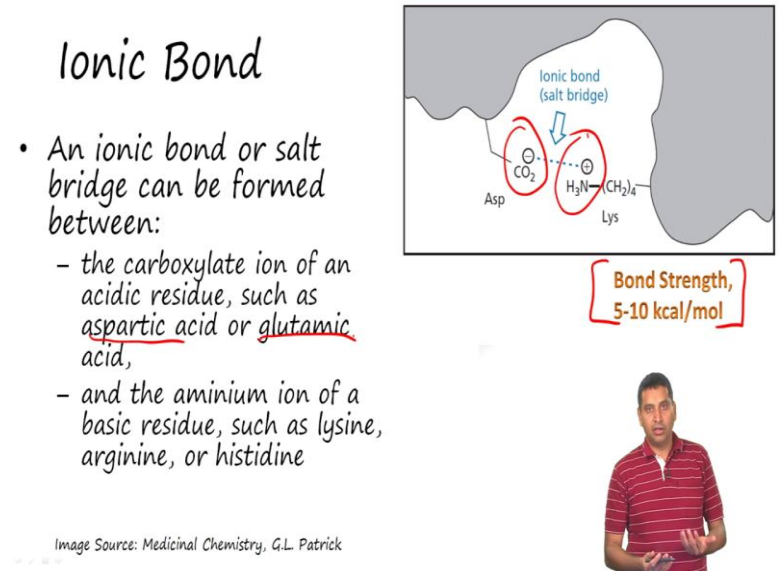

which will exist as carboxylates in neutral pH and the amines are lysine, arginine or histidine which can exist

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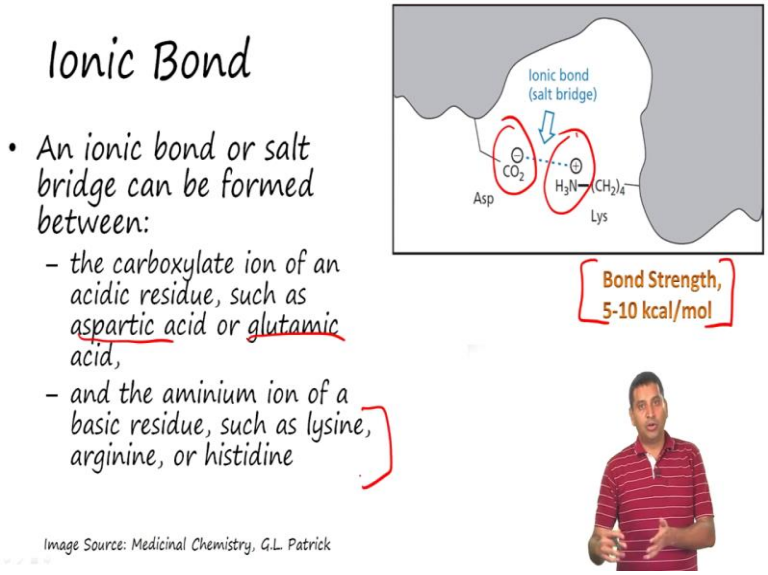

as ammonium in neutral pH, Ok.

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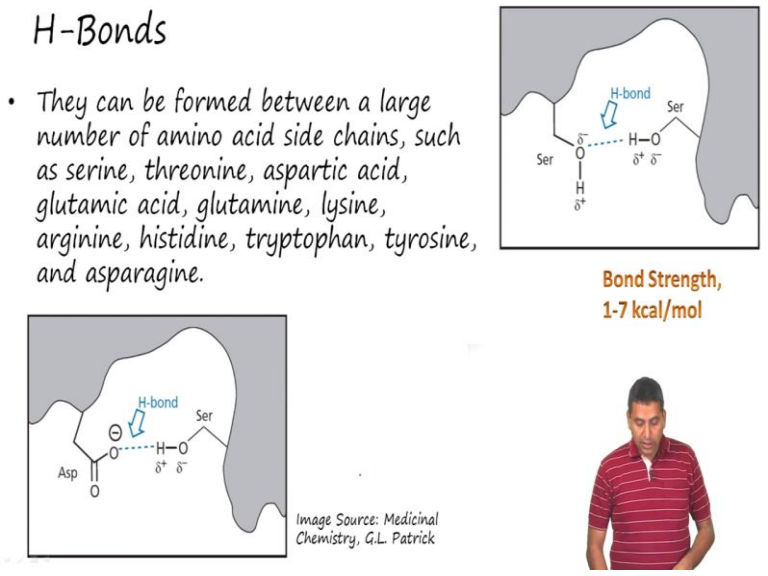

The next important interaction which we refer to earlier was hydrogen bonds. Hydrogen bonds occur when you have an electronegative atom between two hydrogens, Ok. So one of the electronegative atoms is bound covalently to hydrogen and

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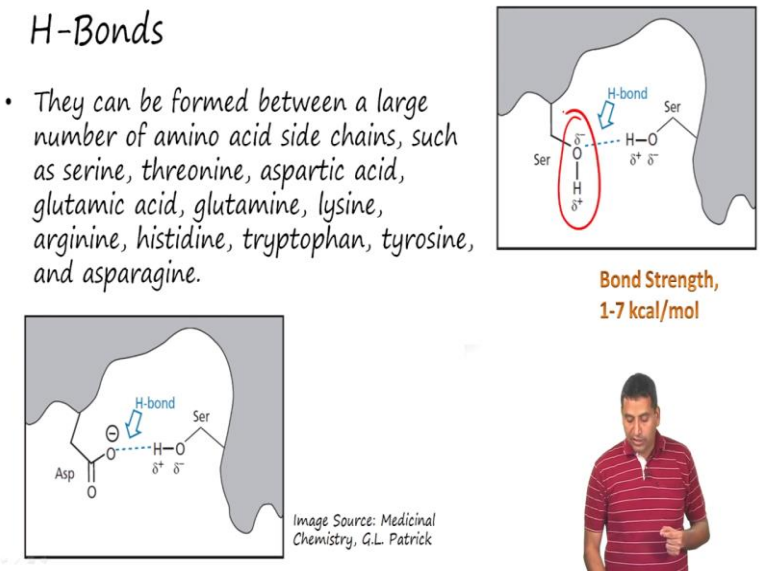

the other hydrogen is bound to the electronegative atom by a what is known as a hydrogen bond, Ok.

Now hydrogen bonds occur typically when you have highly, fairly electronegative atoms such as oxygen, nitrogen or fluorine and the bond strength of these somewhere range between 1 to 7

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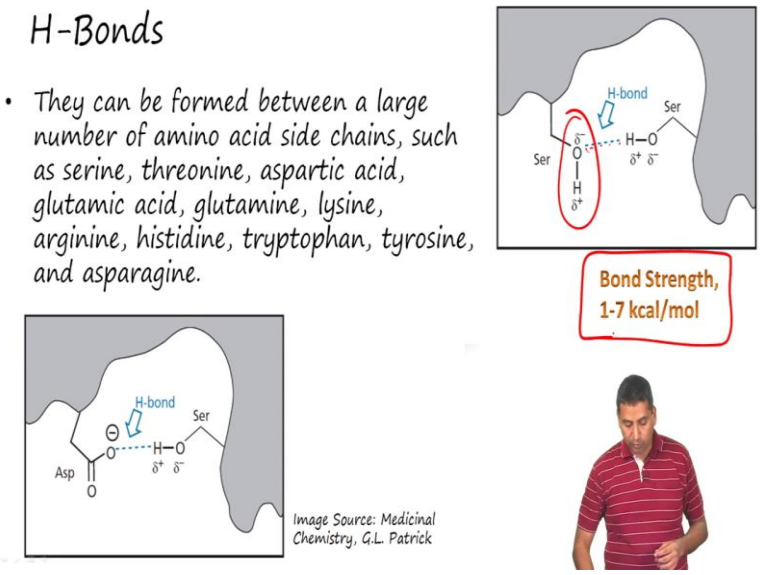

kilocalories per mole, Ok.

And if you look at the structures of amino acids, nearly all amino acids have oxygens and nitrogens in them and so you would expect a range of these sidechains to actually involve, to be involved in hydrogen bonding.

But there are amino acids which have in them a sidechain which can involve in hydrogen bonding. An example of those are serine which has a free alcohol as I showed in the right. And so serine can actually interact with

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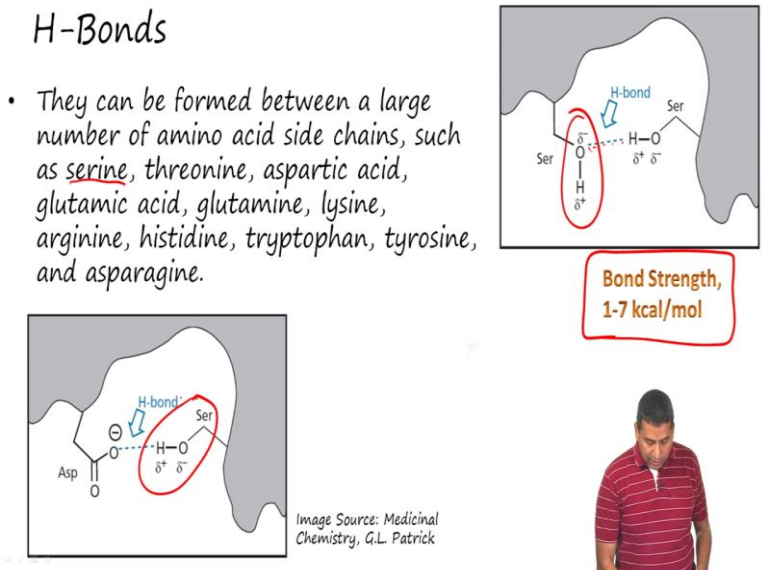

what we earlier referred to aspartic acid which exists as aspartate and it has a carboxylate ion.

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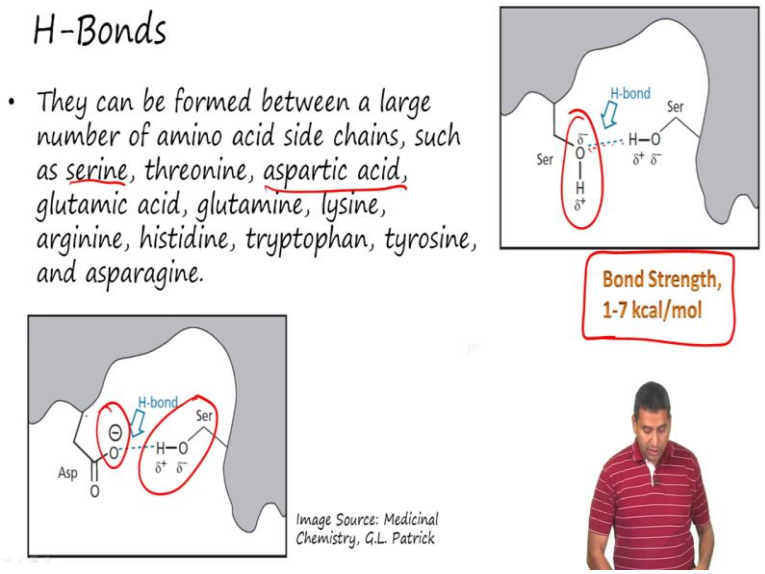

And this carboxylate ion can interact with serine OH very favorably and can form a very strong hydrogen bond, Ok. The other residues which can involve in hydrogen bonds are tryptophan, tyrosine, asparagine and

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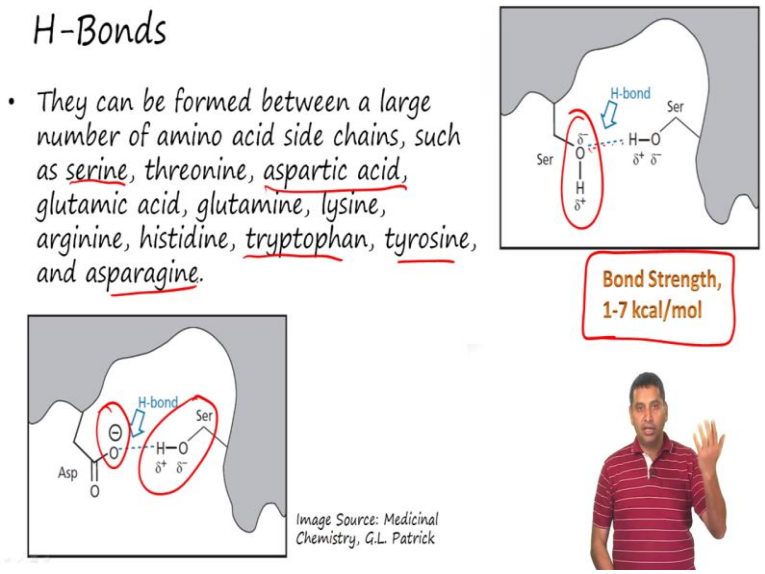

the other basic amino acids such as lysine and arginine and histidine,

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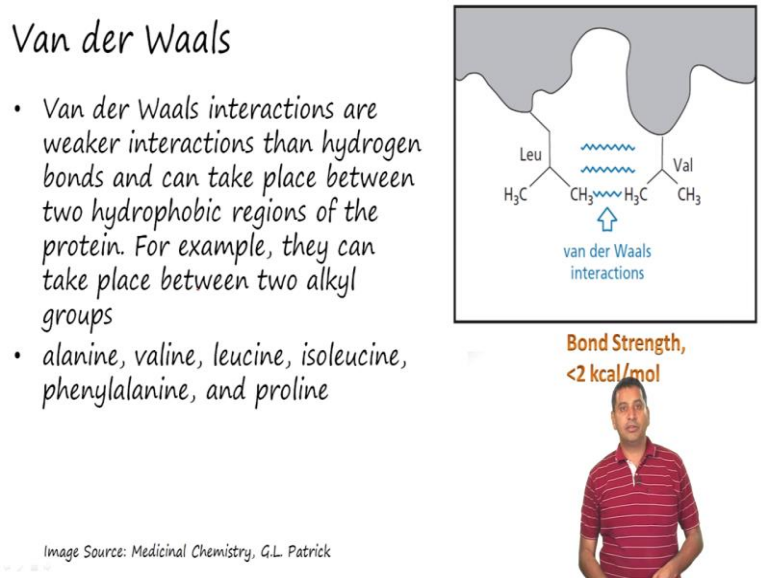

Ok.

The next important interaction is what is known as the vander Waal's interaction. vander Waal's interactions are very weak in nature and typically weaker than a hydrogen bond. And they occur between two hydrophobic regions in a protein, Ok.

So if you look at the structure of valine, it has an

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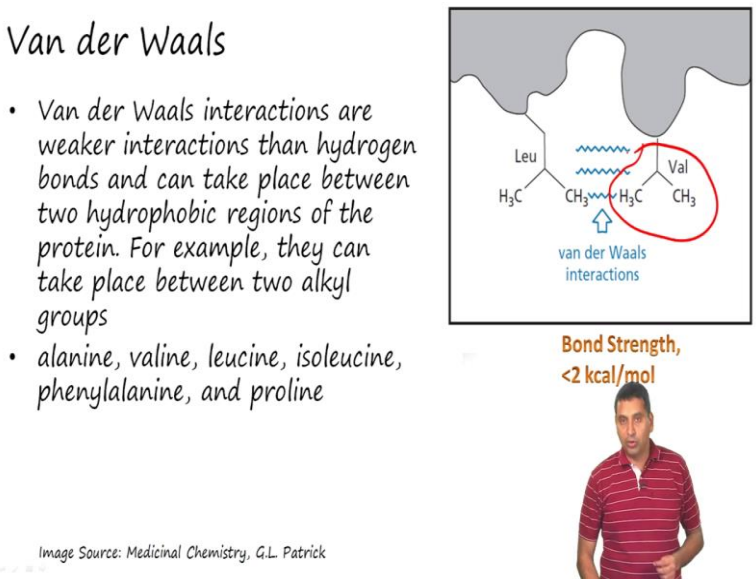

isopropyl group and it can interact with

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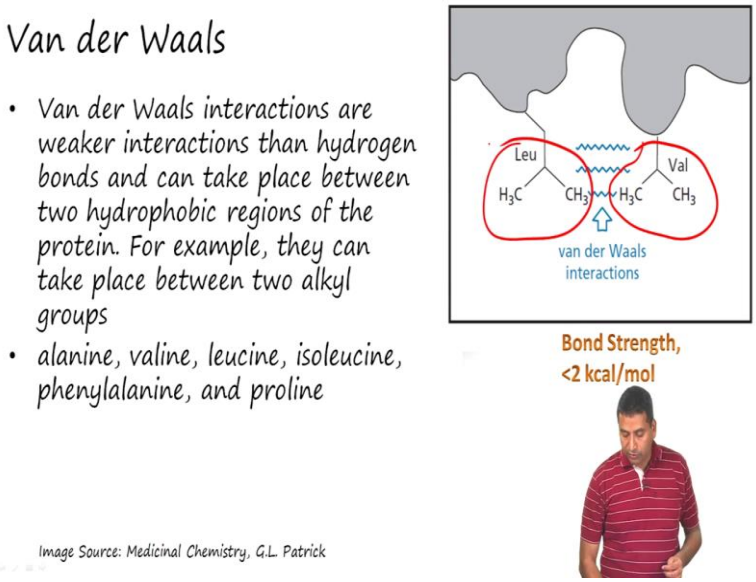

another leucine which also has a similar functional group. And these can weakly interact with each other through what is known as hydrophobic interactions, Ok.

And there are other amino acids which also can involve themselves in such vander Waal's interactions such as alanine, phenylalanine and proline.

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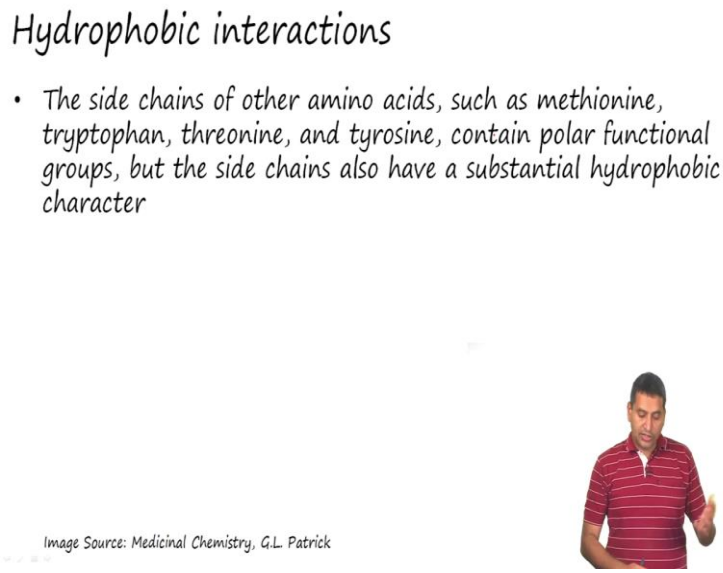

There are sidechains such as methionine, tryptophan, threonine and tyrosine which contain a polar functional group. But they also have some amount of hydrophobic character, Ok.

So depending

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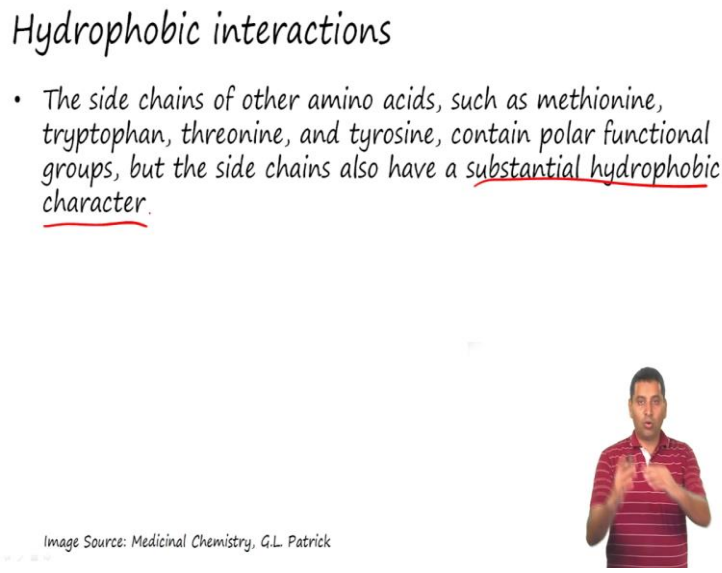

on what functional group is located near it, it can either go through some hydrophobic interactions, Ok. And as I mentioned earlier vander Waal's interactions are quite weak and their bond strengths are typically less than 2 kilocalories

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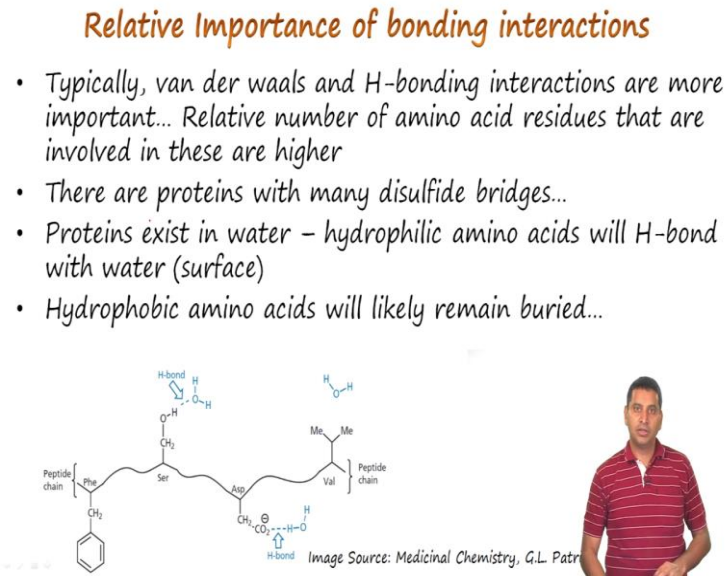

per mole, right.

So now let us look at the relative importance of these bonding interactions. So when you have two cysteine residues they can obviously form a covalent bond and, but these cysteine residues are not that often formed and there are of course many proteins which disulfide bridges but these are a very special case.

So vander Waal's interactions and hydrogen bonding interactions on the other hand are relatively more important because a larger number of amino acid derivatives can be involved in these interactions, Ok.

And as I mentioned earlier, since protein exists in water, the hydrophilic amino acids will

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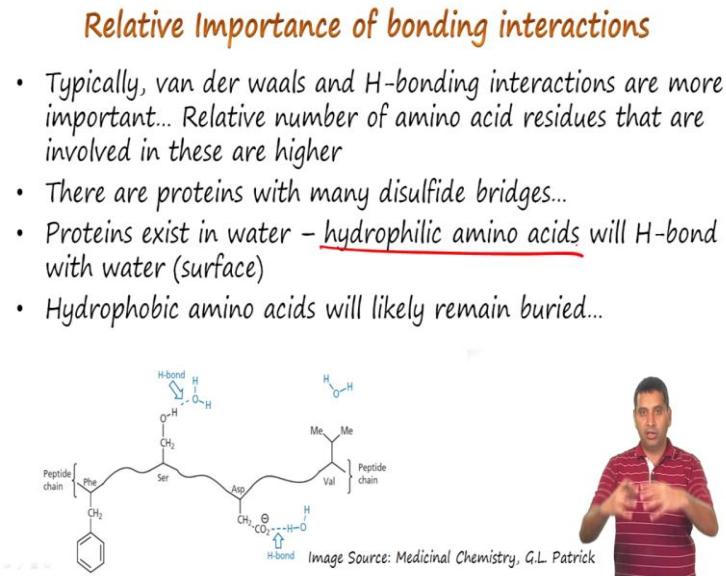

tend to be around the surface and will hydrogen bond with water and the hydrophobic amino acids would remain buried, Ok.

So here is an example of

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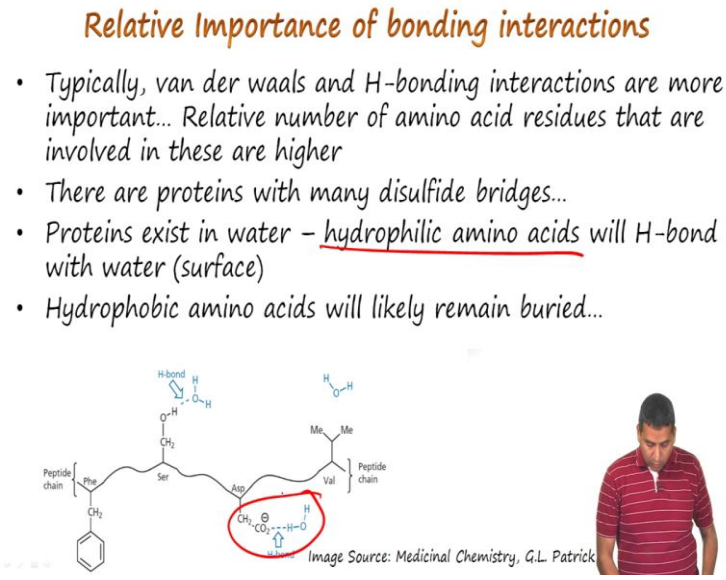

how something can happen on the surface while the peptide chain is folding and something that would probably end up

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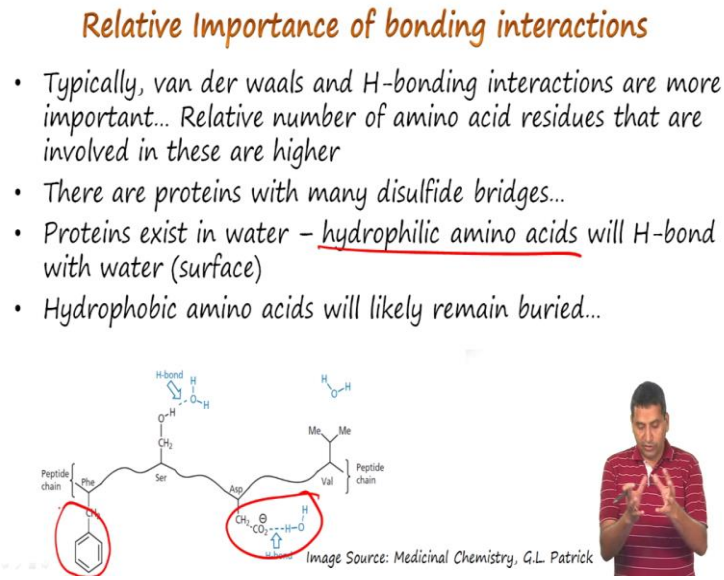

inside the core of the protein, Ok.

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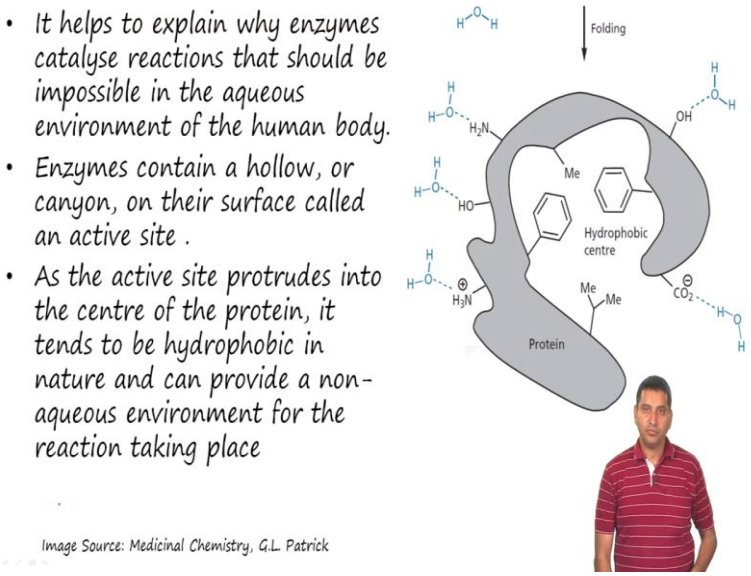

And it also helps explain how, why enzymes catalyze reactions.

Because these, some of these reactions are impossible in aqueous environment and so these hydrophobic domains which are present in the center, they provide an important area where catalysis of small molecules can occur, Ok.

So these enzymes fold up in such a way that they usually contain a canyon hollow area

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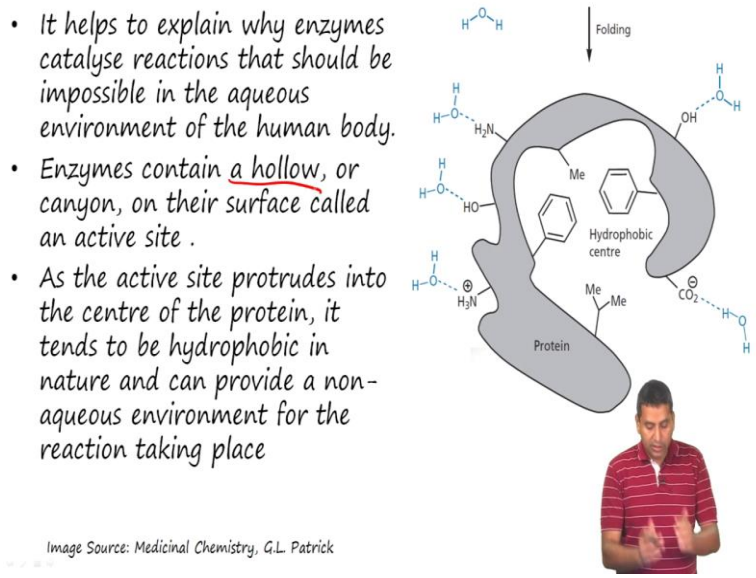

where, which is what we call as an active site, Ok. So imagine a spherical shaped protein and in the cavity of this, in there, there is a cavity which contains some hydrophobic nature wherein a non-aqueous environment is provided.

And now in this non-aqueous environment, small molecules can drift in and reactions can occur. And by small molecules I mean fairly hydrophobic molecules and those can go and bind into the surfaces.

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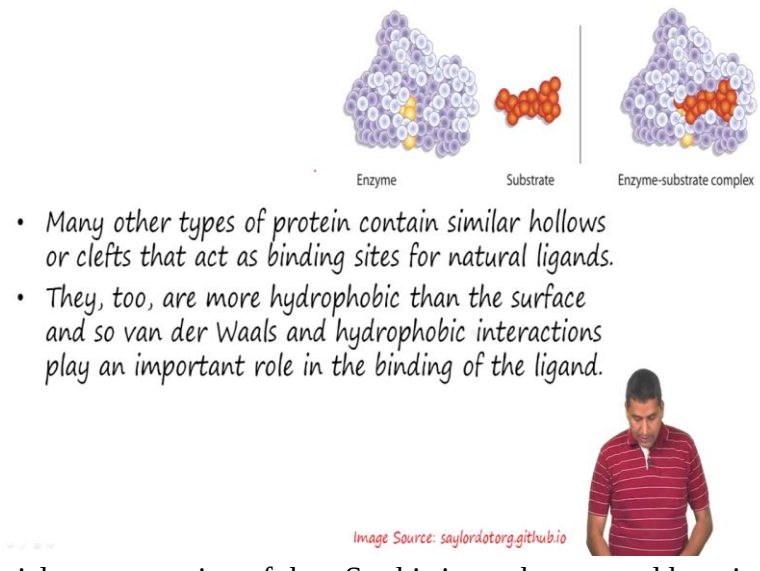

So here is a pictorial representation of that. So this is a substrate and here is

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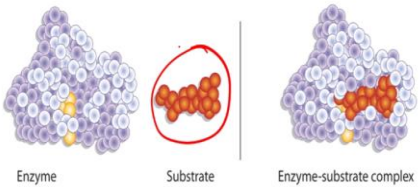

- Many other types of protein contain similar hollows or clefts that act as binding sites for natural ligands.
- They, too, are more hydrophobic than the surface and so van der Waals and hydrophobic interactions play an important role in the binding of the ligand.

Image Source: saylordotorg.github.io

on the left is an enzyme. And as you can see the enzyme has fairly polar nature on the top whereas

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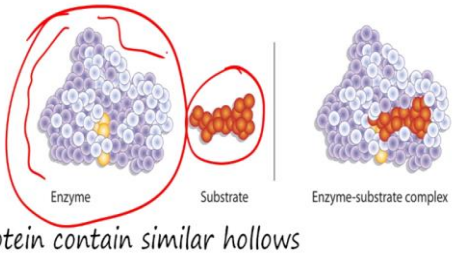

- Many other types of protein contain similar hollows or clefts that act as binding sites for natural ligands.
- They, too, are more hydrophobic than the surface and so van der Waals and hydrophobic interactions play an important role in the binding of the ligand.

Image Source: saylordotorg.github.io

it has an area where the

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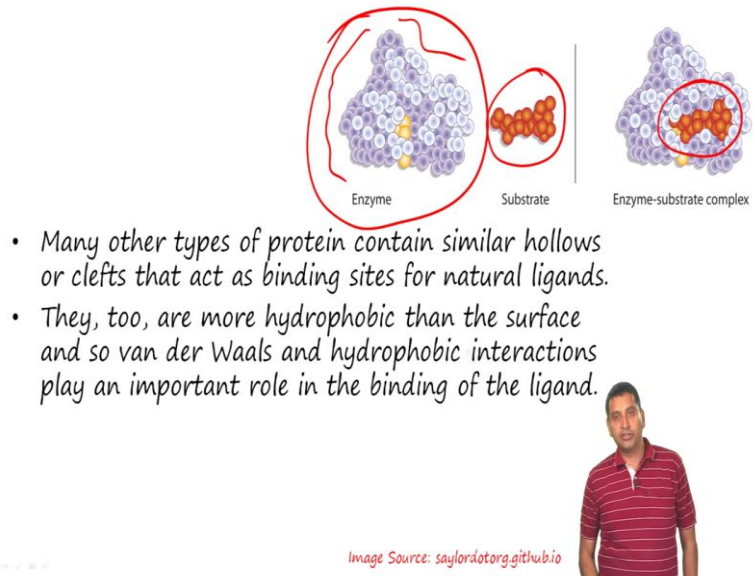

substrate can actually come and bind, Ok. So there are large number of proteins which have these similar hollow areas or clefts where binding of natural ligands or drugs can occur, Ok.

So here again the importance of vander Waal's interactions and hydrophobic interactions are important, Ok. Since the large number of drugs are actually hydrophobic in nature, so these interactions will play an important role in how the protein binds to the drug, Ok.

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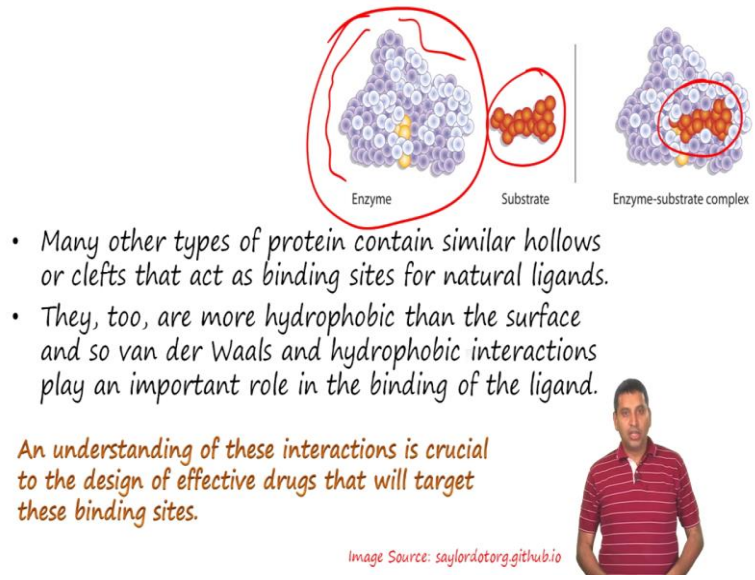

So therefore an understanding of these interactions is crucial to designing effective drugs that will target these binding sites, Ok.

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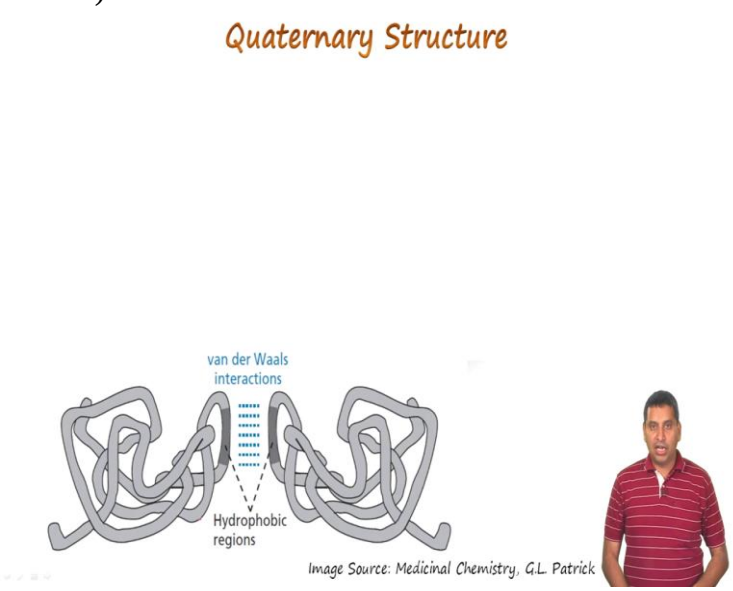

Lastly a protein can actually have also what is known as a quaternary structure. And so these quaternary structures are nothing but, when two proteins interact with one another

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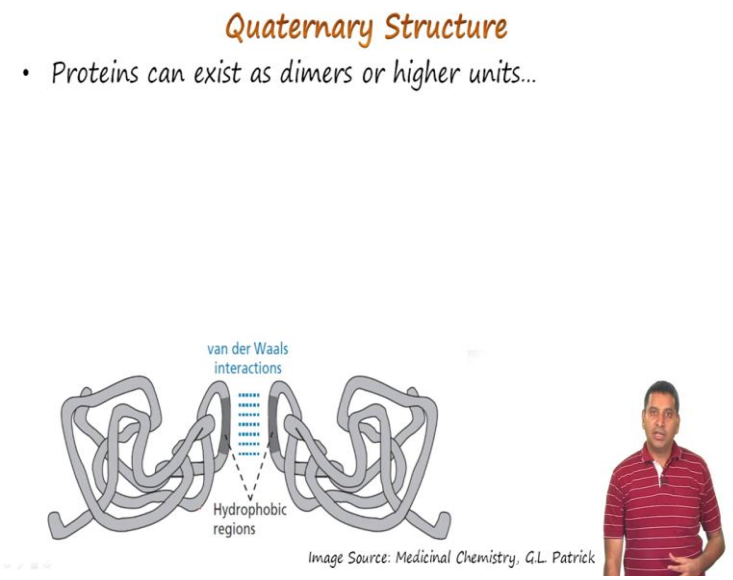

and they can exist as dimers or tetramers and so on, and these can, these

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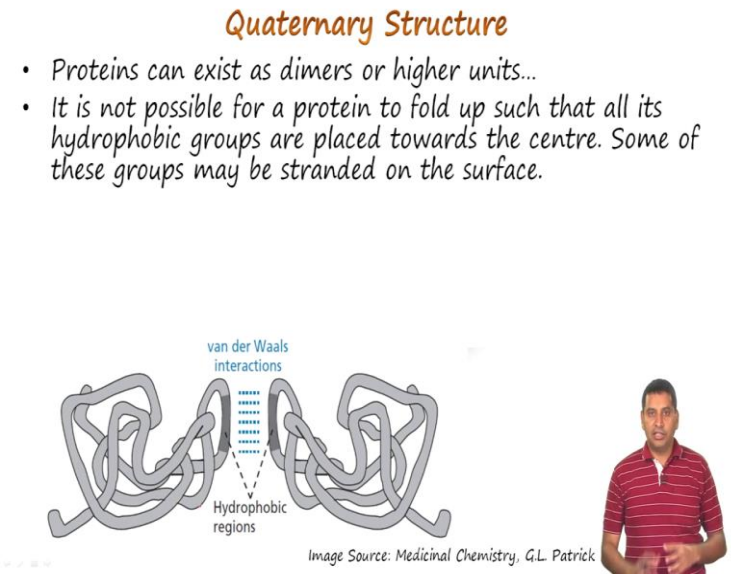

types of interactions can occur.

For example when you have regions of,

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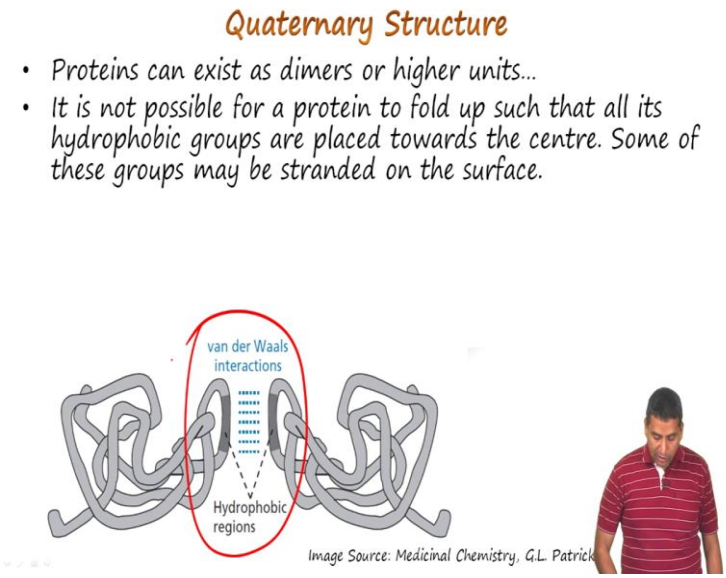

which are hydrophobic in nature and these can get together and they can help the protein to exist as a dimer, Ok.

This provides

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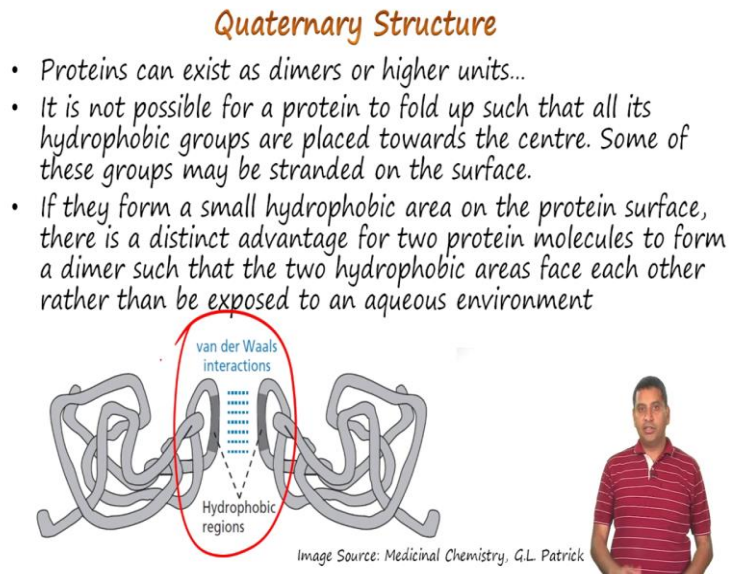

a distinct advantage for two protein molecules because hydrophobic areas face each other rather than be exposed to the aqueous environment, Ok. So

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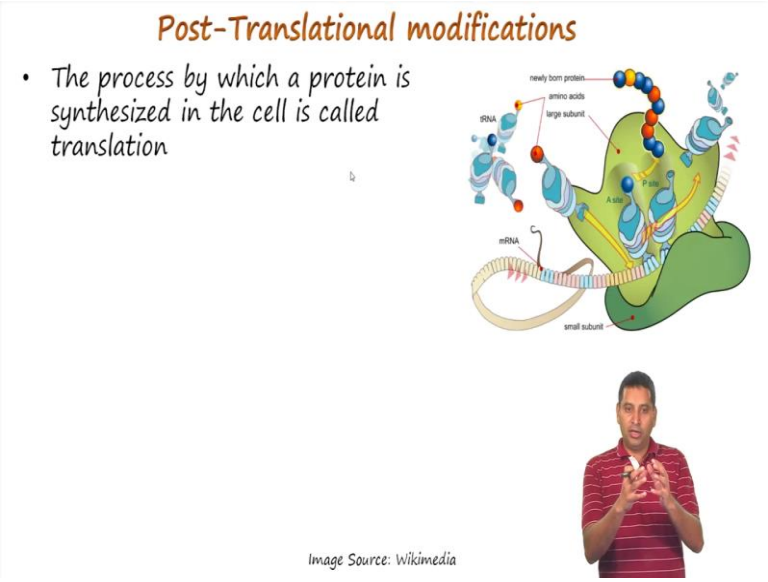

when proteins are synthesized, the initial code of the protein is provided by DNA and the DNA is converted to, the information is transferred to RNA and this process is called transcription.

And the process by which RNA, the information in RNA is actually converted to a protein sequence is called translation, Ok. So after the translation the peptide sequence that is produced then folds up and produces a finally folded protein.

But after translation there can also be modifications which are called as post-translational modifications. And these post-translations are, can assume importance in a number of disease stages. We will look at some of these examples later,

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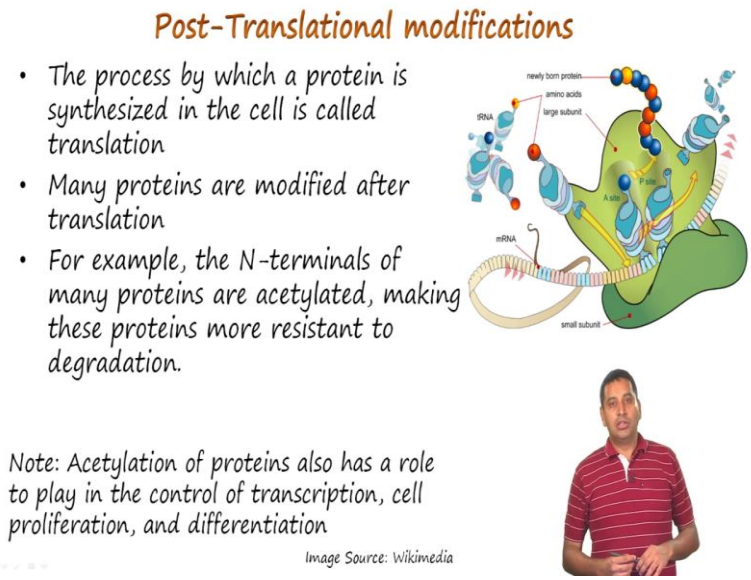

so some of these proteins are modified after translation.

And so for example the N-terminal

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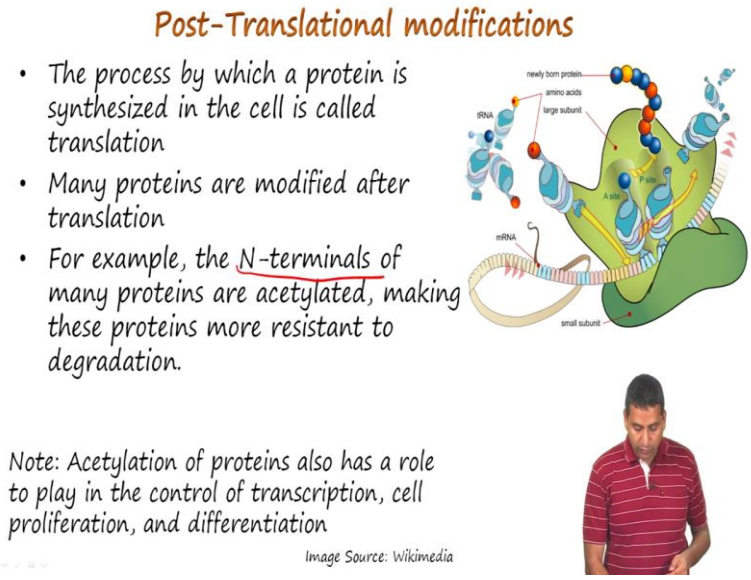

of many proteins are acetylated, Ok and so this acetylation makes these proteins more resistant to degradation by enzymes and so therefore it is a very useful post-translation modification to occur. Acetylation of proteins also has an important role in the control of transcription and of course in cell proliferation and differentiation.

Now

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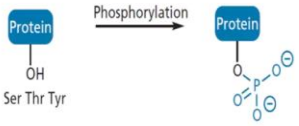

Image Source: Wikimedia

the next post-translational modification which can occurs on alcohol

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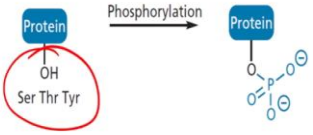

Image Source: Wikimedia

containing amino acid residue such as serine, threonine and tyrosine, Ok. So this phosphorylation is a very

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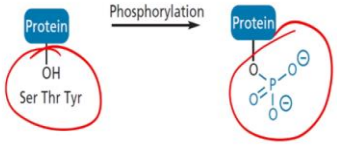

Image Source: Wikimedia

common signaling mechanism and it is also a very important post-translational modification. And

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- Th e serine, threonine, and tyrosine residues of many proteins are phosphorylated
- This plays an important role in signalling pathways within the cell

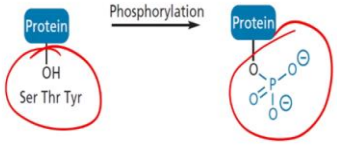

Image Source: Wikimedia

a number of signaling mechanisms are actually mediated by phosphorylation. We look at examples of this much later in the course.

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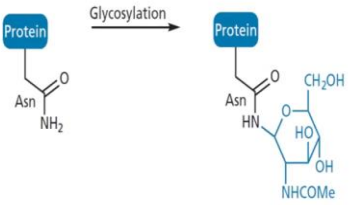

Image Source: Medicinal Chemistry, G.L. Patrick

So the next type of post-translational modification is basically glycosylation where

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- Many of the proteins present on the surface of cells are linked to carbohydrates through asparagine residues.

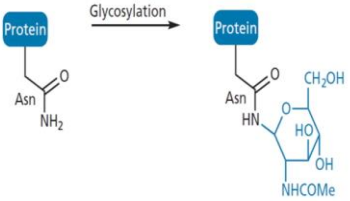

Image Source: Medicinal Chemistry, G.L. Patrick

a protein is modified with a sugar

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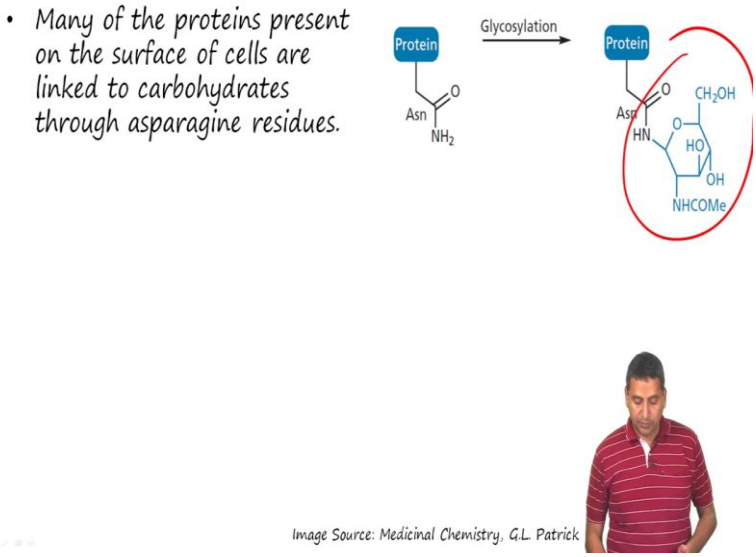

unit, Ok and these sugars are present on the surface of cells

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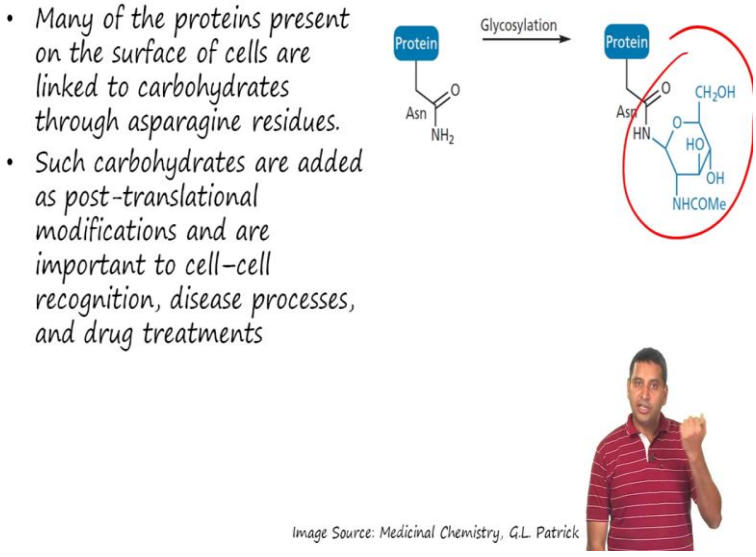

and they are really important when it comes to cell-cell recognition.

And as a consequence they are also key players in many diseases and also

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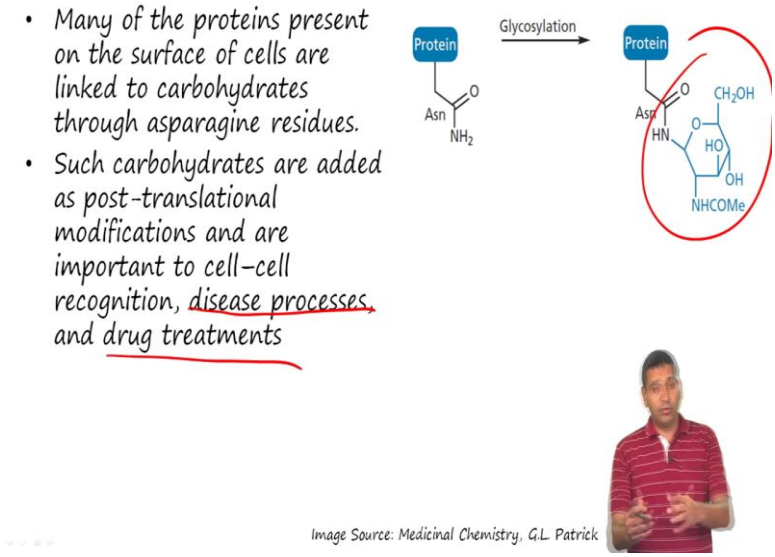

during treatment with a drug this help with determining the outcome of how the drug interacts with a cell.