Medicinal Chemistry
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Anti-Bacterial Agents-2

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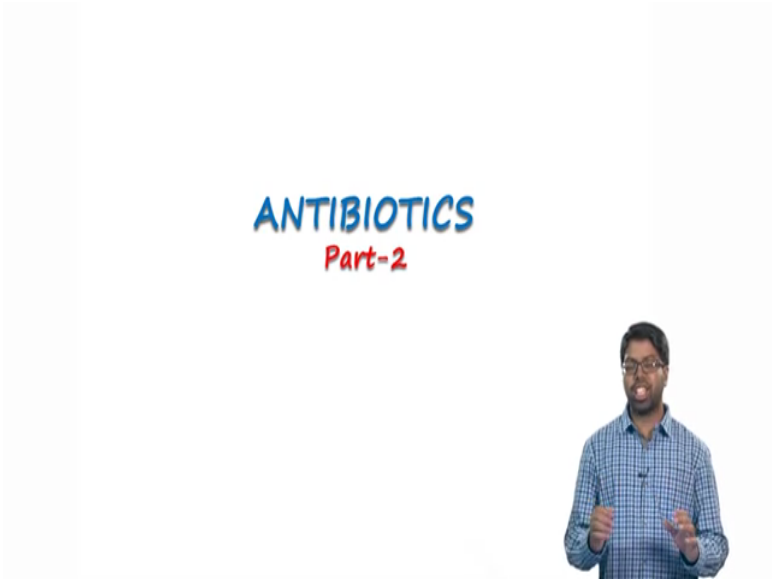

In the last lecture we talked about the antibiotics that either inhibit the cell wall biosynthesis or disrupt a cytoplasmic membrane. So today we will continue our discussion on antibiotics and in this lecture we will focus on antibiotics which inhibit the nucleic acid biosynthesis or protein biosynthesis or metabolic pathways.

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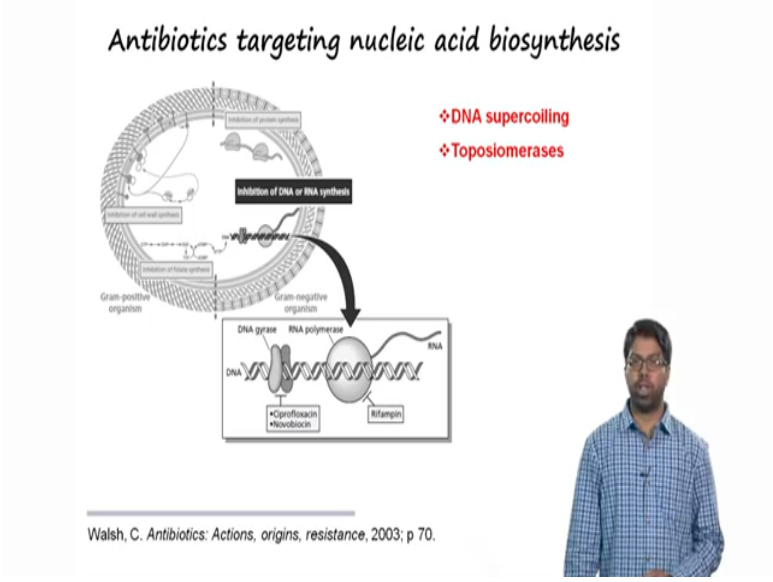

Let us start with the antibiotics that target in nucleic acid biosynthesis, but before we jump into this aspect let me make you familiar with two important concepts one is DNA supercoiling and the other one is topoisomerases.

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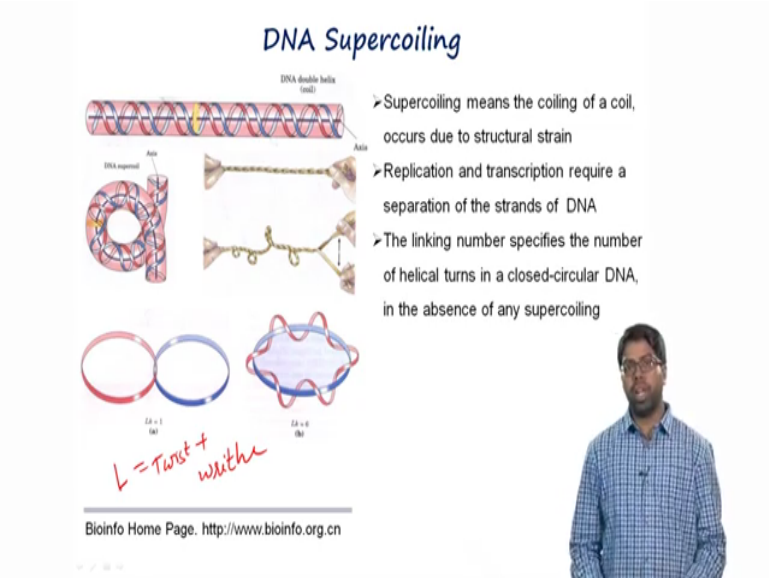

As you know that DNA is two helical strands that have wrapped around each other. So let us say this is the axis about which the two strands are wrapped around each other, now this is called coiling, you can think of telephone cord as an example of this coiling. But in case of replication and transcription process these two strands must be separated and during that process it can induce strain in the DNA which can lead to over twisting or under bounding and this is called as super coiling which literally means the coiling of a coil.

Now you can think of this super coiling in this way let us say if we are going to bend this axis at which this axis may lead to supercoiling. Let me make you familiar with this supercoiling concept by another term called as linking number. So linking number is a number of times that one strand passes over the other. So linking number is the sum of twist plus writhe, twist is the number of helical turns whereas right is the number of super helical turns, you can perhaps think twist as passing over of strands within the helix itself, whereas writhe as passing over strands when one helix crosses over the other.

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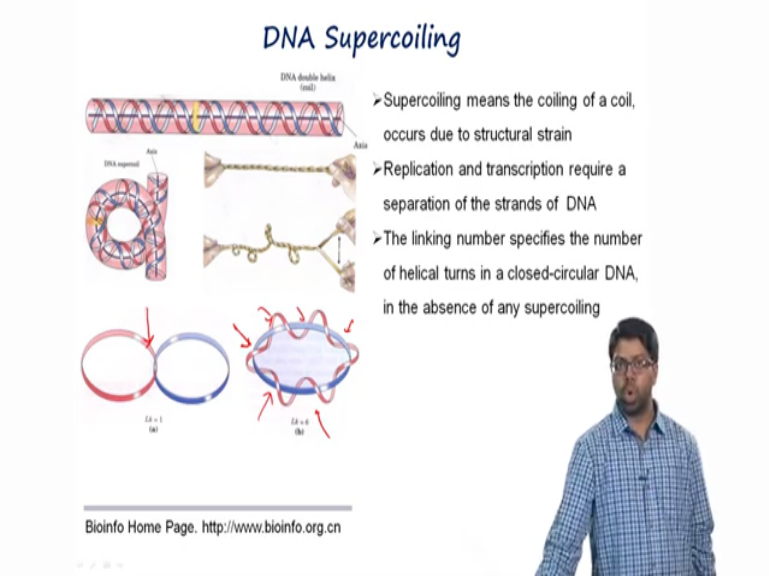

For example here the twist is 1, therefore a linking number is also 1 because it does not have any writhe, there is no super helical turn here. The same thing goes here in this case as well, so here the twist is 1, then 2, then 3, then 4, then 5, then 6 so here the linking number is 6 because they are 6 number of twist, but there is no writhe here.

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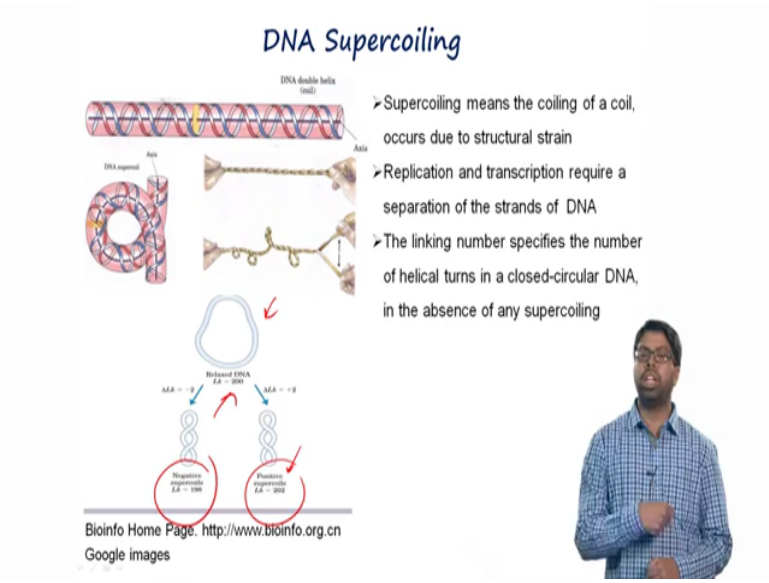

This is the example of relaxed DNA, what happens if the linking number is changed if the linking number of DNA is greater than the linking number of relaxed state of DNA then it is called positively super coiled and if your linking number of a DNA is less than the linking number of the relaxed DNA then it is called negatively super coiled. In other terms you can

think of negatively super coiled DNA as removing of the twist and introducing the writhe in the opposite direction.

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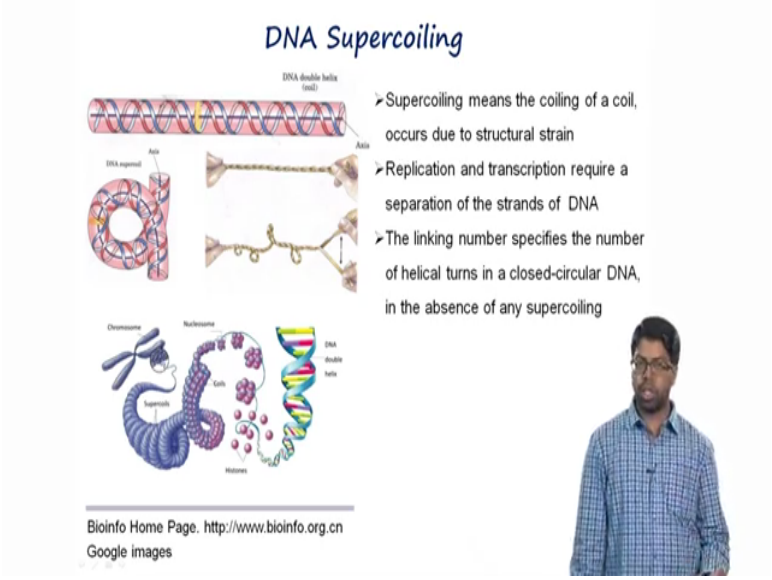

Now you may ask what is the importance of this DNA supercoiling? So this helps the DNA to get packaged in a very organized manner, here the DNA wraps around this histone proteins which forms this nucleosomes which are further coiled and super coil to give chromatin which is then condensed to give this chromosomes which are involved in the cell division process. Therefore, supercoiling is very essential. Now let me explain you this in another way let us say DNA is in a form of a circle, now the two new circles have wrapped around each other, no way they are going to go to the (())(3:16) cells during the process of replication because there is a mathematical theorem saying that if a tool circles have wrapped around each other they cannot be separated unless you cut them.

Because mathematically it is impossible to separate the two strands, so what does the cell do? Cell cuts it, because even cells cannot violate the theorem.

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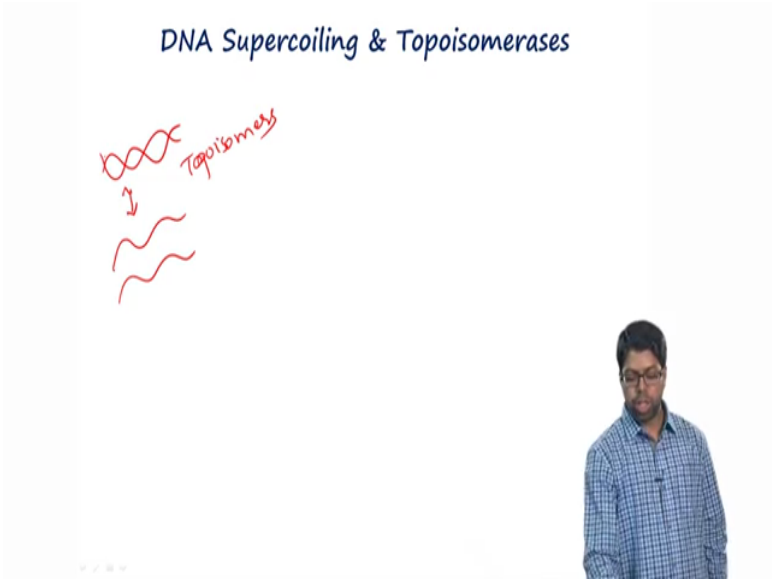

This is the job that is guided by this enzyme called as topoisomerase. Let us say I have a DNA in which the both these strands have wrapped around each other and another DNA in which both the strands are separated from each other, are they chemically different? No they are chemically same, but they are topologically different. In one case they are topologically entangled with each other, in another case they are topologically separated. So they are called as topoisomerase and it turns out there is an enzyme that does this job and they are called as topoisomerases.

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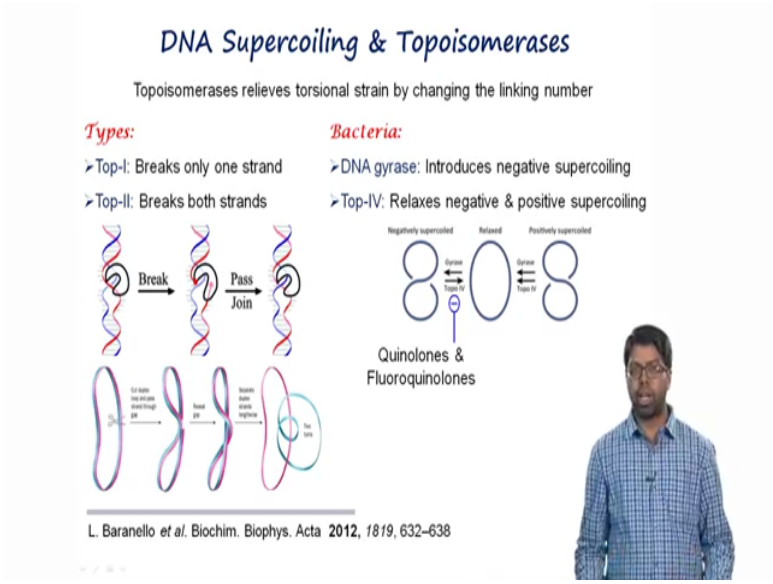

There are two kinds of topoisomerases one is type 1 topoisomerases which cuts only one strand and type 2 topoisomerases which cuts both the strands. So this topoisomerase cuts one

or both the strands, grabs it to end, passes over the other side and joins it. So this process of cut and paste cut and paste is continued until both the strands are disentangle from each other. As we are mostly focused on the bacteria let us see what kind of topoisomerase bacteria have.

It turns out the bacteria has type 2 topoisomerases which can be further classified into DNA gyrase and topoisomerase 4. Now DNA gyrase introduces negative supercoiling, whereas topoisomerase 4 relaxes both negative as well as positive supercoiling. And these enzymes are the targets for the antibiotics such as quinolones and fluoroquinolones.

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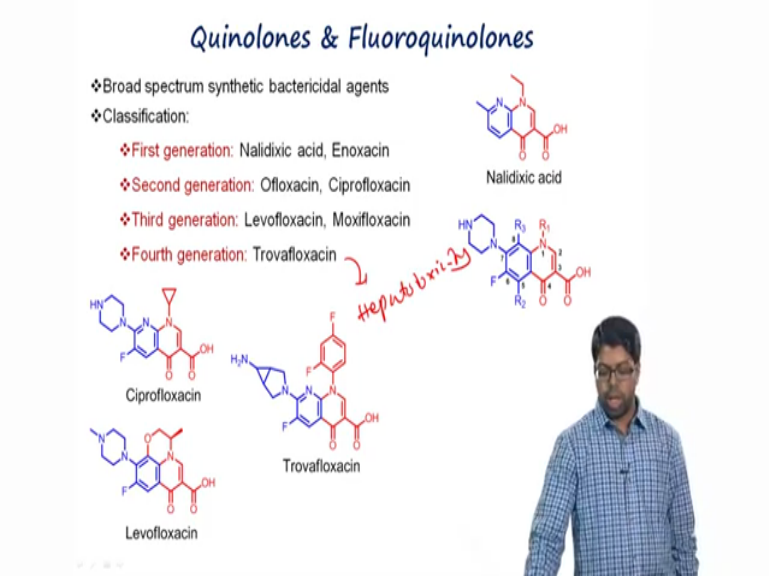

So here these quinolones and fluoroquinolones are broad spectrum antibiotics, again they are (())(5:00) in nature because they are going to inhibit this DNA gyrase in topoisomerase 4 which inhibit the replication of bacteria and that is how the bacteria is going to kill. These fluoroquinolones can be further classified into different generations. For example the first generation fluoroquinolones are highly effective against (())(5:15) organisms such as (()) (5:17) as the generation of the fluoroquinolones progresses they become more and more effective against gram positive organisms as well.

For example in case fourth generation cephalosporin like trovafloxacin it is effective against gram negative as well as gram positive organisms. But unfortunately this drug has been withdrawn from the market because of a severe hepatotoxicity.

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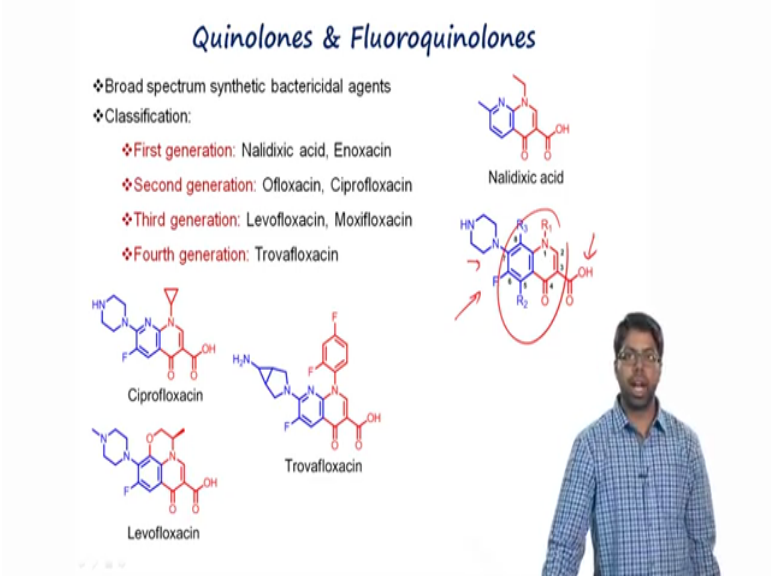

These are some of these structures of the fluoroquinolones and if you see all of them have a common cold structure which is a quinolone moiety, there is a carboxylic acid that is present at the third position, there is a fluorine that is present at the eighth position and a piperazine moiety or any amine based substituent at a seventh position and all these substances are essential for inhibiting this DNA gyrase and topoisomerase 4.

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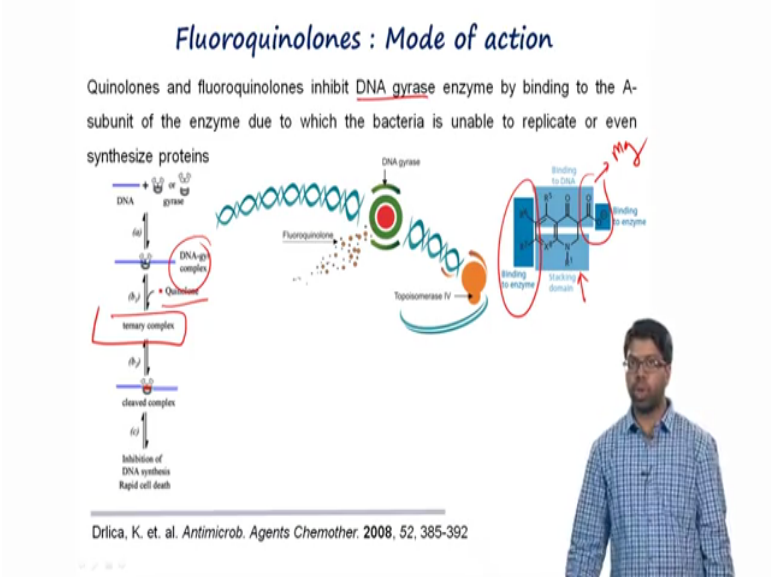

Now let us have a quick look how this fluoroquinolones inhibit this DNA gyrase or topoisomerase 4 enzyme. So once the DNA is prepared for the replication process this DNA gyrase enzyme comes into picture (())(6:13) comes into picture and forms a complex called

as DNA gyrase complex. Now this is attacked by these we quinolones or fluoroquinolones and that leads to formation of this ternary complex.

Now here in case of this ternary complex because of the quinolones scaffold it can have a proper stacking interactions with the DNA and because of this carboxylic acid it is involved in a (())(6:35) with metal called as magnesium present in the active site of this DNA gyrase enzyme (())(6:41) enzyme and its substituents at (6th) 7th position is also involved in having a proper interaction with the enzyme and that is how they are going to inhibit this either DNA gyrase or topoisomerase 4 because of the inhibition of these enzymes the bacteria are unable to replicate and that relates to killing of the bacterium.

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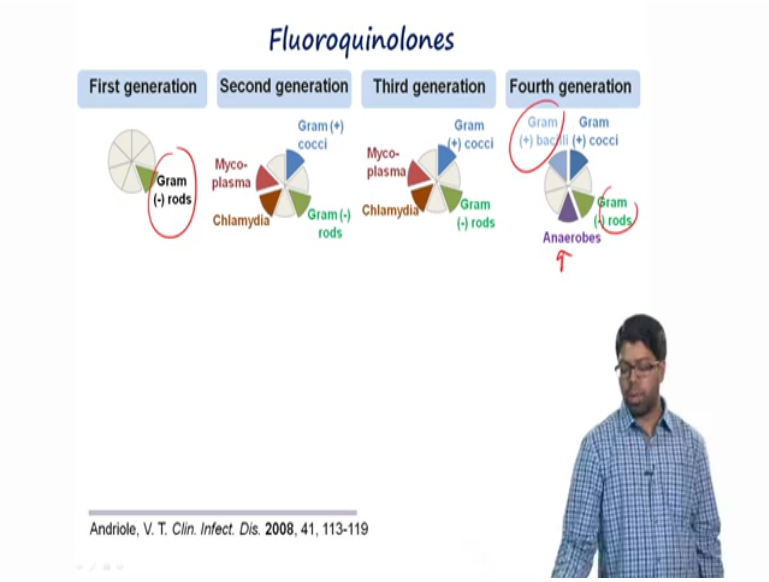

Again as I already mentioned you as a generation of fluoroquinolones progresses they became more and more effective against gram-positive organisms as well. For example here the first generation cephalosporins are highly effective against gram-negative organisms but when you move from first generation to fourth generation they are effective against gram-positive as well as gram negative organisms even they are effective against anaerobic microorganisms too.

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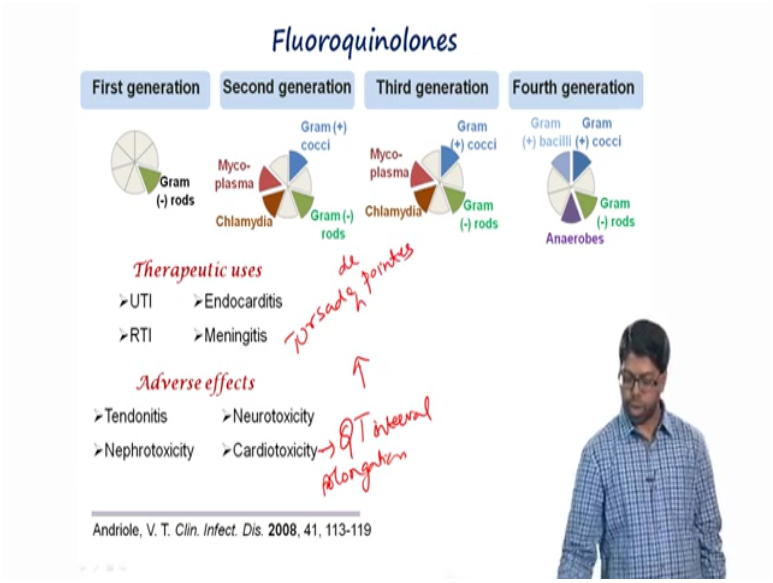

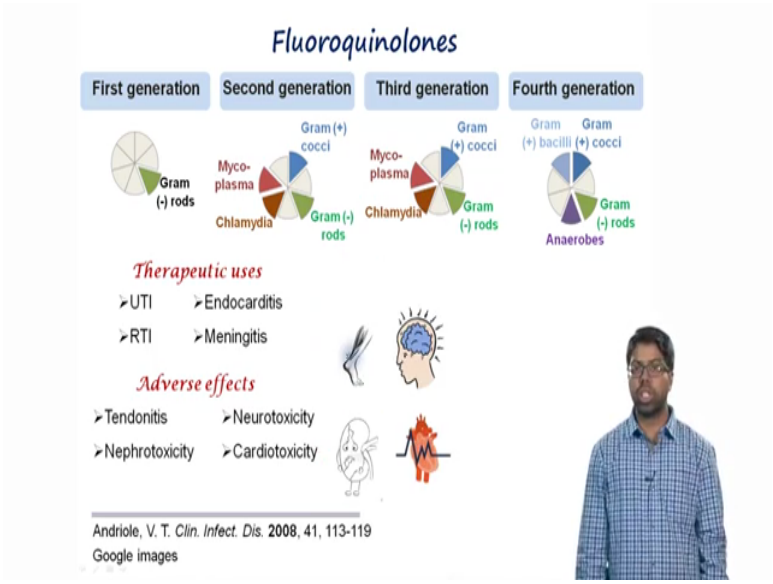

These fluoroquinolones are mostly prescribed for urinary tract infections, respiratory tract infections, endocarditis and meningitis, but these fluoroquinolones are associated with major side effects such as tendinitis which is associated with the inflammation of tendons and it is also associated with neurotoxicity that can damage your nervous system, fluoroquinolones are also associated with nephrotoxicity which leads to a damage of the small subunits that are present inside a kidney called as nephrons, fluoroquinolones are also associated with the serious cardiotoxic effect which leads to QT interval prolongation and this can lead to a pathological condition called as Torsades de pointes that can lead to pathological condition called as Torsades de pointes.

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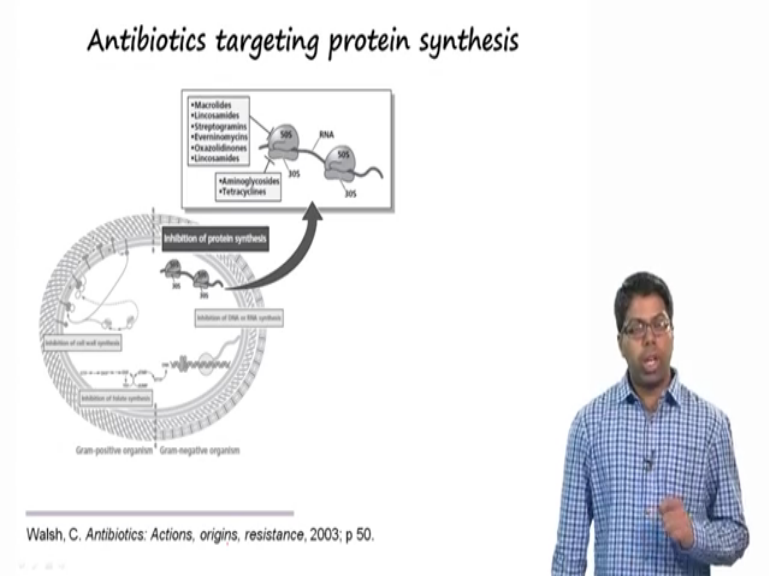

So before going into the specifics of how the antibiotics inhibit protein synthesis, let us briefly review how did ribosomes are involved in this process.

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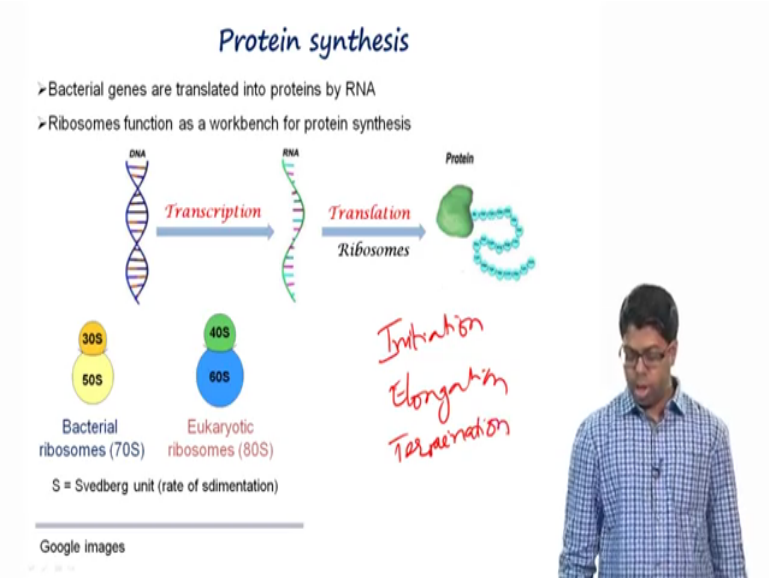

Bacterial genes are translated into proteins by RNA the type of RNA that carries the genetic information from the DNA is called mRNA or messenger RNA and a protein synthesizing machine to which the message is carried to is called ribosomes, bacteria have 70S ribosomes, whereas eukaryotes like humans have 80S ribosomes. Let us take a closer look at the bacterial 70S ribosome it is composed of two subunits one smaller 30S subunit and a larger 50S subunit.

The smaller 30S subunit is a one in which mRNA feeds and in larger 50S subunit carries (()) (8:53) catalytic function, yes I know 30 plus 50 is equal to 80, not 70 but this is not a math mistake here the S stands for Swedberg unit, using the Swedberg unit to measure ribosomes means that things do not always add up perfectly because the weights of sedimentation are not additive like the molecular weights are.

So the protein synthesis in bacteria can be divided into three stages the first stage is called initiation phase, the second phase is called as the elongation phase and the third phase is called termination phase.

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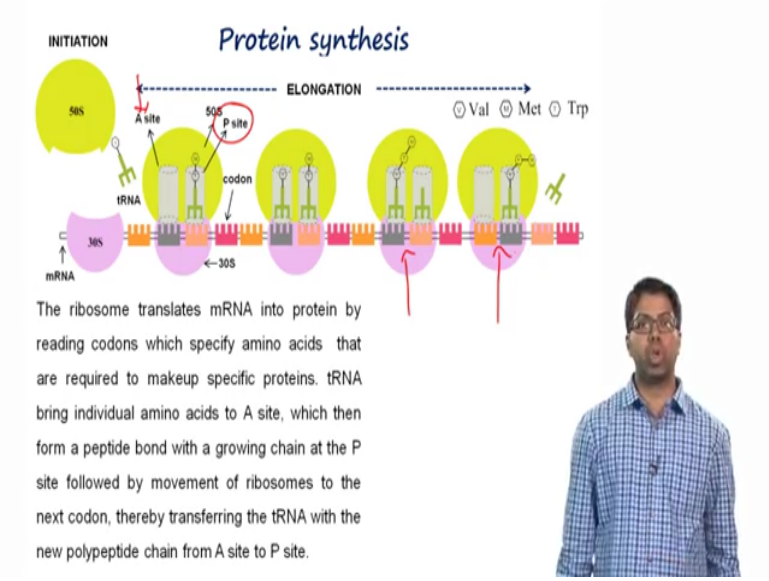

Initiation of the protein synthesis begins with the binding of formyl methionine tRNA to the start codon that is present in the mRNA already bound to 30S subunit this is followed by recruitment of 50S subunit which then leads to formation of a complex called 70S, the ribosomes translates the mRNA into proteins by reading the nucleotide triplets known as codons which specify amino acids that are required to make up for specific proteins.

The transfer RNA or tRNA for short brings the individual amino acid to the amino acyl site that is also called as A site which then forms a peptide bond with the growing polypeptide chain present in the peptidyl site also called as P site. So here you can see that tRNA brings an amino acid called valine which then forms a peptide bond with the peptide that is already present in a P site, so here it forms a peptide bond with the tryptophan and this is how the peptide bond has been formed.

Then the MT tRNA has been released from the ribosome and the ribosome moves from one codon to the next codon, thereby transferring the tRNA with a growing polypeptide chain from A site to P site and this process is continued until the ribosome encounters a stop codon such as UAA, UAG and UGA that signals the end for protein synthesis.

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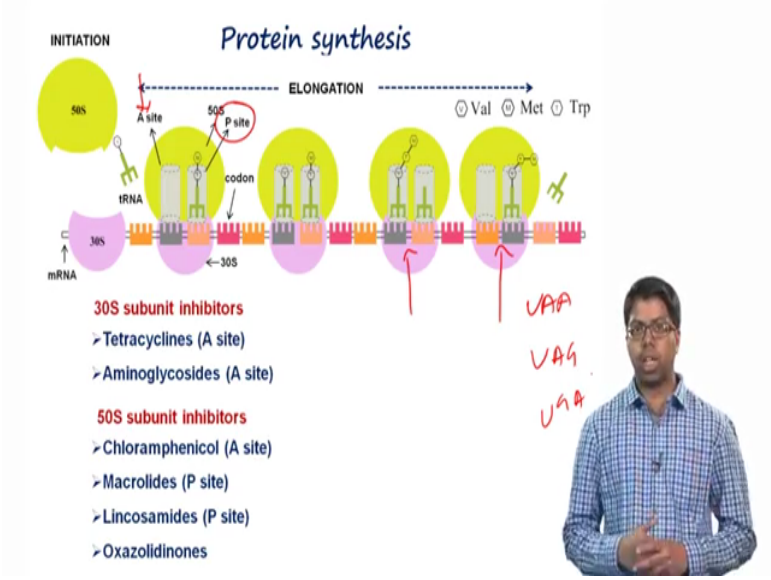

So now you may have guessed that antibiotic act at a specific site on a ribosome and inhibit the protein synthesis. So the antibiotics that inhibit the protein synthesis can be categorized into two classes one is 30S subunit inhibitors that include tetracyclines and aminoglycosides and the second one is 50S subunit inhibitors which include chloramphenicol, macrolides, lincosamides and oxazolidinones, this lecture will focus on a detailed discussion on each of these class of antibiotics.

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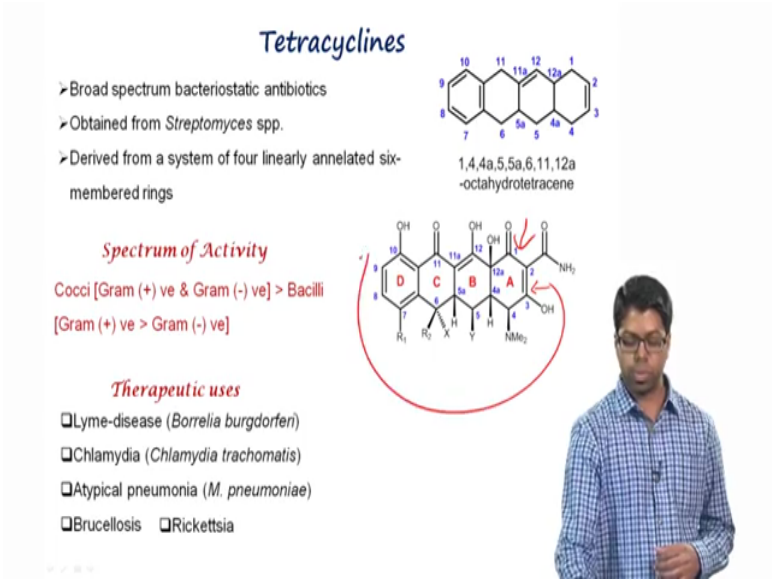

Let us start with tetracyclines, tetracyclines are broad-spectrum antibiotics which are obtained from Streptomyces species and they exhibit bacteriostatic effect. So these tetracyclines are widely prescribed form of antibiotic after penicillins, generally they are highly effective against aerobic gram-positive as well as gram-negative organisms but have very limited activity against (())(11:45), tetracyclines are also effective against a bacterium called as Borrelia burgdorferi a bacterium that is a causative agent for Lyme disease that is characterized by fever, rash, flu like symptoms and joint pain, etc.

Tetracyclines are also good against chlamydia trachomatis a causative agent for a sexually transmitted disease called as chlamydia, they are also good against mycoplasma pneumoniae which is a causative agent for atypical pneumonia that is characterized by lower respiratory tract infections. Tetracyclines are also good against Brucella and rickettsia genes bacterium. Let us have a look at the structure of tetracyclines, tetracycline contains a nucleus that is derived from octahydrotetracene which consists of four annulated six (())(12:27), due to the presence of four rings they are called as tetracyclines.

Here the rings are labelled as A, B, C and D the way it is numbered is from here from 1 to 12 all the tetracyclines have a very similar structure.

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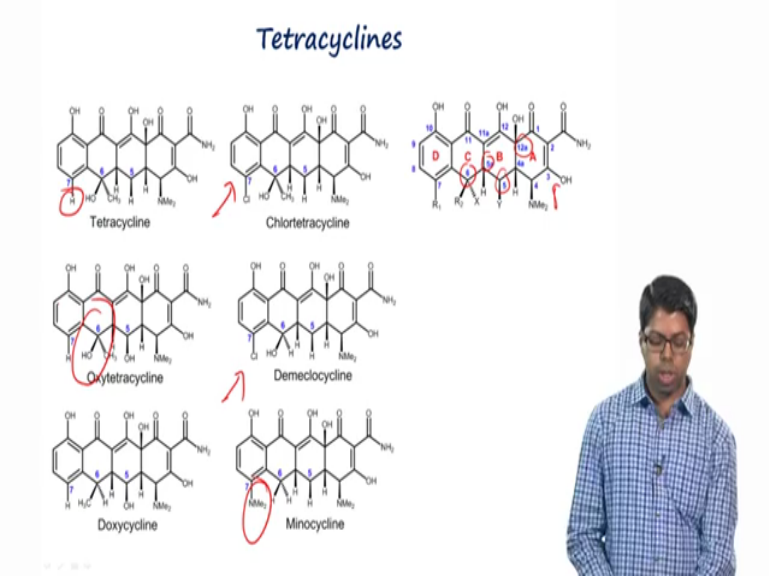

Here the carbon atoms 4 4a, 5 5a 6 and 12a are potentially chiral depending on a substitution. Just by a little change in the substituents at different positions in the basic structure of ring we can get different compounds. For example tetracycline has an hydrogen atom at 7 position just by a mere substituting this hydrogen by an electron withdrawing group like chlorine gives chlortetracycline and demeclocycline, likewise substituting this hydrogen by an electron (())(13:15) group like dimethyl amino functional group gives minocycline. Oxytetracycline has a hydroxyl group at a six position which is absent in case of doxycycline.

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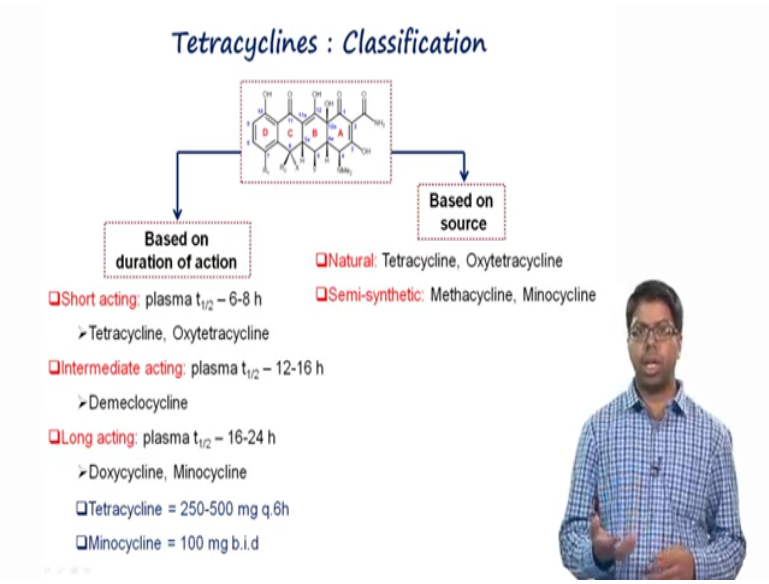

Now these tetracyclines can be classified based on a source it is obtained from. For example natural tetracyclines include tetracycline and oxytetracycline, whereas methacycline and

minocycline are semi-synthetically derived tetracyclines, tetracyclines are also classified based on a duration of action meaning how long they are going to reside in our body, what is their plasma half-life? So this classification is merely on the basis of Pharmacokinetic parameters.

So based on a duration of action tetracyclines can be classified into three classes short-acting tetracyclines, intermediate acting tetracyclines and long acting tetracyclines. Short acting tetracyclines include antibiotics such as tetracycline and oxytetracycline with an average plasma half-life of six to eight hours, demeclocycline is an intermediate acting tetracycline with an average plasma half-life of 12 to 16 hours. Likewise doxycycline, a minocycline are long-acting tetracyclines with an average plasma half-life of 16 to 24 hours.

The tetracyclines and oxytetracyclines have a very short half-life therefore they are administered every four or six times to a patient. Since long-acting tetracyclines are well absorbed with a higher plasma half-life with an average from 18 to 24 hours they can be administered twice a day. Here is a clinical example tetracycline is given at a dosage frequency of 250 to 500 mg every six hours daily to a patient, whereas minocycline is given at a dosage frequency of 100 mg twice a day because it has a longer half-life then the corresponding tetracycline.

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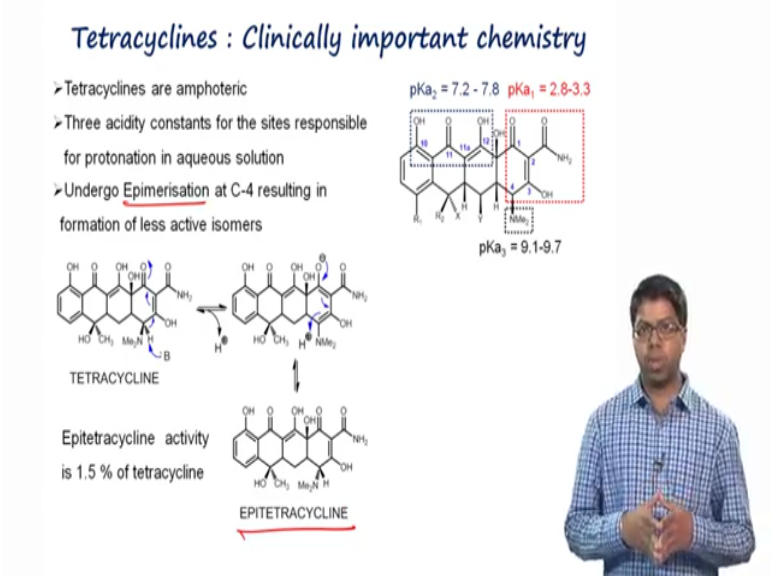

Let us dwell into the chemistry of tetracyclines a bit more, tetracyclines are amphoteric compounds meaning they can form salt with either an acid or a base and they have three acidity constants which are responsible for protonation in aqueous solutions. So this is first

pKa, this is the pKa2, and this one pKa3. Here the conjugated keto-enol system at c1 to c3 is acidic with an average pKa of 3, the diameter lamina functional group at c4 position is basic with an average pKa of 9, likewise the conjugated phenolic enol system at c10 to c12 is neutral with an average pKa of 7.

Another interesting property of these tetracyclines is that they undergo epimerisation, so this epimerisation occurs in a solutions of intermediate pH so here the tetracyclines are converted into inactive isomers called as epitetracyclines and these epimers exist in equilibrium. The important fact is this epitetracyclines have very less activity when compared to tetracyclines, to be precise epimers have only 1.5 percent activity of the tetracyclinesm, due to these reasons tetracyclines need to be freshly prepared and used in order to gain desired maximum activity.

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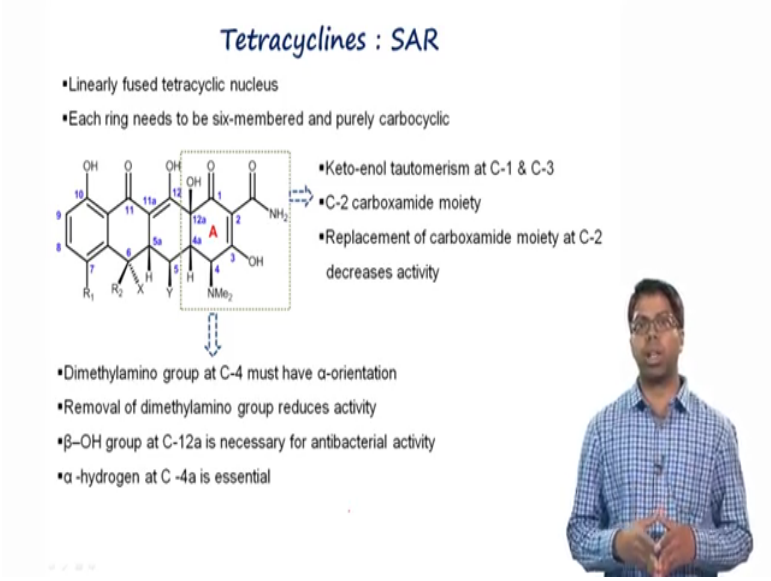

Let us have a look at this SAR of tetracyclines, so it the characteristic structural feature for a tetracycline is (())(16:11) 6 member rings and each ring needs to be carbocyclic meaning you cannot introduce any heteroatom in this ring, otherwise it will lead to loss of activity. The conjugated keto-enol tautomerism at c1 to c3 is essential, the carboxamide functionality at c2 position is also essential, replacement of this carboxamide functionality by any other functional groups such as aldehyde and nitrile will abolish activity, the dimethyl amino functional group at c4 position is also essential removal of dimethyl amino group reduces the activity, the hydrogen and hydroxyl group at c4a and c12a in alpha and beta orientation is also prerequisite for the antibacterial activity of tetracyclines.

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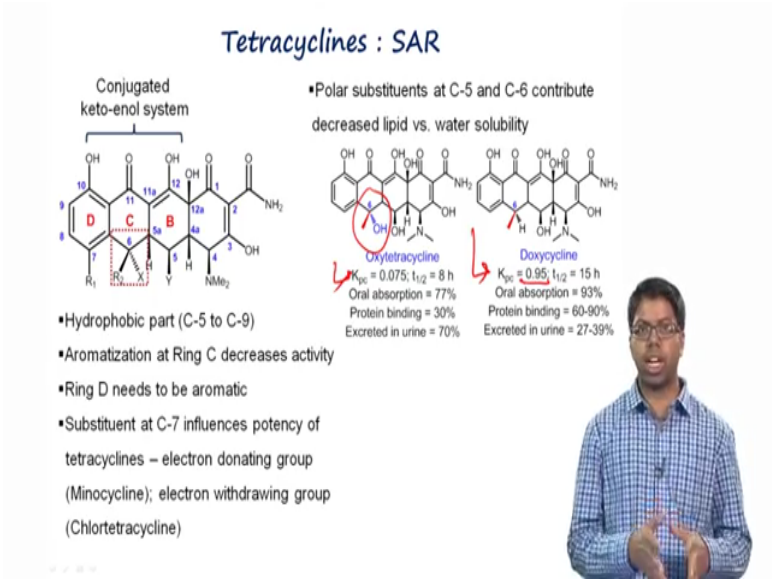

The conjugated keto-enol system at c10 to c12 is also essential, likewise the D ring needs to be aromatic, there is an influence of substance that are present at a 7th position in this D ring. Here electron donating groups like dimethyl amino functional group in case of minocycline enhances to activity, likewise electron withdrawing groups like chlorine also enhances to activity as observed in case of chlortetracycline. Therefore, chlortetracycline and minocycline are more potent tetracycline antibiotics than unsubstituted tetracyclines.

Aromatization at ring C will also lead to inactivity of this class of antibiotics, there is an influence of substituent at a 6th position. Let me explain you this property by taking an example that compares between oxytetracycline and doxycycline, oxytetracycline has a hydroxyl group that is present at the 6th position which is absent in case of from doxycycline, this doxycycline can also be called as 6-deoxytetracycline, 6-deoxytetracycline poses important chemical and pharmacokinetic advantages over their corresponding 6 oxy counterparts, removal of hydroxyl group at the 6th position dramatically changes the solubility profile of the tetracyclines and this effect is significantly seen in terms of octanol water partition coefficient.

Oxytetracycline has a hydroxyl group at the 6th version because of that it is more hydrophilic and it has a lower octonal water partition coefficient, whereas doxycycline is lipophilic which is observed in terms of higher octonal water partition coefficient which is around 0.95, due to this lipophilic character for doxycycline they are well absorbed they exhibit high plasma protein binding, they have a higher volume of distribution and they have lower rate of

elimination resulting in a longer half-life of this class of antibiotics. Therefore, doxycycline has a longer half-life and it is a long-acting tetracycline then corresponding 6 oxytetracycline.

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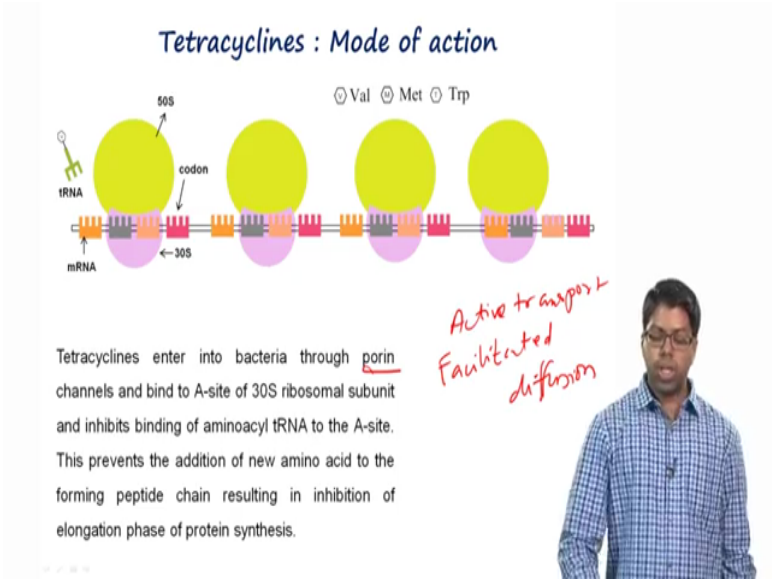

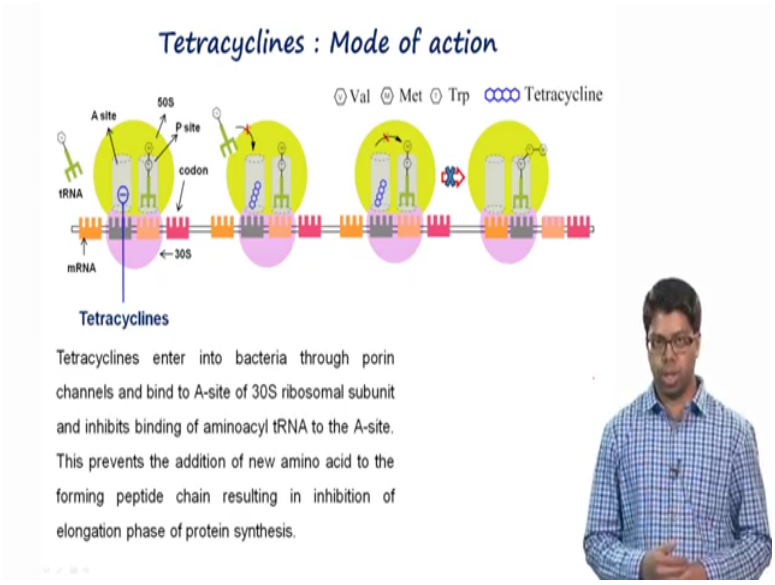

So tetracyclines enter into the bacteria through porins by active transport or by facilitated diffusion, once the enter they bind to the a site of the 30S ribosomal subunit and inhibits the binding of aminoacyl-tRNA to the A site. This prevents the addition of new amino acid to the forming peptide chain and this results in inhibition of elongation phase of the protein synthesis. So to remember you the protein synthesis is divided into initiation phase and elongation phase, tetracycline inhibits the elongation phase of protein synthesis not the initiation phase.

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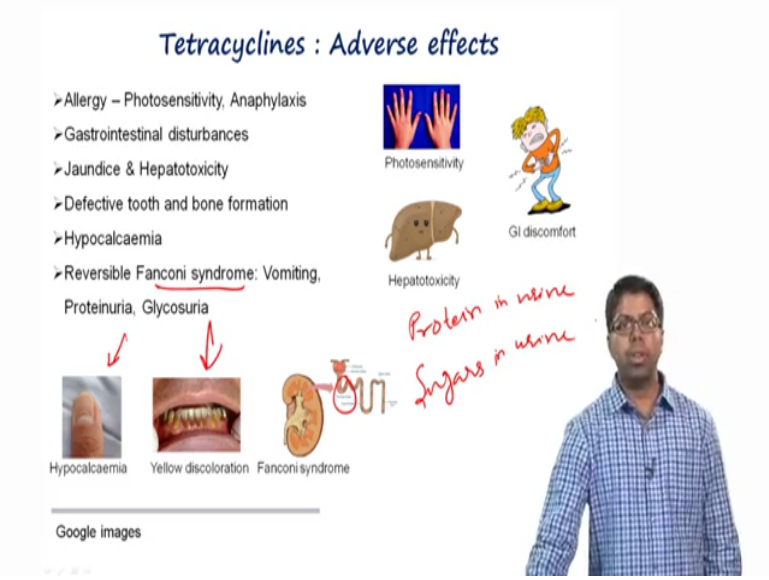

As you are familiar with all drugs are associated with one or other side effect, tetracyclines also have some side effects such as photo sensitivity, gastrointestinal disturbances and hepatotoxicity that refers to damage to a liver cells. Tetracyclines have a strong affinity for calcium and can accumulate in developing tooth and bones leading to discoloration of tooth and inhibition of bone growth. As a result there is a deficiency of calcium called as hypocalcemia.

Tetracyclines are also associated with the red side effect called as fanconi syndrome that is associated with a dysfunction of proximal tubules of the kidney. So this syndrome is characterized by symptoms such as vomiting, proteinuria and glycosuria. Proteinuria is a condition which is characterized by excess amount of protein in urine, likewise glycosuria is which is a condition which is characterized by abnormal amount of sugars in urine. Thankfully this syndrome is reversible meaning that these effects will fade with time once the administration of tetracycline is stopped.

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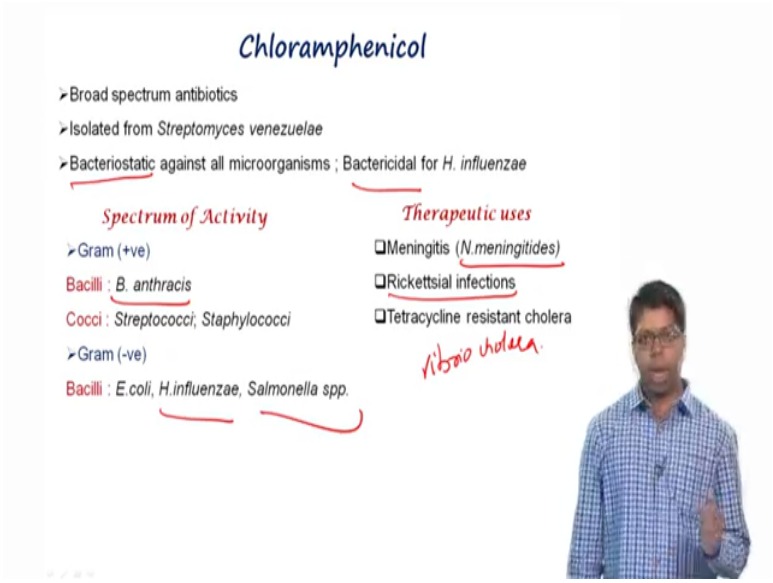

Another class of antibiotic that inhibits protein synthesis called as chloramphenicol so this is also a broad-spectrum antibiotic and this was first isolated in 1947 from the soil sample collected in Venezuela from Streptomyces venezuelae, it exhibits bacteriostatic effect at a lower concentration and bactericidal effect at higher concentration mostly against Haemophilus influenzae which is a bacterium that is responsible for influenza that is characterized by lower respiratory tract infections.

So chloramphenicol is also effective against aerobic and anaerobic both gram positive and gram negative organisms such as bacillus anthracis, Haemophilus influenza, Salmonella species. Chloramphenicol is also effective against a bacterium called as neisseria meningitidis which is a causative agent for meningitis which is characterized by inflammation of meninges that cover the brain and spinal cord. It is also effective against rickettsial infections which are characterized by fever, rash, flu like symptoms, etc.

Chloramphenicol is also good against tetracycline resistant cholera which is caused by vibrio cholera which is associated with symptoms of severe watery diarrhoea leading to dehydration and to the death of the patient if not treated at the appropriate time.

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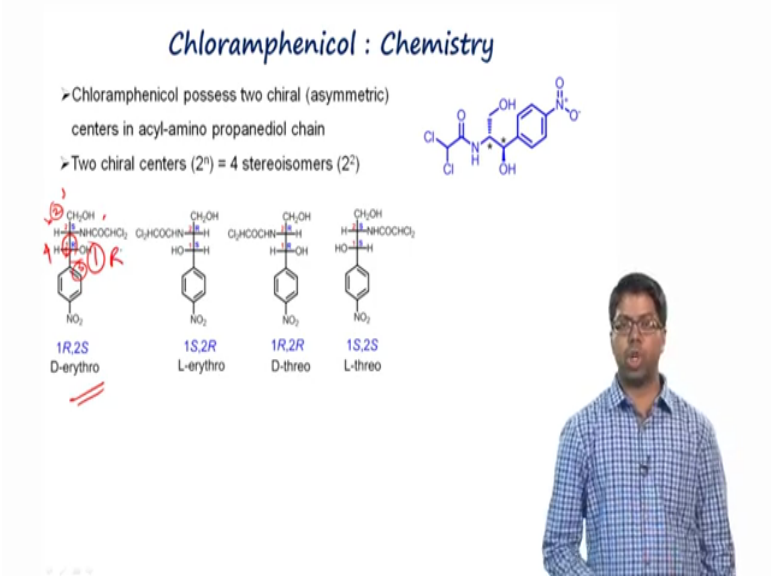

This is how duct chloramphenicol structure looks like it possesses two chiral centres, a chiral centre is the one to which four different functional groups are present, it seems obvious that here these are the two chiral centres and by applying the formula of 2 to the power of n where n is a number of chiral centres they have four stereoisomers possible for this chloramphenicol molecule.

Here these are the four stereoisomers let us assign the RNS stereochemistry for this molecule priority to the stereo centre is assigned by highest priority going to be the atom that is located on the top of the periodic table or to the atom with a heavier atomic number. So in this case oxygen has a higher atomic number so it will get first priority and a least priority will go to the hydrogen atom. Now you have to choose between carbon atoms one to which nitrobenzene group is attached and to the other carbon to which nitrogen carbon and hydrogen is attached because nitrogen dominates of a carbon so this will get second priority and this will get third priority and if you show the arrow it is in clockwise direction so therefore it has R stereochemistry.

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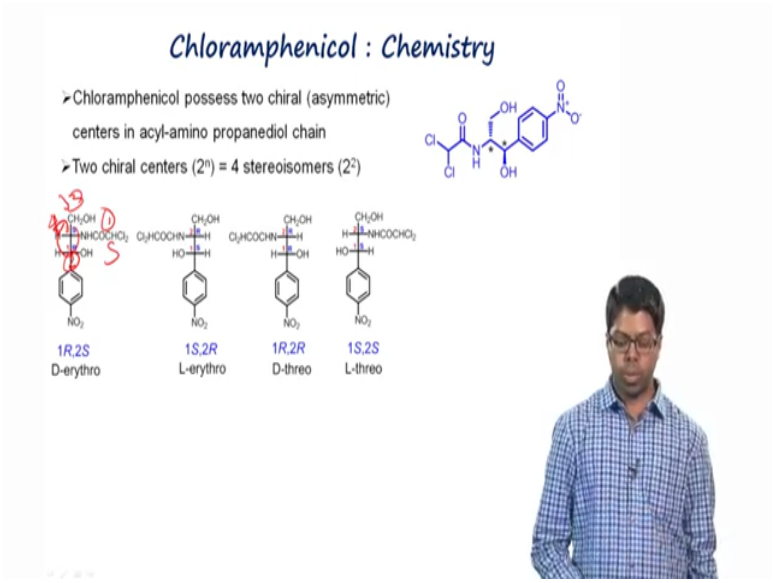

Likewise in this case the nitrogen dominates over other atoms so this will get first priority and the least priority will go to this hydrogen atom and then you have to choose between two carbons, so here the carbon is attached to two hydrogens and one hydroxyl group and here it is attached to one hydrogen one hydroxyl group and nitrobenzene group. Therefore, this gets dominated over this and here if you see it is in anti-clockwise direction so therefore it has a S stereochemistry.

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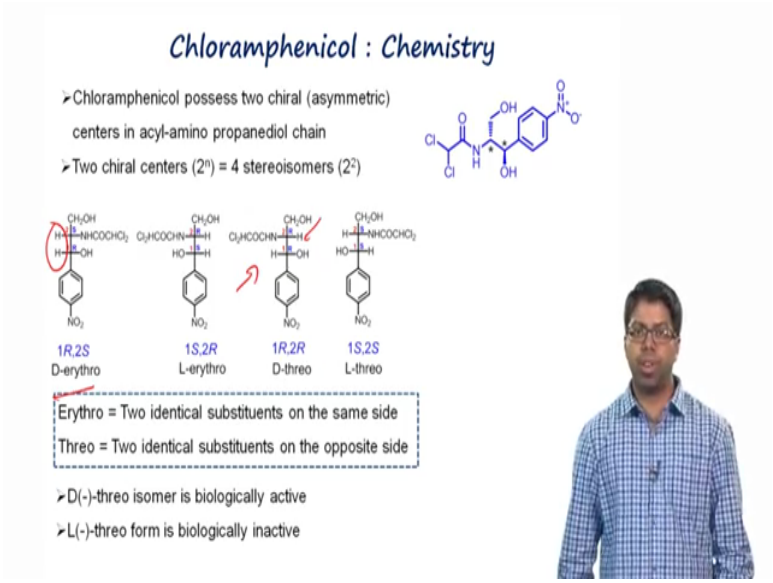

So overall the stereochemistry for this stereo isomer is 1R and 2S. Now these stereoisomers can be further differentiated into erythro and threo isomers. Erythro isomer is the one in which two identical substituents are present on the same side, here the substituent is

hydrogen, the two hydrogen atoms are present on the same side, whereas in case of threo isomer they are present on the opposite sides. And if you look closer these are mirror images of each other therefore among these four stereo isomers there are two pairs of enantiomers. Now the presence of stereo centre in a molecule can lead to differences in the pharmacological activity.

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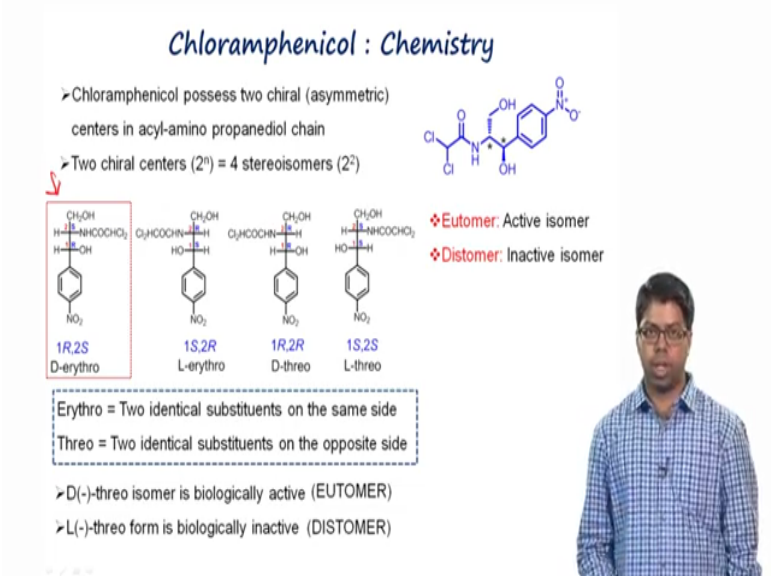

To differentiate the enantiomers in terms of pharmacological activity we use two terms called as eutomer and a distomer. Eutomer is the chiral enantiomer that has desired biological activity, whereas biological unit are inactive isomers are called as distomer. So among these four stereoisomers that the D erythro is the eutomer that means this is the only isomer which is responsible for its antibacterial activity, whereas the other isomers are inactive.

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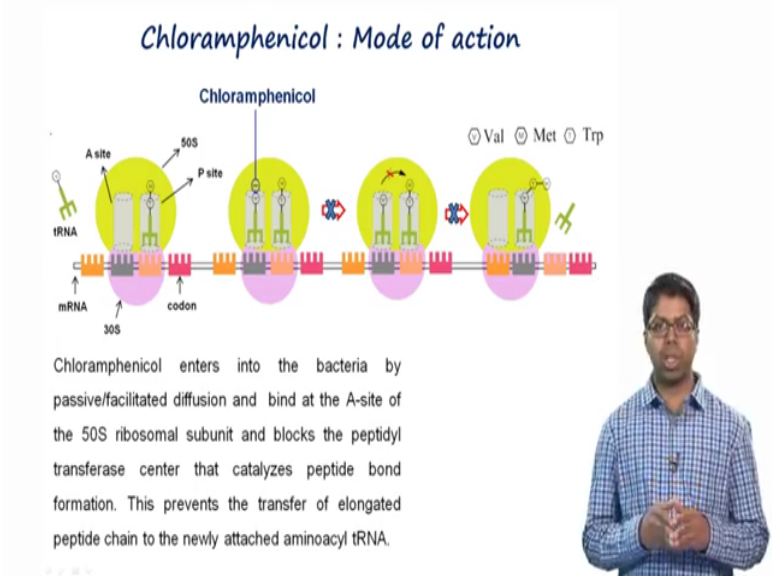

Like any other antibiotic chloramphenicol enters into the bacteria by passive diffusion or facilitated diffusion and binary A site of the 50S ribosomal subunit and blocks the peptidyl transferase centre that catalyzes peptide bond formation. This prevents the transfer of elongated peptide chain to the newly attached aminoacyl-tRNA, which generally results in bacteriostatic effect.

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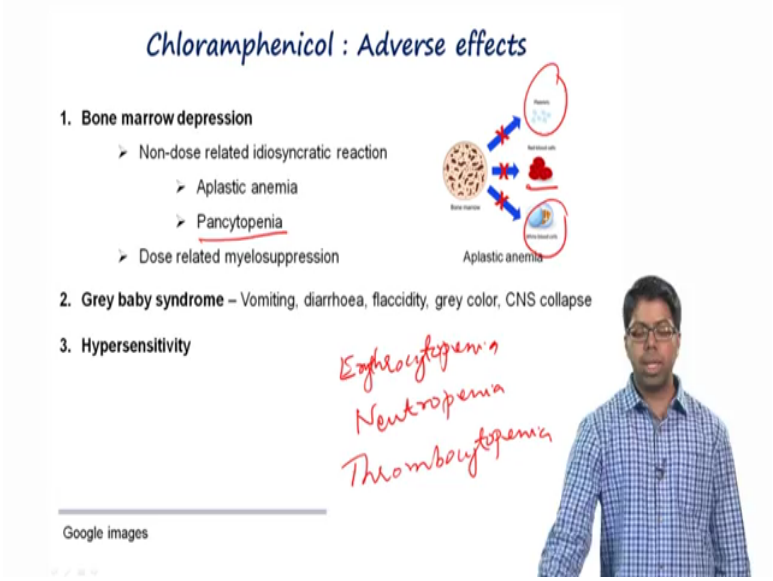

When it comes to side effects chloramphenicol is associated with the dose and non-dose related bone-marrow depressions such as Aplastic anemia this is a rare and sometimes fatal condition which is associated with deficiency of red blood cells, deficiency of white blood cells and platelets. As a result this condition is called a Pancytopenia. Here the suffix penia

always means deficiency. So here in this case there is a deficiency of red blood cells which is called as erythrocytopenia, as well as deficiency of void blood cells called as neutropenia, the deficiency of platelets is call as thrombocytopenia and the combination of the deficiency of these three cells is call as pancytopenia.

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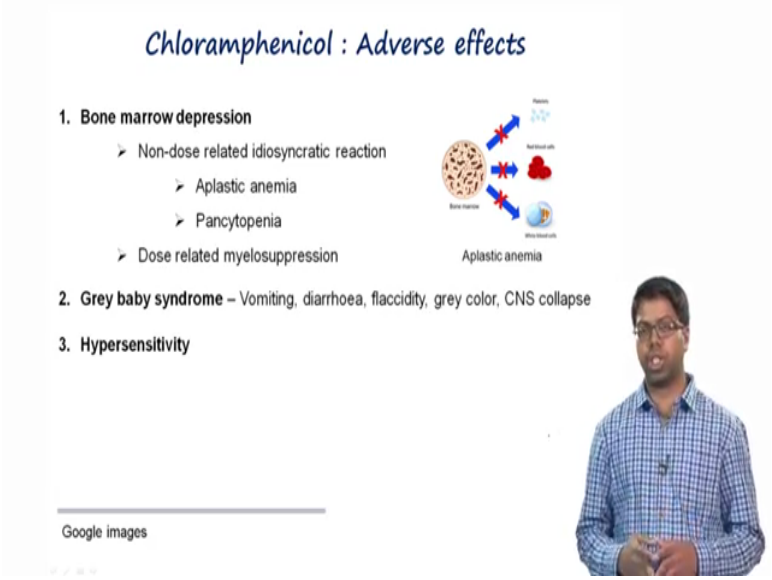

And this serious side effect associated with chloramphenicol's grey baby syndrome, which generally results in the inability of an infant's immature liver to metabolize chloramphenicol, this generally develops in babies and children when chloramphenicol is given to their mother during labour or at some point during pregnancy and this is mostly associated with side effects such as vomiting, diarrhoea, hypotension, CNS collapse and even death of the baby.

Fortunately this effect is not observed in adults because our liver has enzyme called as glucuronidase that converts the chloramphenicol into chloramphenicol gluconate which is a very hydrophilic and polar conjugate and it can be easily excreted in the urine. In rare cases it is possible to have a serious allergic reactions to chloramphenicol as well, due to these side effects chloramphenicol is rarely used nowadays and it is mostly preserved for the severe life-threatening infections for which other antibiotics are not available.

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Next another class of protein synthesis inhibitor is aminoglycosides this are broad-spectrum bactericidal antibiotics which are usually isolated from Streptomyces species, aminoglycosides includes antibiotics such as streptomycin obtained from Streptomyces griseus, another antibiotic is called kanamycin which is obtained from Streptomyces kanamyceticus and Streptomyces fradiae which is a source for another aminoglycoside antibiotic called as neomycin, they are generally used to treat infections caused by gram-negative bacteria that is not to say that do not cover for gram-positives but usually we have better options for those infections.

They are generally used to treat wide range of infections such as tuberculosis, tularemia, plague, subacute bacterial endocarditis, hospital-acquired pneumonia, urinary tract infections and so on but their use can come with a price.

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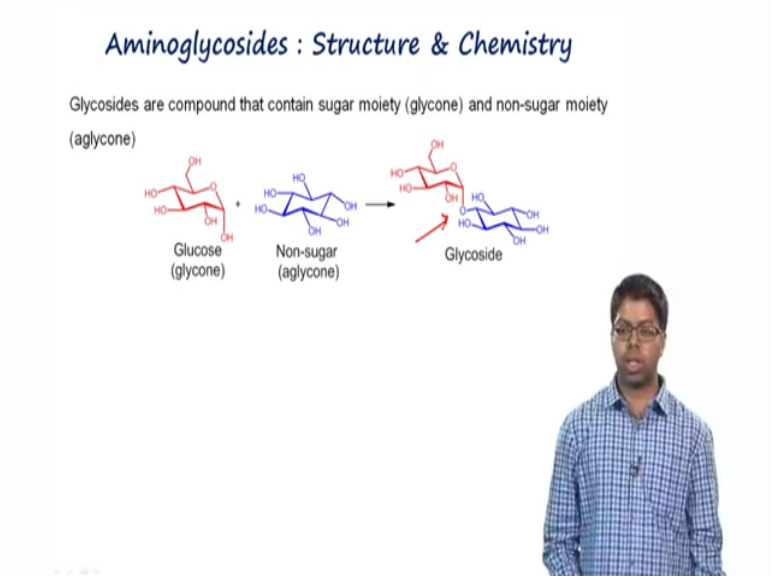

Before going into the chemistry aspect of aminoglycosides let me remind you what a term glycosides stands for. Glycosides are compounds that contains sugar moiety call as glycone and a non-sugar moiety called as aglycone and these moieties are linked by a glycosidic linkage and that is why it is called as glycoside.

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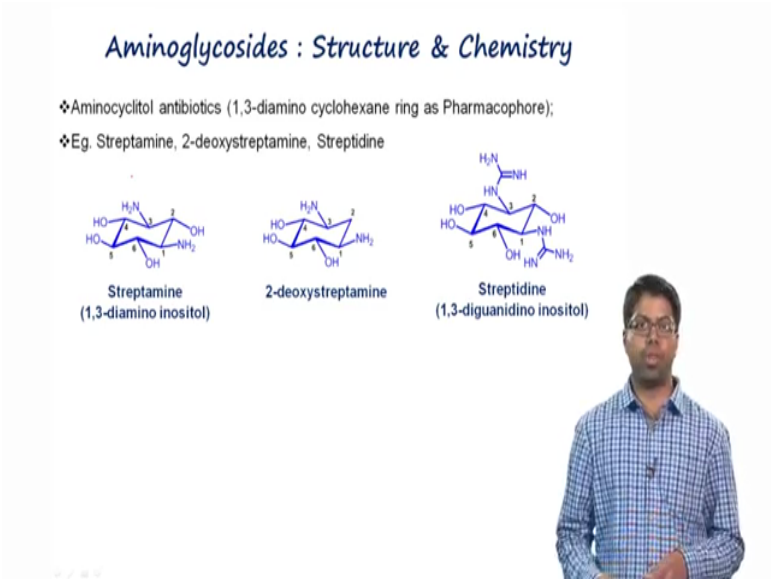

Aminoglycoside refers to a compounds that contain sugar moiety call as glycone which is glycosidically linked to aminocyclitol which is aglycone moiety here. Aminocyclitol is a basic pharmacophore for present in the aminoglycosides and these are some of the examples that belongs to this aminocyclitol family. So aminocyclitol mostly contains 1, 3-diamino functional group in a cyclohexane ring which is decorated with many hydroxyl groups here.

Streptamine is one such example which contains 1, 3-diamino cyclohexane ring with hydroxyl group at second, fourth, fifth and sixth position respectively. If you remove hydroxyl group from the second position of the Streptamine it gives you two deoxystreptamine. Streptidine ring has a guanidine moiety at one and third position respectively instead of amino functional groups. These amino glycosides can be classified based on the identity of aminocyclotol ring.

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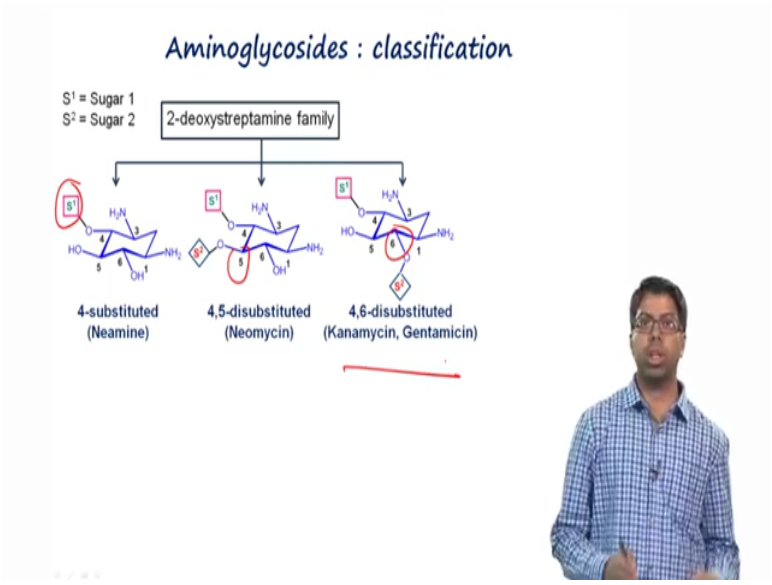

Majority of aminoglycosides contains 2-deoxystreptamine as a central pharmacophoric ring in aminoglycoside based on the substitution pattern in a ring they can be further classified into 4 monosubstituted amino glycosides, 4, 5 disubstituted aminoglycosides and 4, 6 disubstituted aminoglycosides. Here the S 1 corresponds to the aminosugar that is linked at position number 4, whereas S 2 corresponds to sugar that is present at the 5th question or 6th position respectively. Neamine is one such example that belongs to a family of 4 mono substituted 2-deoxystreptamine aminoglycosides, whereas neomycin is an example of 4, 5 disubstituted aminoglycosides, the most commonly used aminoglycoside such as kanamycin and gentamicin belongs to a family of 4, 6 disubstituted 2-deoxystreptamine aminoglycosides.

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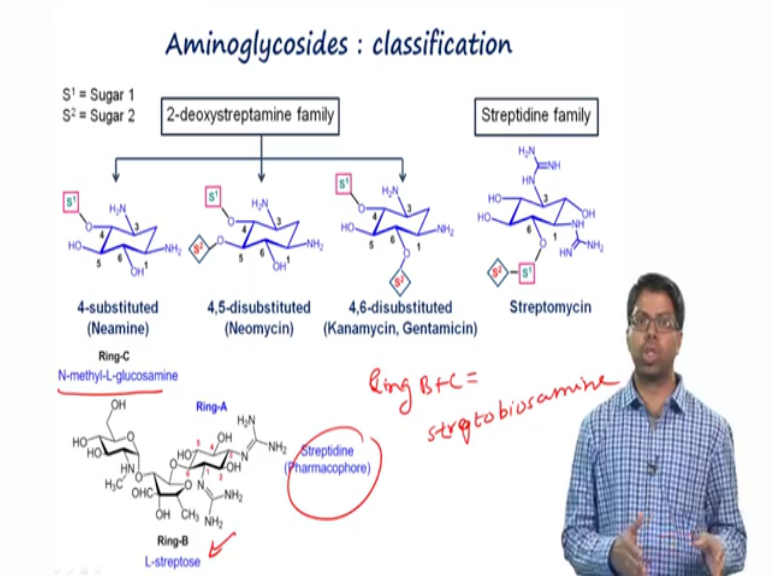

But there is another class of amino glycosides which lacks this 2-deoxystreptamine ring instead they contains a Streptidine ring one such example is Streptomycin. Here is the structure of Streptomycin which contains a streptidine ring that is glycosidically linked to another ring called as L-streptose which is again glycosidically linked to another sugar called as N-methyl-L-glucosamine.

Together during B and the ring C is called as streptobiosamine, on hydrolysis of streptomycin it gives you two components, one is streptobiosamine and the other one is streptidine, this streptobiosamine undergoes further hydrolysis to give N-methyl-L-glucosamine and L-streptose.

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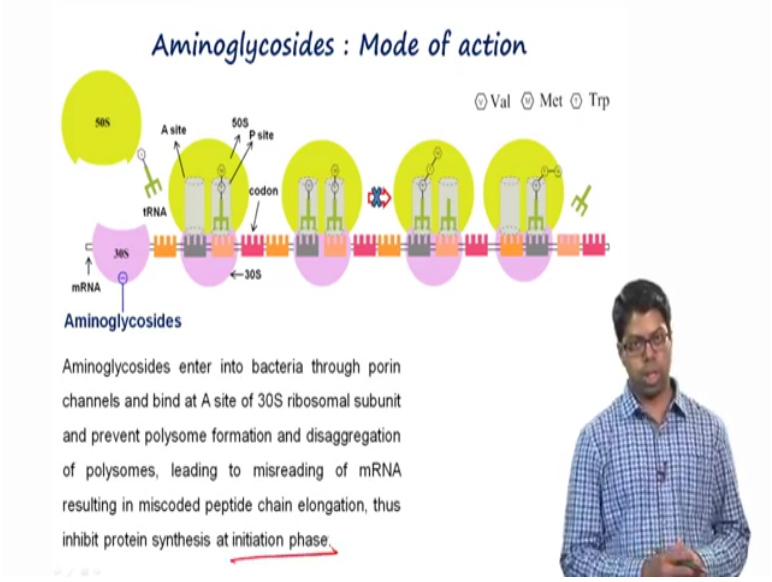

Aminoglycosides in turn into bacteria through active transport or by facilitated diffusion and bind at the A site of 30S ribosomal subunit and it prevents the polysome formation. Further it is also responsible for disaggregation of polysomes into non-functional monosomes leading to misreading of mRNA which results in a miscoded peptide chain elongation and thus it inhibits the protein synthesis at the initiation phase.

This results in inhibition of many metabolic pathways that results in leakage of cellular constants from the bacteria and cell death of the bacterium. To remind you aminoglycoside is the first class of antibiotic which inhibits the initiation phase of the protein synthesis.

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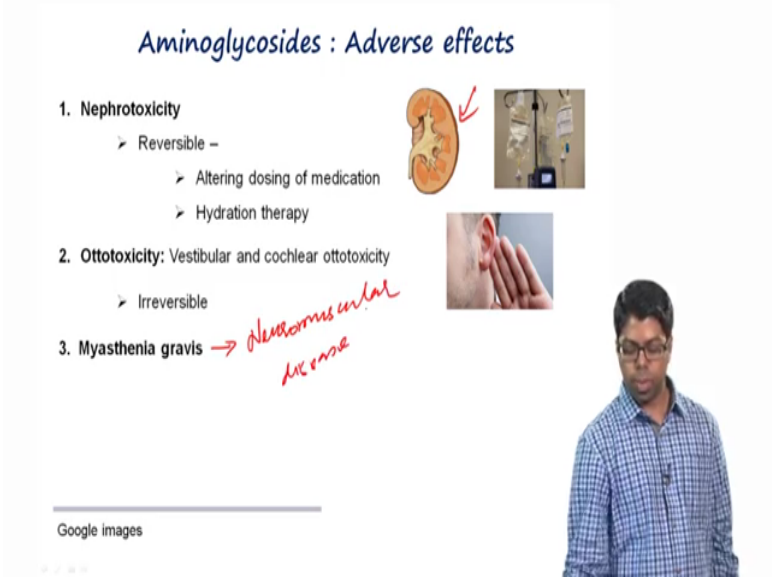

The toxicities of aminoglycosides include nephrotoxicity and ototoxicity. Remember that price I mentioned earlier well there it is, aminoglycosides tend to concentrate in the little subunits called as nephrons present inside of kidneys resulting in aminoglycoside induced nephrotoxicity. However, this condition is reversible meaning we can usually undo any kidney damage by altering the dose of aminoglycosides or by providing hydration therapy such as pumping of water, vitamins, minerals and nutrients into the bloodstream using an IV.

Aminoglycosides also have a tendency to concentrate inside the 8th cranial nerve resulting in aminoglycoside induced ototoxicity, unfortunately this condition is irreversible, it can consist of vestibular and cochlear damage leading to symptoms of hearing loss. Thus, aminoglycosides can cause irreversible hearing loss, aminoglycosides are also associated with a long-term neuromuscular disease called as myasthenia gravis.

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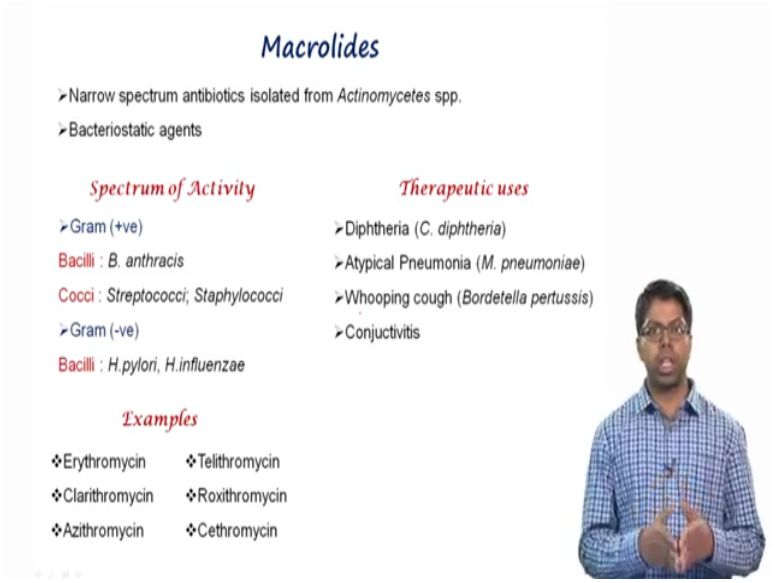

And the next class of protein synthesis inhibitor is macrolides, macrolides are among the widely prescribed form of antibiotic these are narrow spectrum antibiotics and are usually isolated from actinomycetes species, they exhibit bacteriostatic effect, they are predominantly used to treat infections that are caused by gram-positive bacterium and they are active against a limited range of gram-negative bacteria such as streptococcus, staphylococcus, Helicobacter pylori and Hemophilus influenza.

Macrolides mostly prescribed for respiratory tract infections such as atypical pneumonia and whooping cough and they are also effective against clostridium diphtheria which is responsible for diphtheria which is a condition that is associated with severe nose and throat infection, they are also good against conjunctivitis which is associated with inflammation of the conjunctiva of the eye. Some of the popularly prescribed macrolides includes erythromycin, clarithromycin, telithromycin, cethromycin and azithromycin.

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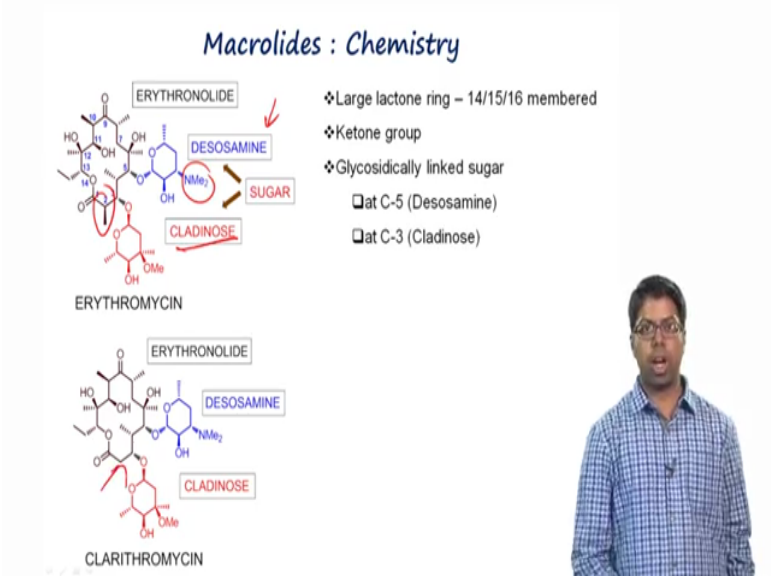

The chemical structure of macrolides contains a large macro cyclic lactone ring with 14 to 16 atoms and this lactone ring is substituted with many alkyl and hydroxyl groups and a ketone functional group at a 9th position, this is one such example called as erythromycin, the macro cyclic lactone ring present in erythromycin is called erythronolide, it is also substituted with sugar (())(32:42) and position respectively by a glycosidic linkage, the sugar that is present in the third position is called cladinose, whereas the aminosugar that is present at a 5th position is called Desosamine.

Another such example of this macrolide is clarithromycin, there is a very minor structural difference between erythromycin and clarithromycin, erythromycin has an alkyl group at a 2nd position which is absent in case of clarithromycin.

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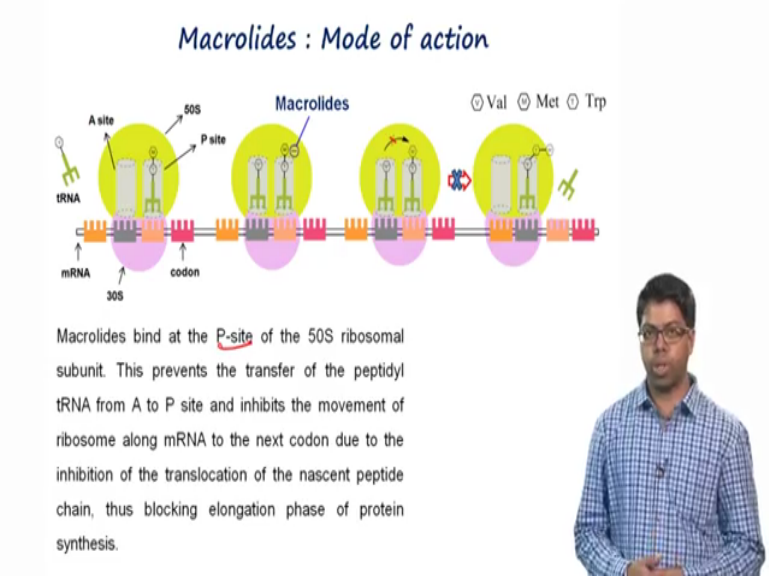

Here the macrolides also enter into the bacteria by active transport or by facilitated diffusion and they bind at the P-site of the 50S ribosomal subunit, which prevents the transfer of peptidyl tRNA from A site to P site and this inhibits the movement of ribosome along mRNA to the next codon and due to inhibition of translocation of the nascent peptide chain and thus it inhibits the elongation phase of protein synthesis.

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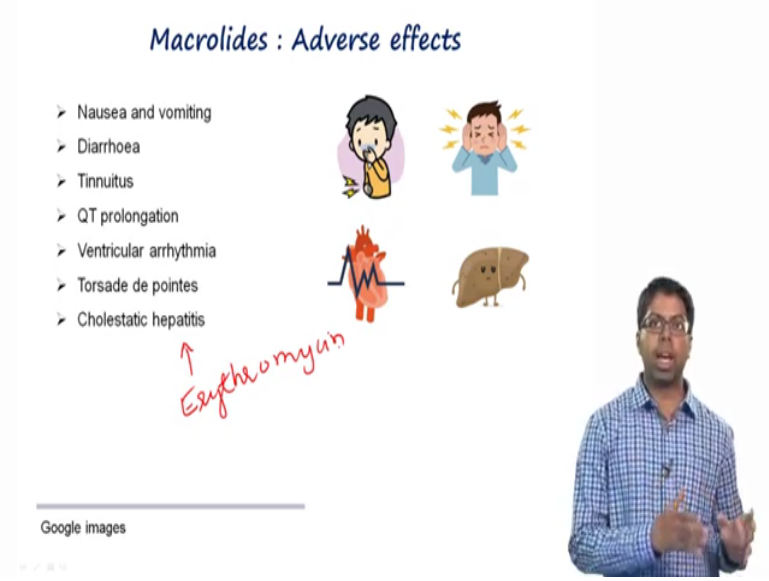

When it comes to side-effects macrolides are associated with various common side effects such as nausea, vomiting, diarrhoea, ringing or buzzing into the ears, less common but serious side effects include QT interval prolongation. QT interval is a part of

electrocardiogram that provides information about the heart and cardiac conditions of a patient generally it is measured in terms of milliseconds.

So in case of men the QT interval is 350 to 440 milliseconds, in women it is around 460 milliseconds. So if this QT interval is greater than 500 milliseconds it can lead to conditions called as ventricular arrhythmia and torsade de pointes. Another serious side effect associated only with the use of erythromycin is cholestatic hepatitis which is associated with the condition of inflammation of liver due to which (())(34:27) flow from liver to (())(34:29).

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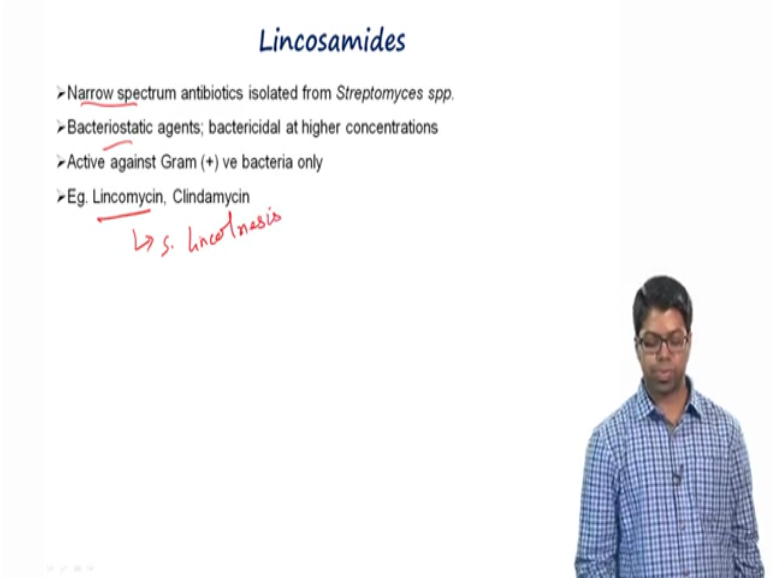

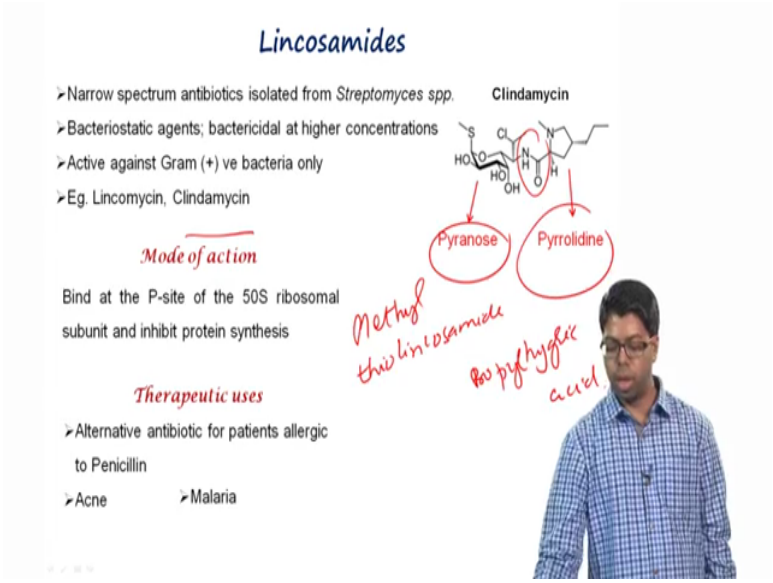

Lincosamides are another class of protein synthesis inhibitor and these are narrow spectrum antibiotics which exhibit bacteriostatic effect at lower concentration and bactericidal effect at higher concentration, the thing is they are active only against gram-positive bacteria and they

are very negligible activity against gram-negative organisms. Lincomycin is a prototypical antimicrobial agent of this class that is obtained from streptomyces lincolnensis. The lincosamides also work like macrolides, they bind at the P-site of the 50S ribosomal subunit and inhibits protein synthesis.

Generally they are preferred as an alternative antibiotics to the patients who are allergic to penicillin, they are also used as topical agents for the treatment of Acne and they are also capable of killing the malaria parasite. Clindamycin is a semi-synthetic derivative of Lincomycin that contains a pyranose moiety and a pyrrolidine ring which are linked by an amide bond. The pyranose moiety present on this Clindamycin is called methyl thio lincosamide, the pyrrolidine moiety present here is an unusual amino acid called prophy hygric acid.

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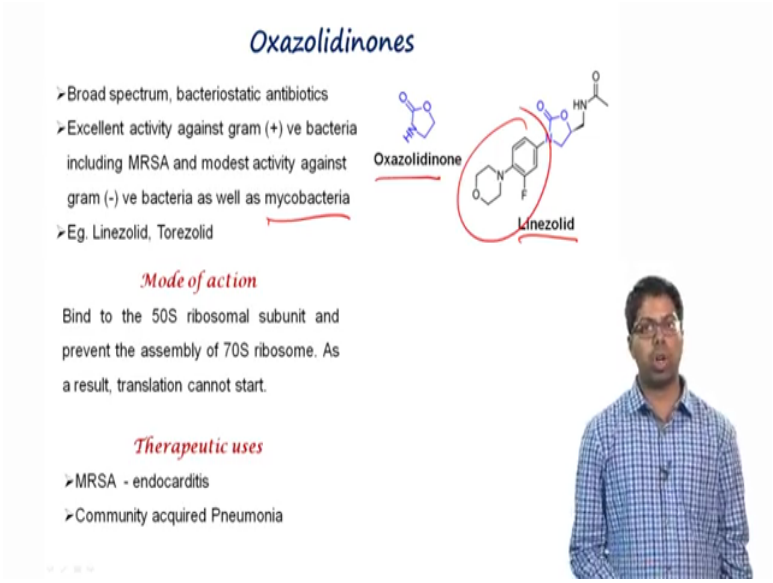

Another class of protein synthesis inhibitor is the Oxazolidinones class of antibiotics, this Oxazolidinones class of antibiotics are relatively recent addition to the anti-microbial wall and have been found very useful in treating infections caused by gram positive bacteria, they show excellent activity against methicillin-resistant staphylococcus aureus, streptococcus and enterococcus all of which have shown alarming weights of antibacterial resistance in clinical settings. They show modest activity against gram-negative, as well as micro bacterium.

Linezolid and torezolid are some of the antibodies that belongs to this family and they have a unique mode of action, their mechanism is more or less similar to aminoglycosides. Here they bind to the 50S ribosomal subunit and prevents the formation of 70S ribosomal complex and

as a result it inhibits the initiation phase of the protein synthesis, this Oxazolidinone class of antibiotics are used for many infections which are resistant to many clinically use antibiotics such as methicillin-resistant staphylococcus aureus cost endocarditis, they are also useful in community-acquired pneumonia.

This is the basic pharmacophore of Oxazolidinone and this is the structure of Linezolid which contains a four substituted phenyl ring in the 3rd position of the Oxazolidinone pharmacophore.

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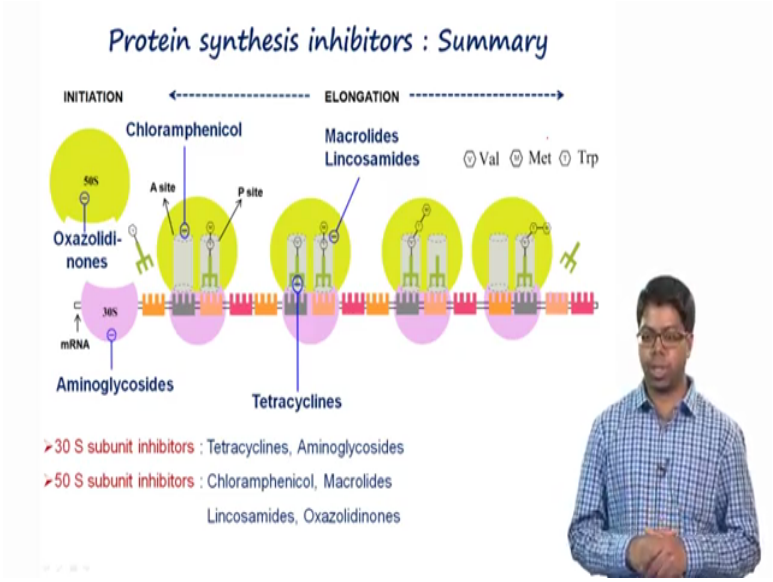

To summarize antibiotic act at a specific site on the ribosome and inhibits deep protein synthesis, some of antibiotics act at the initiation phase of the protein synthesis, some act deelongation phase of the protein synthesis. Aminoglycosides and Oxazolidinones inhibit the initiation phase of protein synthesis. Here aminoglycosides bind to 30S and inhibit the formation of 70S complex, likewise Oxazolidinones like linezolid bind to 50S and prevents the formation of 70S complex, whereas other antibiotics like chloramphenicol, macrolides lincosamides and tetracyclines bind to either 30S or 50S subunit respectively and inhibit deep protein synthesis.

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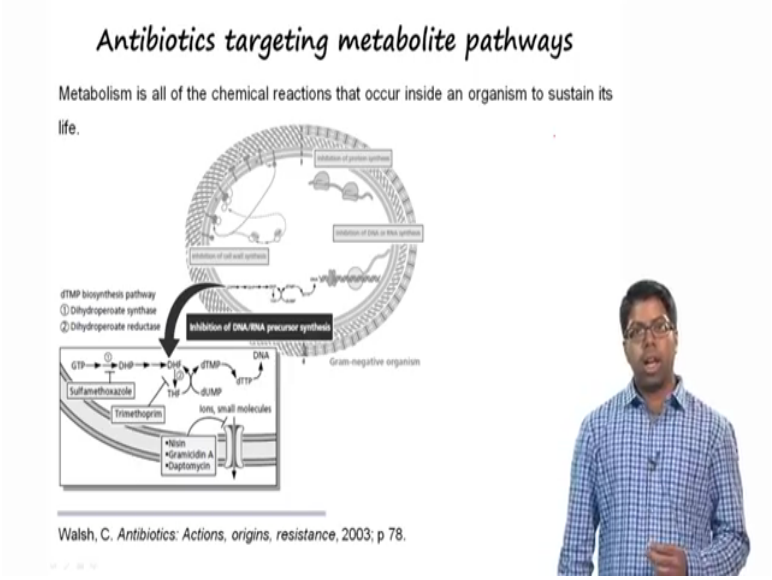

Now let us move to another class of antibiotics that target the metabolite pathways, when you hear the word metabolism you might think of skinny and not so skinny people and how people say things like he has a super-fast metabolism that is why he can eat whatever he wants but still look that good. So what is metabolism? Anyway metabolism is all of the chemical reactions that occur inside an organism to sustain its life, bacteria have metabolisms too that is how they convert the nutrients that you take from the environment into all of the useful molecules they need for their day-to-day lives.

So here we are going to talk to such antibiotics which inhibit the metabolite pathways, one is sulfonamides and the second class of drugs called trimethoprim as these drugs inhibit the metabolite pathways they are also called as antimetabolites.

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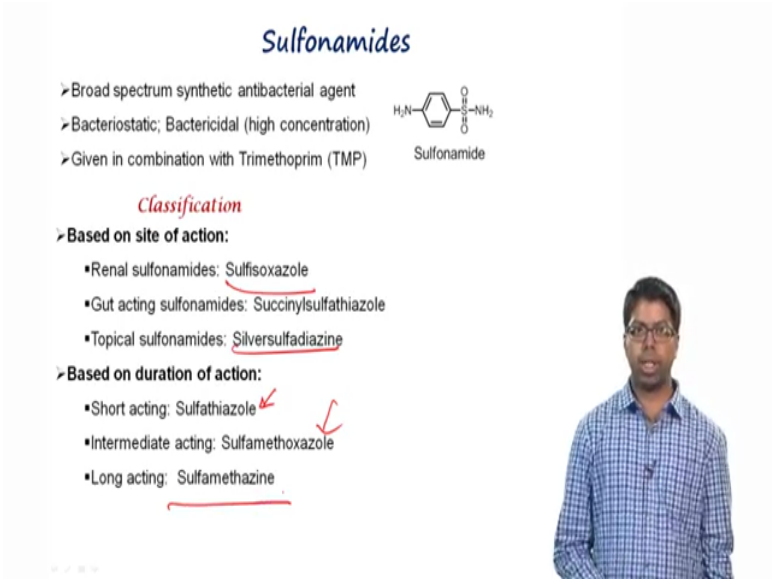

Let us start with sulfonamides, sulfonamides are a broad-spectrum synthetic antibacterial agents that have a common sulfonamide chemical group, they exhibit bacteriostatic effect at lower concentration and bactericidal effect at higher concentration, generally these sulfonamides are given in combination with another folate biosynthetic inhibitor called as trimethoprim, which we are going to discuss in detail in the next coming part of the lecture.

So these sulfonamides are classified based on the onset of action and based on a duration of action for example there are some sulfonamides which can reach in higher concentration in the urine and therefore they are mostly used for bladder infections such as renal sulfonamides, there is another class called as gut acting sulfonamides which are mostly used for gastrointestinal infections, there is another class called topical sulfonamide such as silver sulfadiazine which is mostly used for burns and infections.

Again these sulfonamides can also be classified based on the duration of action, that means how long they are going to reside in a body and what is their half-life. Sulfathiazole is a short-acting sulphonamide, sulfamethoxazole is an intermediate acting sulphonamide, whereas sulfamethazine is a long-acting sulphonamide.

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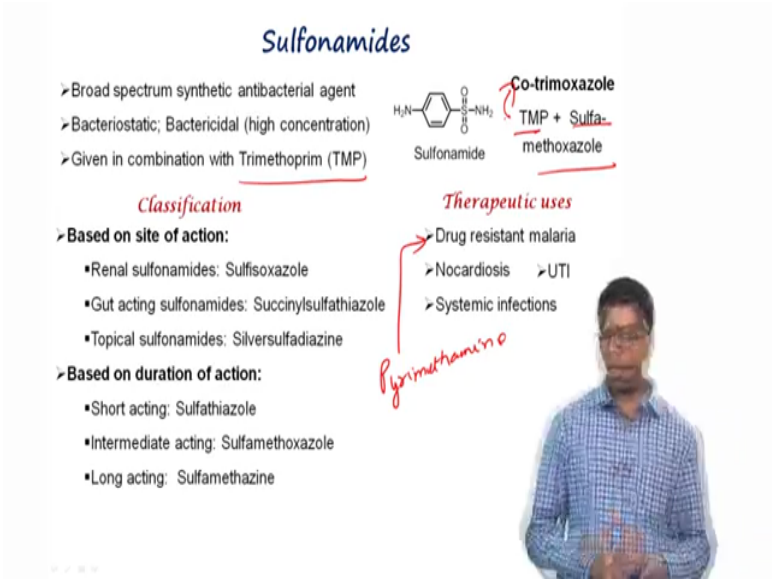

Sulfonamides are used to treat bladder infections as they reach in higher concentration in the urine they are also effective against nocardiosis which is a infection caused by nocardia bacteria, they are also effective against drug-resistant malaria. So in such cases sulfonamides are given in combination with another anti-malarial drug called as pyrimethamine to treat drug resistant malaria, they are also good against many bacterial infections when they are given in combination with another folate biosynthetic inhibitor called as trimethoprim.

So the combination of trimethoprim and sulfamethoxazole which is one of the widely prescribed sulfonamide is called as cotrimoxazole. So therefore sulfonamides are not given alone they are always given in combination with another folate biosynthetic pathway inhibitor call as trimethoprim.

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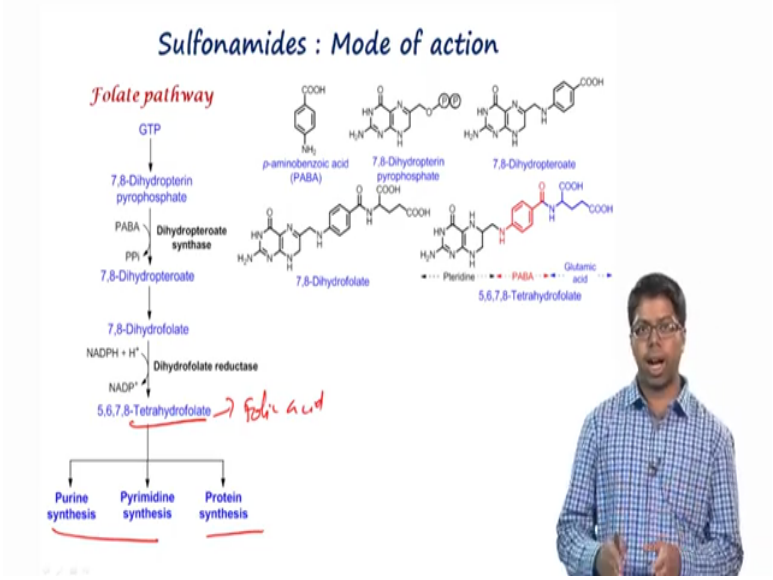

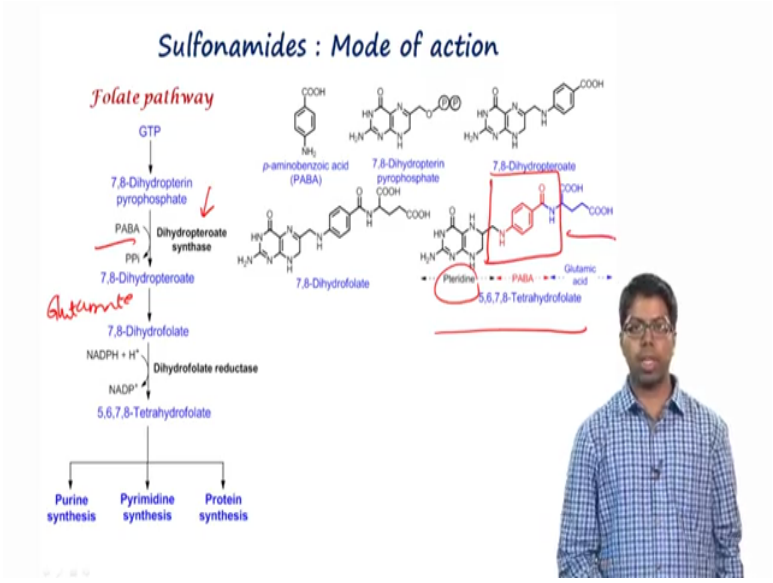

So sulfonamides inhibit a pathway which bacteria used to synthesize tetrahydrofolate which metabolically active form of folic acid, folic acid is a vitamin that is needed in order to synthesize nucleotides and amino acids, basically without folic acid cells would not be able to synthesize DNA, RNA or proteins, therefore it is a pretty important metabolite. So here GTP nucleotide is a common precursor for the synthesis of 7, 8 dihydropterin pyrophosphate, then 7, 8 dihydropteroate is assembled from dihydropterin pyrophosphate and palomino benzoic acid which is abbreviated as PABA for short in the presence of an enzyme called dihydropteroate synthase.

Then this dihydropteroate is enzymatically glutamilated to form 7, 8 dihydropteroate which is further reduced in the presence of dihydropteroate reactors to give tetrahydrofolate, which is

an important precursor for the synthesis of purines, pyrimidines and proteins and this is how the structure of tetrahydrofolate looks like it has a pteridine ring and a para aminobenzoic acid and a glutamic acid moiety.

So now you may have guessed that sulfonamides and trimethoprim inhibits these two key essential enzymes that are involved in a fall it biosynthetic pathway.

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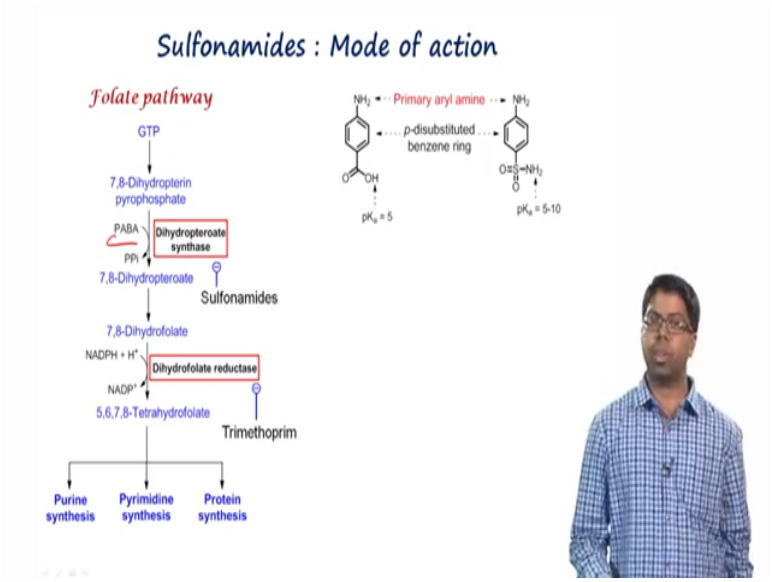

Sulfonamides inhibit the dihydropteroate synthase, whereas trimethoprim inhibit the dihydrofolate reactors enzyme. Sulfonamides are competitive inhibitors for this enzyme meaning they compete with a real substrate of this enzyme which here is PABA or para aminobenzoic acid, if you look at the structure of para aminobenzoic acid and sulfonamide they look a lot alike to us and to the enzyme.

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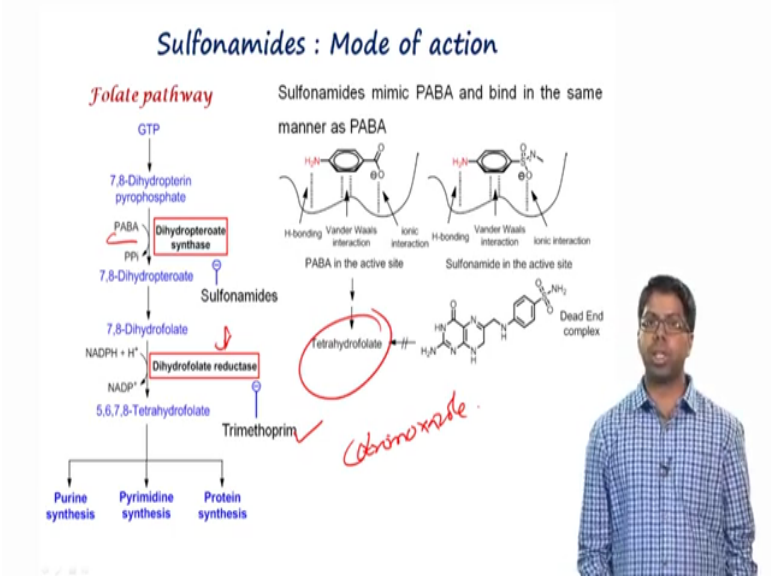

Therefore, the enzyme is (())(41:48) into accepting the sulfonamide molecule into its active site, thereby it prevents the binding of para aminobenzoic acid to the enzyme and thus it inhibits the synthesis of tetrahydrofolate by inhibiting this dihydropteroate synthase enzyme.

Likewise trimethoprim is a potent competitive selective inhibitor for dihydrofolate reductase enzyme which inhibits the conversion of dihydrofolate to tetrahydrofolate. In short these two drugs have a synergistic effect when they are given in combination. So combination of sulfonamide and trimethoprim introduces sequential blocks in the biosynthetic pathway of folate metabolism and thereby the combination is much more effective than either agent alone. So the combination of sulfonamide and trimethoprim is called as cotrimoxazole, the sulfonamide which is given in this combination is sulfamethoxazole.

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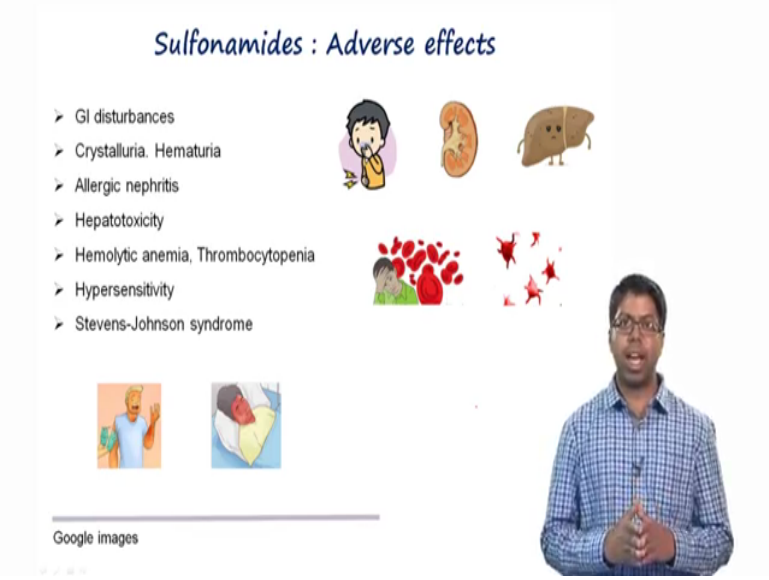

When it comes to side effects it is mostly associated with very less common side effects such as gastrointestinal disturbances, crystal urea, hematuria, hepatotoxicity, etc. It is also associated with hypersensitivity that can range from allergy or rash or hives to anaphylaxis and even Stephen Johnson syndrome it is a very rare syndrome that affects the skin and mucous membrane.

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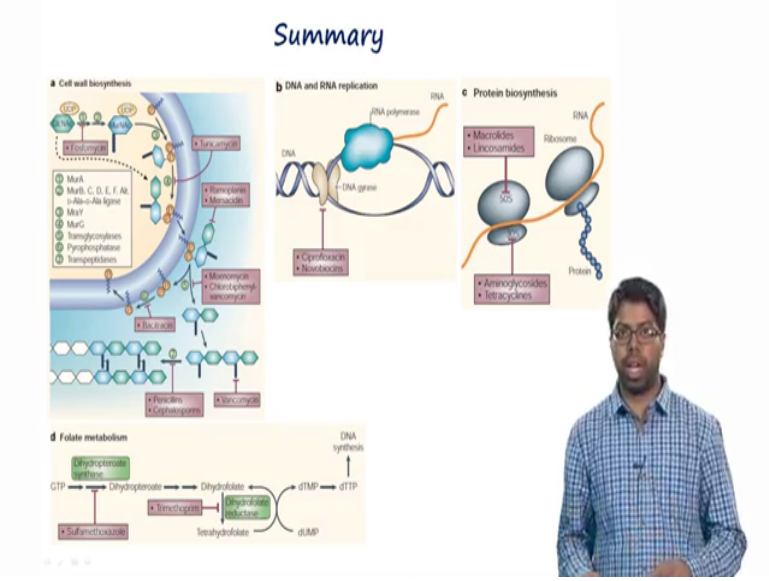

In a nutshell we have covered on various classes of antibiotics, few antibiotics target is cellular biosynthesis, some are going to inhibit either nucleic acid biosynthesis or protein biosynthesis and some are going to target the metabolic pathways. Please remember that each antibiotic is always associated with some other side effect and other thing is overuse or

misuse of any of these antibiotic can lead to development of resistance against the respective antibiotic by the bacterium. Therefore, the sound knowledge of antibiotic is essential in order to treat the appropriate infection for a given individual at a given time, thank you so much.