Overview and Integration of Cellular Metabolism

Prof. Arindam Ghosh

Dr. B.C. Roy Multi-Speciality Medical Research Centre

Indian Institute of Technology Kharagpur

Week 10

Lecture 49: Disorders of Bilirubin Metabolism

Hello everyone, welcome to our lecture series on Overview and Integration of Cellular Metabolism. We are done with heme metabolism and when we ended heme metabolism we discussed that we will be discussing on bilirubin metabolism which is the topic of this class. Now, we will be covering the concepts of how bilirubin is up taken and it is excreted and that leads to if there is any problem in that pathway it leads to various disorders. Now those disorders can be right there from birth which is our congenital and it can be acquired. So, all of them lead to a condition that is known as hyperbilirubinemia where is more bilirubin. Anyway we will be classifying jaundice, we will be noticing how the metabolic parameters are altered in different types of jaundice and thereafter we will be mentioning various tests how we can distinguish various types of jaundice.

Now in the last class you already saw this slide where we discussed what is the normal value of bilirubin, what is the cut off limit beyond which we will term the disease to be jaundice and what is latent jaundice right. So, hyperbilirubinemia that is a condition where there is excess bilirubin in blood can be I mean due to various causes. First cause can be due to a reason when it is present right from birth ok that is known as congenital and there may be reasons that can lead to a adult person acquiring this phenomena. So, that is then we call it acquired hyperbilirubinemia all right.

So, let us first discuss congenital hyperbilirubinemia all right. So, congenital hyperbilirubinemia refers to inherited disorder of bilirubin metabolism and it always almost always presents at birth due to which it is also known as neonatal jaundice. Now, the reason may be due to abnormal intake or conjugation or excretion of bilirubin right and those reasons are present from birth that is why they are known as inherited defects. Anyway we are discussing the pathway by which bilirubin is uptaken and it is excreted all right. So, we can see over here bilirubin actually combines with albumin as we have discussed.

Now albumin it reaches the sinusoidal surface when reaches the sinusoidal surface albumin is dissociated and this bilirubin is actually going inside into the hepatic sinusoids via facilitated diffusion right. It is not dependent on energy and it can actually freely go in and out it is bidirectional. Now what actually prevents or helps bilirubin that so that this motion can occur inward there are two mechanism. Number one bilirubin actually combines with various ligands which are actually functionally similar to glutathione S transferases all right. So, when bilirubin is captured it facilitates so that the movement is actually inward ok.

Because this bilirubin is being constantly utilized number one by attaching to the ligand right or number two by conjugating with UDP glucoronic acid. This you already know by the enzyme by the sub enzyme UGT1A1, UDP glucoronucile or glucoronyl transferase. So, number one it binds to ligands and number two it is conjugated this is how this bilirubin which is actually water insoluble becomes soluble right. Next what happens as we all know this conjugated bilirubin can actually freely cross the biliary canaliculi right. There is a protein actually which helps in this movement of bilirubin right.

This is known as MRP2 or multidrug resistance protein 2 right. This is the major mechanism. However this bilirubin can actually be excreted by another ATP dependent cassette transporter and it can also be reuptaken by a minor transporter that is known as organ an organic anion transport protein 2 or OATP2. However, there have been studies where it has been shown that this OATP2 plays a very minor role in all bilirubin metabolism right. But the main thing to remember are this thing albumin it is getting dissociated from albumin thereafter it is getting either bound to the ligand glucothinase transferase it is getting conjugated by UGT1A1 and subsequently after the conjugation it is removed or I mean taken up by the canalicula into the canalicular surface by MRP2 or multidrug resistant proteins 2 which is present at the canaliculi alright.

You need to be very clear about the anatomy what do you mean by sinusoidal surface what is the canalicular surface basically this is the hepatic cell that is being shown here. So, if you understand all of this it will be much easier for you to I mean note down all the reasons why the inherited or conjugated hyperbilirubinemia are formed. Now conjugated hyper I mean the inherited or congenital I am sorry congenital hyperbilirubinemia that is born I mean the babies are born with that hyperbilirubinemia may be 2 types conjugated and unconjugated mind it the terms you should not confuse congenital means from birth and that congenital can be of 2 type. Number 1 where the bilirubin I mean the rise of the bilirubin is mainly unconjugated and number 2 where the rise of the bilirubin is conjugated I mean conjugated bilirubin goes high. So, there can be 2 classification of hyperbilirubin.

So, first we are discussing the inherited disorders of bilirubin metabolism causing unconjugated hyperbilirubinemia and there are 3 main reason number 1 Krigler-Nadzor syndrome type 1 Krigler-Nadzor syndrome type 2 and Gilbert syndrome these you need to remember these names right and these are the only 3 names you need to remember when we are discussing with unconjugated neonatal hyperbilirubinium or unconjugated neonatal jaundice right. So, let us see what are the differences between these 2 you can note it down you can make your own tabular sheet and you can note down these points by pausing the videos right. So, number 1 this Krigler-Nadzor syndrome is actually caused by defective conjugation naturally since it is unconjugated hyperbilirubinemia the only problem in conjugation. So, in Krigler-Nadzor syndrome type 1 there is virtually no conjugation because the activity of UDP glucoronacil transferase 1A1 is almost missing whereas, in type 2 it is not fully missing at least 10 percent of the activity is somewhat present. So, there is some degree of conjugation in type 2 that is why it is a milder disease compared to type 1 type 1 is a severe disease where there is an excess amount of unconjugated bilirubinium alright.

What happens in Gilbert syndrome this activity is reduced, but it is generally 30 percent. So, Gilbert syndrome is even milder compared to Krigler-Nadzor type 2 syndrome alright. So, this is the basic problem in conjugation which is defective in all of these 3 syndromes and it is the amount of enzyme activity that differentiates all these 3. So, now let us look at the outcome in Krigler-Nadzor type 1 what happens since it is not conjugated unconjugated bilirubin is excess because there is absolutely no conjugation as I told you in the previous class unconjugated bilirubin is insoluble. However, it can bind with albumin and ultimately somehow it can cross blood brain barrier and it gets deposited in the brain leading to carnic teras and ultimately it causes brain damage the entire central nervous system is coated with bilirubin right.

In type 2 serum bilirubin value is around 8 to 18 mg mind it is still very high more than 2 is what physicians are worried about we are talking about 8 18 and 40 right. Whereas in this case in Gilbert syndrome it is around 5 mg per dl right and there have been I mean this Gilbert syndrome also presence in adults ok we will see very soon and it also increases during fasting intercurrent illness etcetera. So, Gilbert syndrome is basically intermittent it goes again it comes back whereas, these two are present right from the birth and these two are much more noticeable compared to Gilbert syndrome. Moving on the inheritance it is autosomal recessive both are autosomal recessive type 1 type 2 whereas, Gilbert syndrome is also autosomal recessive, but it is much common compared to the type 1 and type 2 figular nazir syndrome. In fact, 9 percent of population are found as homozygous and 4 percent exhibit clinical jaundice intermittently it is common, but it is less severe and the upper two are rare, but very

severe form of diseases.

So, maybe there is a this is a way by which nature has protected all human beings that the much severe disease is much rarer and whereas, the milder disease is common right. Next bilirubin conjugates if you look at the level of conjugate they are almost absent because there is no activity here some amount of conjugates are present preferably bilirubin mono glucuronide I told you bilirubin is conjugated in two steps first it becomes mono and then it becomes diglucuronide right. So, in these two some amount of conjugated bilirubin is present, but portion of mono glucuronide is more in general diglucuronide is more than mono glucuronide alright diglucuronide is more than 80 percent and mono glucuronide is 20 percent. So, here percentage of mono glucuronide is increased alright. Now treatment the drug of choice to treat all of them to treat kernic teras and the symptoms there are neurological symptoms that happens due to the position of bilirubin in the brain is phenobarbital, but this has got little or no effect in case of friglanazir type 1.

As phenobarbital how it phenobarbital reduces phenobarbital actually induces the enzyme glucoronyl transferase it is a cytochrome p450 based enzyme I already told you how phenobarbital in previous classes you can look back if you have missed that phenobarbital actually induces bilirubin conjugation by increasing the activity of UDP glucoronyl transferase. In fact, phenobarbital increases any conjugation that is done by UDP glucoronyl transferase bilirubin is one such substrate right and in this case phenobarbital treatment completely normalizes because the enzyme activity is already 30 percent if that enzyme activity somehow increased there will see I mean the hyperbilirubin will simply vanish ok. So, these are the 2scientists who discoveredthe syndrome Victor Kiegler and John Najar actually they first noticed a disease that is causing jaundice as well as severe neurological dysfunction or damage right and after they work together and they jointly named the diseases Kiegler Najar syndrome. So, let us discuss since it is very important the only I mean the most important thing you need to know the major things have often already been discussed it is very fatal it appears in first 24 hours it is so severe right and generally phototherapy should be done right. We have already discussed the mechanism of phototherapy what phototherapy does is solubilizes the unconjugated bilirubin transiently so that it can be excreted and phototherapy actually increases the life expectancy otherwise the baby will die before the age of 2 it is if untreated right and you know what happens during emergency the bilirubin can be removed by plasma pharise it is a process by which the entire plasma is filtered ok.

There is an N's compound that is tin mesoporphyrin which is a competitive inhibitor of microsomal heme oxygenase right. What it does it actually prevents production of bilirubin we already saw how heme is converted to biliverdin and bilirubin and heme

oxygenase was one of the key enzymes this compound if heme oxygenase is inhibited there will be no bilirubin to start with and there will be no hyper bilirubinemia right. We should know that the phototherapy is mostly effective when the we are dealing with small babies when as and when the age increases phototherapy becomes ineffective right and then the life the patient will die. So, the life expectancy adolescence and beyond, but not full life expectancy right. However, can we cure it liver transplantation is the only curative therapy because here the problem in the liver enzyme right.

So, a liver where the enzymes are actively working it can cure the patient. In one patient liver cell transplantation reduces the serum bilirubin level by 50 percent there are multiple case scenarios which have been studies and we have come to the conclusion that liver transplantation is the only curative therapy ok. So, this is the common I mean picture you have seen in phototherapy right how phototherapy happens we discussed in last class. So, you see the way I mean the patient looks the permanent brain damage the abnormal eye movement the I mean the abnormal mouth movement this is still image, but still it is a sine qua non what I can say it is almost pathognomic if this look with severe jaundice right from the history of birth strongly suspect triglarnazar type 1 syndrome right. Next we come to causes of conjugated hyperbilirubinemia again you have to remember two names Dubin Johnson syndrome and Rotor syndrome ok.

So, what happens let us see in Dubin Johnson syndrome the conjugated hyperbilirubinemia is a result of defective exogenous transfer of anionic conjugates from hepatocytes into bile what is this let us understand. In Rotor syndrome what happens it in there is a mixed hyperbilirubinemia there is conjugated, but there are also unconjugated bilirubin. So, what happens in Rotor syndrome this is a hepatic storage disorder that leads to defective clearance of bilirubin. But we need to know we have studied the bilirubin metabolism in the hepatocytes. So, where lies the exact problem Dubin Johnson syndrome the exact problem lies in MRP 2.

So, MRP 2 what it was doing it was actually taking up the conjugated bilirubin diglycoronide and via the canaliculi it was secreting into bile right that is defective that is why the conjugated bilirubin increases in the hepatocytes ok. Next what happens in Rotor syndrome the minor pathway that is OATP I told you OATP 1 B 1 and OATP 1 B 3 these are very minor pathway that actually transfers organic ion and there are problems in these proteins due to mutation in the gene SLCO 1 B 1 and SLCO 1 B 3. This name of the genes and name of the protein are important from multiple choice question, but for Viva you may not be expected to answer all of them specially for an undergraduate student you can just mention this is the hepatic storage disorder where there is problem in removing of conjugated bilirubin due to defective transfer proteins ok. Just by giving a generic answer you can seek your marks, but any competitive exam definitely you need

to remember the name of the mutant gene and the mutant proteins. So, regarding the incidence and the rarity it is a benign rare autosomal recessive disorder and generally it is found in Jews so, 1 in 1300.

Whereas, this is also again a benign autosomal recessive disorder in this aspect more or less these are similar right. So, both of them are mild Criglan-Naja type 1 was severe it leads into death these cases no. Next what happens regarding the bilirubin level we saw how high it was in Criglan-Naja type 1 type 2 and it was mild in Gilbert where as in Dubein-Johnson it is conjugated bilirubin it is very mild compared to those diseases around 3 to 5 right. Suggesting the existence of alternative pathway for excretion of bilirubin diglyl chloride this is the major research area because if MRP 2 is deficient right and studies have shown the OATP are not fully reliable. So, mass there must be some other pathways of bilirubin excretion and those are still being studied upon and in rotor syndrome again as we discussed there is mild hyperbilirubin both conjugated and unconjugated which is leading to this mixed variety of hyperbilirubin right.

The very characteristic symptom or finding in Dubein-Johnson syndrome if we look at the macroscopic I mean look of the liver if liver biopsy is taken or in a patient if in a patient of Dubein-Johnson syndrome which have been abdominal surgery is done or due to same any other reason in case of postmortem analysis of the liver the liver is due to liver is found to be black in color due to accumulation of pigment. Now contrary to many what many believe there this is due to accumulation of bilirubin diglyl chloride it is actually no conjugated bilirubin accumulation is not causing this black pigmentation it has been found to be polymerized epinephrine metabolites because not only bilirubin diglyl chloride that MRP2 also removes many other organic proteins or anions that are also not removed in case of Dubein-Johnson syndrome and that is leading to the black pigmentation mind it the hyperbilirubinemia is due to lack of removal of conjugated bilirubin, but this black liver disease is not due to accumulation of conjugated bilirubin it is due to accumulation of polymerized epinephrine. In rotor syndrome there is no pigmentation. So, this can distinguish these two diseases alright. Now there is a compound bromosaltheline the when it is bromosaltheline is injected ok we can see the study the conjugation pattern of bilirubin may injecting bromosaltheline and study its excretion a time curve is maintained what is the level of bromosaltheline that is regurgitated back to the plasma.

So, a characteristic curve these are all studies regarding liver. So, specialized were hepatologist they often do these studies, but for us what we need to know BSP injection gives a double hump characteristic curve in case of Dubein-Johnson syndrome and there is no double hump curve in case of rotor syndrome. However, BSP clearances low slower ok compared to normal because it also goes to a conjugation path when

conjugation is defective. Next the excretory pattern the characteristic urinary porphyrin excretion pattern is found in Dubein-Johnson syndrome, but not in rotor syndrome right. In rotor syndrome the porphyrin excretion pattern is like any other cholestatic disease will be reading what is doing a cholestatic disease where bile flow is I mean obstructed or static in the liver.

So, rotor syndrome urinary porphyrin excretion pattern simulates those type of diseases all right. So, we are done with conjugated hyperbilirubinemia I mean congenital hyperbilirubinemia right do not make this mistake congenital means from birth. Next we want to acquired hyperbilirubinemias which are mainly diseases of adults right. So, let us see what are there. So, adult hyperbilirubinemia I mean acquired can also start after birth mind it congenital or inherited means there are some disorders in the enzymes or proteins right.

Acquired is there is no such disorder, but they are caused due to external factors. Some external factor can kick in at very early age that is absolutely normal this is known as physiological jaundice right. So, what happens in the it may happen in the second day of the birth the age right. So, the transient it actually moves of the previous ones they do not disappear even after treatment. So, the transient hyperbilirubinemia which is due to number 1 excess RBC destruction and also immature hepatic system of conjugation specially in preterm babies if the liver is not properly developed they may actually having a difficult I mean deficient conjugating mechanism, but as and when the baby grows up the conjugating mechanism the UGT enzymes they are expressed properly and ultimately this is vanished this goes away and it seldom goes above 5 mg per dl and it generally disappears by second week of life.

So, much milder physiological transient, but a cause of acquired hyperbilirubinemia. This is a term that is known as breast milk jaundice what happens in this actually it is a physiological jaundice, but this physiological jaundice is still prolonged right. Why because this is a high level of estrogen derivative in maternal blood which is excreted through milk right these are babies that are only feeding on mother's milk. So, this material that is derived from estrogen this is in metabolite has been found to inhibit the glucoronyl UDP glucoronyl transferase system alright. So, this again the pathology is same, but this is acquired it is not the effect is not present in the baby, but it is coming from the mother right.

Also some other drugs like sulphur drugs etcetera that actually dissociates the bilirubin and albumin conjugate that may also cause disease in the newborn. So, all these are reasons of acquired hyperbilirubinemia in babies. Now, let us move to reason of acquired hyperbilirubinemia in grown ups or adults right. So, this is a known bilirubin metabolism

pathway where we already know it is being formed it got into a liver small intestine via the intrahepatic circulation it goes it is again goes back to the liver urobilinogen is excreted urobilin starcobulinogen urobilin and starcobulin rurinans tool we already know this. So, adult what happens adult hyperbilirubinemia the defect lies over here right somewhere in here.

So, where it can be right it can be that there is an excess amount of bilirubin that is shunted into the system. So, the whole metabolic pathway there is an excess load so that everything is high right. Next there may be a situation where the liver cells are not functioning properly not congenital not inherited, but due to some problem acquired there may be causes were acquired which are acquired liver cells are not functioning properly. And there may be reasons when even if liver cells are functioning properly the amount of RBCs in circulation are normal, but after conjugation there is problem there is anatomical problem there is obstruction right.

So, we will explore all of these. So, first variety where there is an excess RBC in the system is hemolytic jaundice. Now, again hemolytic jaundice can also be in new born and it can be adult mind it this is not congenital this is not in it this is acquired, but still it is present in the babies right. So, hemolytic disease of the newborn what happens a very common scenario due to mismatch of blood group. This can be an ABO blood group mismatch or an RH blood group mismatch, but the most common scenario which leads to hemolytic disease of newborn is due to RH incompatibility between the mother and the fetus. A situation where the babies are RH positive you know what is RH positive suppose my blood group is O positive you know be A positive someone may be O negative B negative.

So, this positive and negative this is actually the RH factor derived from vicious monkey you must have studied in physiology right. So, baby if he is or she is RH positive and if the mother is RH negative then there is a reaction between antigen and antibody. Often it has been seen that the first baby skips this phenomena, but definitely if the second baby is born with a RH positive, but blood group to an RH negative mother it leads to severe hemolysis and ultimately leads to a condition which is known as a ethroblastosis fetalis characterized by a high level of hemolytic component and ultimately downstream products in blood. So, what happens when RBC is lysed ultimately due to excess hemoglobin excess bilirubin will be formed there will be excess bilirubin glucuronide since or there is no problem in anatomical pathway there will be excess antiherpatic circulation excess 0 bilinogen will be excreted in urine. However, there is a limit to which this excess amount of bilirubin can be conjugated.

When this amount of bilirubin goes below 20 mg per dl the capacity of bilirubin to be

conjugated with albumin I am referring to the albumin bilirubin conjugation it exceeds right. If bilirubin cannot be conjugated with albumin it cannot simply go to the liver to get metabolized. So, up to 20 mind it an excess amount is already going into the liver, but still if the capacity so much exceeded that there is no conjugation activity in the liver then what happens all the unconjugated bilirubin will be high in the serum right and it will be deposited in the brain leading to the all the problems that were discussed in triglarnager type 1 treatment again by phototherapy, but all of this is an acquired defect where there is an excess unconjugated bilirubin all right. Whereas in case of adult, adults can also have a situation where there is an excess hemolysis in the system why due to certain disorders those are congenital or hereditary spherocytosis, glucose 6 phosphate dehydrogenous deficiency leading to hemolytic anemia, autoimmune hemolytic anemia, carbon tetrachloride toxicity. So, all of them what it does it leads to excess amount of bilirubin that exceeds the capacity to bind with albumin right it remains unconjugated in blood is absence of bilirubin area because unconjugated bilirubin can never be excreted in urine right it is only the soluble albumin that is actually excreted.

However, there is excessive excretion of urobilinogen in urine because once urobilinogen is converted to urobilinogen in gut it can be excreted and also stercobulinogen in feces. So, this is about hemolytic region of jaundice in both babies and adults. Next we move on to obstructive jaundice. What happens in obstructive jaundice? See conjugated bilirubin is excreted in blood. So, ultimately what will happen you see if there is complete obstruction the bile cannot go to the small intestine right it is in the small intestine where this bilirubin I mean bilirubinin conjugated bilirubinin bile is actually converted to urobilinogen by the intestinal bacterias and stercobulinogen right.

So, if there is complete obstruction in the common bile duct due to any reason what will happen in the hepatocytes there will be excess amount of conjugated bilirubin right that may even back flow into the systemic circulation. However, there will be no conjugated bilirubin that is going into the gut hence there is no urobilinogen. Hence there is a condition where there will be no stercobulinogen and I already told you stercobulin stercobulinogen to stercobulin gives the characteristic reddish brown colour to the stool. Hence the stool in obstructive jaundice will be absolutely looking pale looking or clay coloured stool alright. So, there may be reason why the obstruction occurs we will be discussing it very soon.

Now what we need to know is during obstruction there is regurgitation of bile in urine and since this is conjugated bilirubin urine will be very high coloured urine will be very high coloured ok. So, you see over here the common causes of obstructive jaundice are chronic aptic hepatitis, biliary cirrhosis, lymphoma that is tumour that are suppressing

the common bile duct primary hepatoma and even the initial stage of viral hepatitis that is known as obstructive stage where there is stasis in the liver that is known as intrahepatic cholestasis right. So, all of these conditions are actually intrahepatic, but some of them in some of them the tumour may be so large that it presses the common bile duct beyond the liver. Those are stones in the gallbladder biliary tract carcinoma in the head of the pancreas enlarge lymph node or lymphoma in the porta hepatis that is the near the opening of the bile duct to the second part of the duodenum which you already know from your anatomical knowledge right. So, reason where bile flow is stopped inside the liver and reasons where bile flow is stopped outside the liver both may contribute to obstructive jaundice pathology and the findings are as we discussed in the last slide.

Now, what happens in the third case that is hepatocellular jaundice? In hepatocellular jaundice the metabolism of bilirubin is I mean hampered. So, liver is not functioning. So, if liver is not functioning properly what will happen? The conjugation in the liver will decrease in pure hepatocellular jaundice. So, if we are strictly speaking hepatocellular jaundice where a function has been totally hampered the liver will not conjugate the bilirubin because one of the important function of liver cell is to conjugate the bilirubin, but is not doing so hence unconjugated bilirubin should have been increased free bilirubin means unconjugated. However, since the diseases often are due to inflammatory reason liver swells up inflammatory edema it what it does it compresses the intracellular canaliculi where bile are actually passing and therefore, there is an element of intrahepatic cholestasis that is actually known as obstructive phase of viral hepatitis because the hepatocellular jaundice mostly it is caused by disease of inflammation of liver that is hepatitis and it is caused by hepatitis virus like A B C D E or G right.

So, what happens in clinical finding we find mixed type of phenomena. So, there are both components of obstruction and there are both components of I mean hemolysis right actually. So, both unconjugated and conjugated bilirubin is increased right and bilirubinemia bilirubin urea will also occur and you know the urobilinogen level in urine may be normal or even may be decreased right because urobilinogen is generally decreased in case of conjugated and there are conjugated element there may or may not be conjugated element in hepatocellular jaundice right. So, if we classify the type of jaundice depending on syndromes or symptoms these are the ones that you need to remember. So, all of these may come as a multiple choice question you should note what are the conjugated causes of conjugated hyperbilirubinemia which is mainly also referred to as prehepatic or hemolytic and the reasons are abnormal red cell antibody drug reaction thalassemia hemoglobinopathy all of these are leading to either from birth or leading to a situation where there is an excess preload excess load of RBC the material

before going into the liver is problematic.

So, it is prehepatic in hepatic the main problem is problem of the liver either due to hepatitis virus acquired or due to condition which are directly injuring the liver cell. For example, autoimmune hepatitis alpha-antitrycin deficiency all these things are what we are doing they are contributing to liver injury right. Lastly post hepatic after liver has done its job there is problem in excretion. So, there may be cholestatic jaundice due to gall stone carcinoma head of pancreas lymph node enlargement etcetera right. Minded the Dubin Jonson rotor syndrome also falls under conjugated or obstructive hyperbilirubinemia right.

In fact, Dubin Jonson falls here and rotor falls here because in rotor I told you there are both conjugated and unconjugated component. Vandenberg reaction is one reaction by which we are we can actually differentiate whether the bilirubin is direct or indirect we have already discussed in the reaction mechanism in last class you can go and see just we need to note that in case of obstructive jaundice is direct positive whereas, in hemolytic jaundice where it is increased there is unconjugated hyperbilirubinemia it is indirect positive. But one thing you need to know in hepatic jaundice the it gives a milder positive reaction to start with then when we mix with it alcohol it gives a full colour hence in hepatocellular jaundice or hepatic jaundice the reaction is biphasic this is the new thing that you need to know right. Now we are left with how the common metabolic parameters are altered in case of different type of jaundice. So, when we are considering bilirubin so, I told you only conjugated bilirubin is soluble in water right.

So, when bilirubin is not conjugated when there is unconjugated bilirubinemia this bilirubin cannot be excreted in urine right. Hence this pre hepatic jaundice where there is unconjugated bilirubinemia this is also known as acolyuric jaundice right. Whereas, in case of obstructive jaundice what happens to the bilirubin this bilirubin is conjugated, but it cannot be excreted into the system right. So, there is no formation of urobilinogen, but this bilirubin itself is excreted in urine which leads to a choluric jaundice. So, high coloured even mustard oil colour urine may be found in obstructive jaundice.

So, mind it when urine is high coloured we suspect obstructive reason when there is excess jaundice, but there is no bilirubin in urine we may suspect non I mean unconjugated hyperbilirubin right. So, this is about bilirubin. Next urobilinogen. So, how do we test bilirubin? Bilirubin is actually detected by Fouchettes test right.

Next we are discussing urobilinogen. Urobilinogen you already know how urobilinogen is formed when conjugated bilirubin goes into the gut it is converted to urobilinogen by the intestinal bacteria. So, if there is no urobilinogen in gut in case of obstructive

jaundice there will when there is no conjugated bilirubin in gut there will be no urobilinogen. So, in obstructive jaundice urobilinogen absent or decreased. In hepatosaccharide what happens generally when in case of initial phase when there is obstruction there is no urobilinogen in urine, but ultimately when the edema clears all right when the severity of the disease decreases urobilinogen start to appear in urine. So, appearance of urobilinogen in urine in case of hepatitis is often regarded as the first sign of recovery.

Again let me tell you edema, hepatitis active inflammatory stage obstructive phase obstructive phase no urobilinogen, but as and when the obstruction clears due to medication due to food habit like that you already know, but I mean you should know that apart from phototherapy right that is the treatment of neonatal jaundice in case of adult jaundice there are medicines that help in liver to I mean this augment this bilirubin metabolism. There are drugs like erso deoxycholic acid that have been clearance of bilirubin and bile salts we are prescribed lighter diet we should avoid foods from outside that may be contaminated with hepatitis virus to start. So, all of these when it decrease the load on liver the edema is cleared up right and ultimately urobilinogen starts to appear in urine and how we can detect urobilinogen by erlich's aldehyde test right that has already been discussed when we were discussing perfiled test. Next bile salts right so, what happens normally bile salts are present in bile, but are not seen in urine. However bile salts are excreted in urine in case of obstructive jaundice alright you should know this bile salts sodium taurocolate and sodium glycolate because bile is being regurgitated to the urine right it is cannot goes via the colonically into the gut.

So, bile salts are present in urine this is also excess amount of bile salts that are excrete I mean raised in blood. So, level of bile salts it causes symptoms like itching and pruritus anyway it is tested by haze sulphur test and positive haze sulphur test in urine it indicates an obstructive jaundice ok. So, here we see the total I mean parameters it is a comparative analysis of different type of jaundice unconjugated bilirubinemia. So, you should be now able to write this on your own you just need to note down the parameters and fill up on your own. So, unconjugated bilirubinemia increased in prehepatic jaundice conjugated it is increased in post hepatic jaundice whereas, both are I mean both unconjugated and conjugated can be increased in hepatocellular jaundice.

Two very important things that you need to know that has not been discussed in detail because this is belongs to the enzyme ology domain the liver enzyme markers alkaline phosphatase is extremely high in case of obstructive jaundice alright. And these enzymes that you already know and discussed during transamination ALT and AST those are raised during hepatocellular jaundice where in other case it may be normal. Mind it since hepatocellular jaundice has got some obstructive component alkaline

phosphatase may increase in case of hepatocellular jaundice right. Next these three have already been discussed bile salts obstructive conjugate bilirubin is present in case of hepatocellular jaundice I mean bilirubin in urine right these are tests of blood these are tests of urine you should not be confused. So, urine bilirubin may also be present in hepatocellular jaundice due to the obstructive component.

Urobilinogen it is present very high in case of prehepatic it is absent in post hepatic whereas this one earliest manifestation of its recovery and presence of urobilinogen in urine alright. So, urobilinogen production is I mean increased in early phases whereas, the in later it is decreased as production is low ok. In case of feces the urobilins are present therefore, it is normal in prehepatic jaundice in hepatocellular jaundice may be normal or decreased, but in case of obstructive jaundice it is almost always decreased and this gives leads to a clay coloured jaundice in urine. Mind it urobilinogen when it is there is obstructive jaundice right urobilinogen production will be hampered and therefore, it will be low in urine whereas, later the excretion of urobilinogen will be normalized in urine alright.

So, do not confuse right. So, to conclude we have discussed the pathway of uptake of bilirubin and heme in total in I mean considering all the three classes we have discussed what are the congenital and acquired reasons of hyperbilirubinemia, we have discussed the causes of jaundice, what are the alteration of common metabolic parameters and different type of jaundice and the tests by which we can diagnose and differentiate all these three types of jaundice alright. So, these are my references. So, those were my references I. Thank you for your kind attention.