Hematology – Biochemistry

(Numbering is according to the 5th set of slides on the website)

ONLY EXTRA NOTES

Slide 1

- Lifespan of the RBCs depends upon the states of its necessary constituents; such as critical enzymes (like G6PD). For example, decreased ATP and proteins can cause ionic imbalances and other functional impairments that may not be reversed.

- The whole process starts by degradation of globin portion (proteins) into amino acids which are then reutilized.

- Heme degradation is initiated by the enzyme heme oxygenase; it works on the alpha methine bridge to produce Carbon monoxide (CO). This is the only source of CO in the body, and it's believed to have a role in signaling pathways.

- Notice that the iron is extracted in the form of ferric (Fe^{+3}).

- The bilirubin is produced in only little amounts; it's a very potent anti-oxidant as it can be re-oxidized into biliverdin, and that biliverdin re-extracts electrons (is reduced) from NADPH to form bilirubin again. Those electrons are used in the anti-oxidation mechanism (this end product is similar to uric acid; the latter is an end product that is also a potent anti-oxidant).

Slide 2

- Bilirubin is insoluble, thus it needs to be attached to albumin to be transported through the blood. There might be some competitive interactions with bilirubin by some drugs having high affinities for albumin, thus detaching this bilirubin from the albumin.

- After bilirubin-albumin complex reaches the liver, it (unconjugated bilirubin) enters there by facilitated diffusion. It then undergoes conjugation by the enzyme transferase; this enzyme adds glucuronic acid (glucuronic acid has a carboxyl group on the 6th carbon while gluconic acid has that carboxyl group on the 1st carbon) to propionate residues to form ester bonds and thus, the soluble bilirubin diglucuronide (conjugated bilirubin) is formed.

- After that, the conjugated bilirubin is actively secreted into the bile to continue its degradation. Notice that this bile goes to the intestines and the bacterial enzymes there take the mission to get it ready for excretion by removing the conjugated glucuronate. Bilirubin is converted into urobilinogen (converted after that into urobilin to be excreted with urine) and stercobilinogen which is therefore partially oxidized to give stercobilin (component of feces). Notice that if the stercobilinogen is left for more time under the air, it undergoes further oxidation and gives more stercobilin. This additional amount makes the feces darker in color.

Slide 5 (see last year's slide 7 in the 4th set of slides)

- A summary.

- Note: Bile pigment is bilirubin; it's different from bile acids (form bile salts) that are made from cholesterol.

Slide 8

- Hemolytic jaundice is also called prehepatic jaundice. The normal daily production of bilirubin is about 300 mg. Liver can normally conjugate up to 3000 mg of bilirubin as a maximal capacity. If there is a massive hemolysis (like in HbS, PK or G6PD deficiencies), excessive amounts of bilirubin are being produced which the liver cannot take care of, thus the excretion in bile, urobilinogen in urine and unconjugated bilirubin in blood are all increased.

- If there is a hepatocellular jaundice, the damage to liver causes the conjugation capacity to be decreased (higher unconjugated blood bilirubin), the secretory mechanism to be impaired (lower secretion of conjugated bilirubin) and the urobilinogen to be increased in urine.

- In obstructive jaundice, high levels of conjugated bilirubin are present in the blood (because they cannot be taken through the bile to the intestines to be modified and excreted). This conjugated bilirubin can also cause obstruction and damage to the liver, and that will impair its function (conjugation capacity … etc), so there might also be high levels of unconjugated bilirubin as well as conjugated one as a result of this damage.

Slide 9

- The lower curve in the first diagram is the premature one.

- Infants with toxic bilirubin levels can be put inside an incubator and undergo phototherapy. We give them blue fluorescent light to convert the insoluble bilirubin into another soluble isomer.

Slide 10

- Genetic deficiency of conjugation is more common than deficiencies in secretion mechanisms.

- Laboratory test: it's one of the most used and requested tests to measure the amounts of conjugated and unconjugated bilirubin. The reaction used in this test is called Van Der Bergh reaction; we react Diazotized sulfanilic acid with the soluble conjugated bilirubin and they form red azodipyrroles (because this conjugated bilirubin reacts properly, it's called direct bilirubin), and then we measure this direct bilirubin. Then we repeat the test but this time with the random bilirubin sample (mixed conjugated & unconjugated) that needs to be measured; here we add a solubilizing material which is methanol in order to make everything soluble to be able to react with the sulfanilic acid. Here we measure the total amount of bilirubin (mixed). Finally, we subtract the direct (measured before) from the total amount, and we get the unconjugated bilirubin (indirect; it's called this because it cannot interact directly as it is insoluble).

(Last 9 minutes of the lecture talk about a new topic, however their slides are not available yet)