Hematology – Biochemistry

(Numbering is according the 3rd set of slides on the website)

ONLY EXTRA NOTES

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- Notice the examples (not for well-detailed memorizing but for knowing the general idea).

- In Riverdale Hb, the B6 Glycine (small amino acid) is replaced by arginine (bulky amino acid), thus causing an instability in the tertiary structure.

- In Hammersmith Hb, Phenylalanine (hydrophobic) is replaced by Serine (hydrophilic), thus producing weakness (instability) of heme binding.

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- Sickle cell anemia is common in Black Americans.

- In electrophoresis at alkaline pH, HbA moves toward the anode (+) because of its negative glutamate (fastest to move), HbS moves slower because of the valine (hydrophobic) and the slowest is HbC because of the positive side group of lysine (almost remains near the cathode).

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- RBCs with normal Hb are flexible, but here they are rigid and fiber-like, thus no pass through capillaries happens, subsequently blocking of the capillaries in many organs and that causes anoxia, pain and sometimes death of cells.

- Sickle cell trait people (one normal gene product and another abnormal one) have one half of normal Hb which interrupts the other abnormal Hb half from forming polymers (like when proline interrupts the formation of helical structure in Hb chains). So, those people have normal life but should avoid exercises and living in high altitudes especially for those who are at high risks of infarctions.

- Trait people have natural resistance to malaria because the plasmodium (malaria parasite) attacks RBCs, thus by having one half of abnormal Hb, RBCs half-life becomes lower so the parasite will not survive nor complete its life cycle.

- There are overlaps between high incidence rates of sickle cell anemia and malaria in Africa (resemble also the overlap in Jordan Valley between G6PD deficiency rates and malaria's. We see high incidence rates of G6PD deficiency there because a long time ago, there were high rates of malaria so people with genes responsible for G6PD deficiency had better survival opportunities).

- Management of disease (not trait): they need frequent blood transfusions especially in severe cases, frequent hydration, analgesics and antibiotics (against infections). Hydroxyurea is an antineoplastic drug; it's mentioned here because it increases the proportion of HbF in the body. This fetal Hb acts as the normal Hb in sickle cell trait people, and that means that this HbF will interfere with the polymerization of abnormal Hb in diseased people and thus, will decrease the severity of the disease. This also resembles cases with hereditary persistence of fetal hemoglobin (HPFH); those people develop milder sickle cell anemia.

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- Normal Hb doesn't have protruded hydrophobic residues from beta chains. In HbS, beta chains have valine instead of glutamate and those hydrophobic residues will protrude outside the beta chains. On the other hand, there are hydrophobic pockets (grooves) in all the deoxy- forms and they surprisingly fit with the protrusions of valine, thus enhancing the formation of aggregates (they form only in the deoxy- HbS).

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- Anything that increases the deoxy- form will increase the severity of the disease by enhancing aggregation, and anything decreasing the deoxy- form will relieve the aggregates.

- Notice that the mentioned examples are all negative effectors (that cause shift-to-right), so they all decrease affinity > increase the deoxy- form > enhance aggregation & severity.

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- Normal derivatives have different absorbance spectrums (wave lengths) and this is important in diagnostic procedures.

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- Either deficient enzyme or alteration in amino acids sequence (tyrosine instead of proximal histidine for example) can cause inherited methemoglobinemia.

- Minor amounts of HbM are naturally formed (electron transfer may accidently happen), but if this happens, it'll be taken down by the so-called reductase.

- Cyanosis means very low affinity for oxygen (near zero) resulted from excessive accumulations of HbM (no binding to oxygen but to water).

- If methylene blue dye is not the proper treatment (in G6PD deficiency for example), we use ascorbic acid.

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- Upper mechanisms are well-known anti-oxidant processes; however, if HbM is formed, reductase can eleminate it.

- Notice the examples of some oxidant drugs/chemicals that may contribute to ferrous oxidation and HbM formation.

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- If Hb encounters a sulphur-containing compound (H_2S) and the conditions of HbM formation are met, sulphahemoglobin will be formed.

- It cannot be treated (unlike HbM), so we have to wait for the RBCs to disintegrate and lyse.

- CO interrupts oxidative phosphorylation (poisoning).

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- In free heme, there will be poisoning at even natural concentrations of CO present in our bodies (free heme affinity for CO is 20000-25000x more than affinity for O_2). In Hb and Mb, the affinity for CO is 200-210x, 25-50x more than affinity for O_2 , respectively. This concept has been explained in old studies as follows: In free heme, there is no close distal histidine, and the bound CO will have a linear mode of binding. However, when the heme is within the Hb molecule, the distal histidine will cause a steric hindrance to occur and thus, the angle will become 120 (bent) and this definitely decreases Hb's affinity for that CO. Recent studies have come up with new reasoning.

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- New studies revealed that in the oxygenated Hb, the electrons on the 2 oxygen atoms will be more concentrated toward the oxygen closer to histidine (thus has a partial negative charge), and this charge will make some hydrogen bonds with the distal histidine, and that bond will increase the stability and affinity for the Hb toward oxygen. As a result, the ratio between the affinity of Hb for CO compared to its affinity for oxygen will be decreased from 25000x to about 200x, because the affinity for oxygen is increased **NOT** because the affinity for CO is decreased like old studies.

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- Notice the hyperbolic shape when the CO.Hb concentration is increased, causing a shift-to-left. The CO binds the Hb from one side, and the other side will bind and entrap oxygen with high affinity > no delivery.