Sid is a high school student who has decided to start exercising before school. After eating an early dinner the night before and skipping breakfast that morning, Sid goes to the gym. He feels fine at first, but shortly into his work out he begins to experience muscle fatigue, heavy breathing, increased heart rate, lightheadedness. Sid begins to hyperventilate and passes out and is transported to the emergency room. Doctors run tests and find he has low blood glucose. The doctors test Sid’s insulin and glycogen. Insulin is what transports glucose and glycogen can be degraded to glucose. They discover that Sid’s insulin is in normal amounts and is acting normally. His glycogen levels, however, are very low. This contributes to his low blood glucose levels because there is not as much glycogen as is necessary to degrade to raise Sid’s glucose levels.

The doctors consider Sid’s muscle fatigue. Sid had just begun exercising, so shouldn’t have tired so quickly. They test his muscle oxygen uptake and find that his muscles are not getting enough oxygen. The doctors question why his muscles would get low oxygen, and decide to run a pH test of Sid’s blood. The results show that Sid has a high blood pH, showing that his blood is more basic than normal. The doctors suspect this is a result of low levels of CO₂ being accumulated into the blood. They run tests and find that Sid’s blood also has low CO₂. Why did Sid not have enough glucose or CO₂? Since Sid didn’t have breakfast, gluconeogenesis should have proceeded in order to raise his glucose levels.
However, Sid still has low glucose levels. The doctors test Sid’s levels of gluconeogenesis intermediates and find that he has a high level of pyruvate and low levels of every other intermediate. Pyruvate is needed to run gluconeogenesis and get the glucose needed to raise Sid’s blood sugar. However, it seems that the pyruvate is not being converted to anything, inhibiting gluconeogenesis. The doctors search for a solution and find that his ATP levels are very low. They conclude that Sid does not have enough ATP to make gluconeogenesis proceed. ATP is necessary for the conversion of pyruvate to oxaloacetate, which is the first step in gluconeogenesis.

Since ATP is generated from the Krebs cycle, the doctors decide to run yet another test and find the levels of Sid’s Krebs cycle intermediates. They find that Sid has accumulated a large amount of succinate, and has very low levels of fumarate and malate. Because of this, they suspect that Sid’s Krebs cycle is inhibited at the oxidation of succinate to fumarate. Succinate is not being converted to fumarate, causing high levels of succinate and low levels of the intermediates resulting from this reaction (fumarate and malate). Because the Kreb’s cycle is not finishing, Sid has low levels of ATP, NADH, FADH₂, and CO₂. This explains Sid’s inhibited gluconeogenesis, low glucose levels, heavy breathing, and low muscle oxygen. The doctors confirm that this reaction is inhibited by testing Sid’s levels of succinate dehydrogenase, the enzyme that catalyzes the oxidation of succinate to fumarate. Sid does indeed have a deficiency in succinate dehydrogenase.

Biochemical Explanation:
Glycolysis and blood chemistry-

Low ATP levels will affect glycolysis at the phosphofructokinase control point, causing glycolysis to proceed. ATP is a product of glycolysis, so a high level of ATP would inhibit glycolysis. Low CO₂ causes lower levels of bicarbonate being made and low free H⁺ ions in the blood. This causes hemoglobin to switch to the R state, holding onto O₂. Not as much oxygen is released by hemoglobin to be transported to the muscles, causing Sid’s body to tire quickly. Oxygen would also not be transported to the brain, which is probably the cause of Sid’s unconsciousness. Normally, H⁺ ions are used to make ATP. With low levels of H⁺, Sid’s low ATP level is reinforced. So low levels of each results in activating glycolysis at the phosphofructokinase control point and again at the pyruvate kinase control point where low ATP activates the reaction of phosphoenolpyruvate to pyruvate. This results in the completion of glycolysis, giving the products of pyruvate and ATP. ATP is being generated each time glycolysis happens, so eventually Sid’s ATP levels would raise high enough to inhibit glycolysis. After some time, glucose would slow down, or even stop, being converted to pyruvate. Sid’s glucose levels will slowly raise back up due to the deactivation of glycolysis.

Gluconeogenesis-

When glycolysis is activated, the pyruvate created would in times of starvation cause gluconeogenesis. However, this process is energetically expensive and requires the energy from ATP being broken down to ADP. The first step of gluconeogenesis requires ATP to be converted to ADP, phosphorylating pyruvate to oxaloacetate. However, with Sid’s low levels of ATP, this will happen very slowly, if at all. Without running gluconeogenesis to
get glucose, pyruvate is accumulated in excess. With low $O_2$ levels in the muscle due to hemoglobin being in the R state, that pyruvate is converted to lactate. This protonates the blood, lowering blood pH, favoring the T state of hemoglobin. Sid’s high blood pH will eventually be lowered due to this increase in lactate. However, hemoglobin in the T state does not hold on to oxygen. The protons in the blood from the formation of lactate stabilize the T state of hemoglobin. So hemoglobin still does not act as an effective transporter of oxygen since it is holding on to protons, limiting oxygen supply to the brain and the muscles. Equilibrium between the T and R state should eventually exist because of the increase in lactate and the increase in protons in the blood. Because Sid has low oxygen and CO$_2$, his breathing became fast and strained. He began to hyperventilate, trying to increase his oxygen intake. However, this led to him letting off even more CO$_2$, further decreasing both CO$_2$ and O$_2$ levels.

Pyruvate is also converted to Acetyl-CoA. This requires thiamine, riboflavin, and niacin. Because of this process occurring more, Sid’s levels of those three vitamins should also be increased. More Acetyl-CoA is accumulated. This Acetyl-CoA can go to the Krebs cycle, but since the Krebs cycle is not completed, it will result in further increase of succinate. Too much Acetyl-CoA also will cause fat synthesis. So if Sid continues to be unable to produce glucose in times of starvation, he will increase his fat levels.

Glycogen metabolism-

With glycolysis activated, glucose is converted to pyruvate. Without gluconeogenesis also proceeding, that pyruvate cannot be converted back to glucose in times of fasting. Consequently, glycogen levels decrease because there is decreasingly less
glucose to be converted to glycogen. Therefore, glycogen degradation will occur while possible to give Sid energy. If all the glycogen is used up, and Sid is unable to increase his glucose by gluconeogenesis or glycogen degradation, blood glucose will be low enough to warrant hypoglycemia. This can cause impaired function of the brain, fatigue, and unconsciousness. This contributed to Sid’s quick fatigue and caused him to pass out.

Pentose phosphate shunt-

The pentose phosphate shunt starts with glucose-6-phosphate. With decreasing levels of glucose during fasting, inhibited gluconeogenesis, and glycogen degradation until there is no glycogen left, this pathway cannot even begin. Without this pathway, the products, ribose and NADPH, cannot be created. Ribose is important in RNA and DNA and NADPH is used to make fat.

The problem started in the Krebs cycle. With a deficiency in succinate dehydrogenase, Sid can’t complete the oxidation of succinate to fumarate very effectively, if at all. Because of this, he accumulates a lot of succinate. The excess of succinate will prevent the Krebs cycle from moving forward, preventing the CO₂, NADH, FADH₂, and ATP products. Succinate cannot be converted back to any of the previous intermediates of the Krebs cycle because the reactions that lead to succinate are one-way reactions. The decrease in CO₂, NADH, FADH₂, and ATP lead to inhibition of gluconeogenesis and glycogen degradation. The caused Sid to have low blood sugar, and resulted in decreased oxygen transport to Sid’s muscles and brain. This caused Sid’s muscles to tire quickly, caused him to breathe heavily, and then caused him to enter into an unconscious state.