FRAMING ANALOGY - BATTERIES NOT INCLUDED

Christmas morning, 1987, 5:40 a.m.

Six-year-old Billy Walton squirmed in his bed and looked at the clock. His parents had told him the night before, firmly, that Santa doesn't come until 6 in the morning, and if he went downstairs to get his presents before then, the elves would take them back to the North Pole. But they just said he couldn't go downstairs. They didn't say he had to be asleep—and who could possibly sleep when the Terror Tank 8000 was waiting downstairs?

It was the toy of his dreams: a remote control tank that could climb walls, jump over holes, and fire both lasers and missiles at the same time. The first TV commercials for it came on the day after Halloween while Billy was eating his leftover candy and watching G.I. Joe. The day after that, Billy wrote the first of 54 letters to Santa—one for every day between Halloween and Christmas Eve—requesting a Terror Tank 8000. Some letters he placed in the mail; others he gave to any white-bearded, chubby old man he encountered, in case this was Santa in disguise, checking (as he always threatens to do) who's naughty and who's nice. He even stopped picking on his little brother, knowing that he and the Terror Tank 8000 could make up for it later.

Six o'clock! Billy leapt out of bed and catapulted downstairs. One box was bigger than any of the others under the tree; as his parents and little brother stumbled sleepily after him, Billy tore the wrapping off the glorious Terror Tank 8000, pried the box open and the toy from its wrappings, and pressed the button on the remote control.

Nothing happened.

While Billy burst into tears, his mother checked the label on the box to see what might have gone wrong. "Uh-oh," she said. "Batteries not included. We need 20 D batteries—18 for the truck and two for the remote control."

"It's not a truck, it's a tank!" Billy wailed.

"Hey, settle down," his dad said. "Settle down. Look at this, buddy, I came prepared." He produced two 10-packs of D batteries. "Help me get these in there."

"Mike, you didn't buy those at Hardware-R-Us, did you? I got an extension cord there the other day and it blew out my hairdryer." Together, Billy and his father installed the batteries and tried again to begin the Terror Tank 8000's first mission of mayhem. But the Terror Tank 8000 didn't climb the wall; instead, it bumped against it. It couldn't leap over the sink; it just fell in. It would go forward, but only slowly. The

laser lights were dim and the missiles, instead of soaring across the room like in the commercials, just dropped. "Dad, why isn't it working?"

"I'm sorry to say that I think your mom is right—sorry, babe, that came out wrong. What I mean is that I bought these batteries for cheap. They look fine, but it seems they don't work so well. Just to be sure, let's check them in something else." He rummaged in the kitchen drawer and pulled out a flashlight, which worked fine with its present batteries; with the new batteries, though, its light was dim. "Well, buddy, there's your answer. The tank just can't get enough energy out of these cheapo batteries. The good news is that when stores are open again, we can get some regular batteries and the Terror Tank 8000 should be able to ride again."

Scientific Connection

Energy is the capacity to do work; the more energy you have the more work you can do. Of course, if you don't have any energy then you can't do any work. If there is an energy failure in a system, the observable sign is that elements of the system stop working or don't work as well as they should. In this case the work that Billy wanted to see was the fast movement, glowing lasers, and firing missiles of the tank. However, because the batteries didn't have enough energy stored in them, the tank could not do all of the cool things that it was supposed to. It moved, but slowly instead of fast; the laser lights were dull instead of bright; and the missiles didn't really work at all. In the same way, parts of a biological system working poorly or not at all can be a sign of an energy-source problem. The mitochondria are the battery of the cell: it is responsible for producing energy so that cellular work can be done. People with mitochondrial disorders have a set of bad batteries in pretty much every cell of their body. Usually tissues that require lower amounts of work to function tolerate this better, but tissues that require a lot of work to function (heart muscle, skeletal muscles, and nerves) suffer severely.

Mitochondrial disorders fit into a spectrum depending on how many diseased mitochondria the sufferer has per cell. This means that two people with the same disorder can have totally different disease processes based on the proportion of diseased mitochondria to healthy ones. Some people are barely affected while others die in childhood. Just as with the Terror Tank 8000, the proportion of good batteries to bad ones determines the overall functioning: more good batteries than bad means better functioning, and the opposite is also true.

One other fact makes mitochondria stand out: mitochondria are responsible for replicating themselves, so they have their own DNA. All of the mitochondria in your body originate in the oocyte, which is the genetic information you get from your mother's side. The proportion of good to bad mitochondria in that oocyte determines how severe the disease will be in your body. Typically mitochondrial diseases cause problems with multiple systems of the body; as noted above, the most striking abnormalities are associated with the muscles and nerves because those tissues require a lot of energy to function. Here are some examples.

MITOCHONDRIAL DISEASE 1

You are an ophthalmologist. A 20-year-old woman comes to your office and wants to know why she is losing her vision. In the past few months her vision has progressively decreased in both eyes and now she is nearly blind. Questions reveal that she's not the only one in her family whose vision has suffered: she has two brothers who both went blind much earlier in life. Her mother had progressive loss of vision, but never went completely blind.

Scientific Connection

This is a mitochondrial disease known as Leber's hereditary optic neuropathy (LHON). The target tissue is the nervous system, as evidenced by the degeneration of the optic nerve and the development of blindness. This disorder most frequently presents as a loss of vision in both eyes leading to blindness at a young age. This vignette also captures the spectrum of the disorder, with two brothers affected much earlier than their sister and a mother who has a slightly milder case. This means that the mother inherited fewer of the oocytes with diseased mitochondria from her mother; the early blindness of the two boys means that out of everyone in the family, they inherited the greatest percentage of diseased mitochondria per cell. The variability is due to the different numbers of diseased mitochondria in the oocytes that gave rise to each child. All the children are affected, as is the pattern of inheritance with mitochondrial disorders.

MITOCHONDRIAL DISEASE 2

A normally healthy nine-year-old girl is having an after-school snack at the kitchen table when she realizes that she can't move her right arm and leg. She wants to call for help, but she can't speak. She gets her family's attention by knocking a glass off the table with her left arm; they rush her to the hospital, where doctors determine that she has had a stroke. When tested, her serum lactate is 5.6 mM (normal is <1.5 mM) and questions about her family's medical history reveal that she had a little brother who died suddenly before his first birthday.

Scientific Connection

This is a case of MELAS syndrome: Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes. Like LHON above, it is caused by mitochondria that do not work as well as they should. The mitochondria cannot make enough energy to satisfy the work needs of the nervous system.

This lack of energy caused the little girl's stroke. A stroke occurs when the cells of the brain don't have enough energy to keep working. The result is a loss of function, like the inability to move the limbs on half of her body and the loss of speech. She has a high blood level of

lactate because the only way to make energy outside of mitochondrial mechanisms (oxidative phosphorylation) is glycolysis. In the absence of working mitochondria, lactate is the result of glycolysis, which is why the doctors tested for it in the case of this stroke. High levels of lactate can acidify the blood and disrupt the electrical workings of the nervous system and the heart. Her little brother also had this disorder, but he had more diseased mitochondria per cell and died of a lethal stroke at a very young age.

MITOCHONDRIAL DISEASE 3

You are a pediatrician. Your newest patient is a young boy whose guardian tells you that he has been periodically falling, twitching and losing consciousness. The boy is in the tenth percentile for height and shows signs of mental impairment. He has progressively lost his hearing and is now deaf, and your tests reveal that his vision has been deteriorating as well. The boy has difficulty walking and coordinating motions; his reflexes are perfect but his muscles are universally weak. You take a sample of his muscle tissue and examine it: under the microscope the mitochondria look clumped together and the muscle cells are ragged, as though they have been ripped apart.

Scientific Connection

This is a case of MERRF: Myoclonic Epilepsy with Ragged Red Fibers. It is a mitochondrial disease that typically presents with seizures, ataxia (inability to coordinate muscle movement), deafness, vision loss, muscle weakness, stunted growth and poor mental development. The tissues with high-energy demand, like the nervous system and the muscles, are heavily affected. The loss of hearing, loss of vision, seizures, poor mental development, and loss of coordination are all evidence of energy failure in the nervous system. The weakness of the muscles and their torn appearance under the microscope is evidence of energy failure in muscle tissue. The muscle cells don't have enough energy to do their job and survive so they choose to do their job and die, resulting in their ragged, ripped appearance.

MITOCHONDRIAL DISEASE 4

A woman brings her young son in to your office because of frequent and recurring infections. The boy is short for his age. His mother says that he is winded every time he goes upstairs and that he tires easily in general. Your questions reveal that she had a brother and an uncle who had similar symptoms. A blood test shows extremely low numbers of white blood cells, which explain his frequent infections.

Scientific Connection

Barth syndrome is another mitochondrial disease. It's characterized by increased risk of infection, rapid fatigue and constant feeling of being tired, delayed growth, learning disabilities, and poorly working heart. Death usually is due to heart failure or infection. Once again, this disease shows a pattern dominated by energy failure in muscle tissue. As a result there is generalized muscle tissue weakness, evident in both the skeletal muscles and in the heart. Unlike the previously discussed mitochondrial disorders, the inheritance pattern associated with this is X-linked recessive, which is why the mother's uncle and brother are affected as opposed to her and all her children. While mitochondria are responsible for replicating themselves and making most of their own proteins, some of their proteins are made from information in the nucleus, which accounts for this pattern of inheritance.

MITOCHONDRIAL DISEASE 5

You are a first-year medical student doing a physical on a woman in a hospital. When you look into her eyes you notice an unusual color in both of her retinas. You ask her to follow your finger with her eyes and she can't move her eyes from side to side. When you ask her to stand up and walk to the other side of the room, she does so with a wide unsteady gait like she is drunk. Her muscle strength is poor and she has a history of heart problems.

Scientific Connection

This woman has Kearns-Sayre Syndrome. It is characterized by abnormal retinal pigment accumulation, opthalmoplegia (inability to move eyes from side to side), myopathy (generalized muscle weakness), ataxia (poor coordination), heart problems, and diabetes. This disease has all the hallmarks of mitochondrial dysfunction including reduced function of the nervous system, skeletal muscles and heart.

Take Home Message: Mitochondrial diseases cause energy failures in multiple tissues. The tissues with high energy demands suffer the most dysfunction. The skeletal muscle, cardiac muscle, and nervous tissue are the most frequently affected. The degree of severity depends on the proportion of diseased to healthy mitochondria per cell.