

Conversion Into Krebs Cycle Intermediate

THE CASE OF THE NOT SO STINKY DIAPER

Robert Jenkins, Jr., lay on his back on a soft white sheet. He moved his arms and legs tentatively, as if he wasn't sure if they worked, and stared at the faces leaning over him. "Does he know who I am, Mommy?" his older sister Mary asked.

Pamela smiled exhaustedly at her energetic seven-year-old. "He will real soon, especially if you do what you promised me before he was born. You remember how we practiced on your dolly? Show me how you can do it."

Mary carefully lifted Robbie's legs, undid the old diaper and wiped his behind with it. "Remember, don't try to throw it out right away," Pamela cautioned. "Put it to the side and get the new one on him first. This baby belongs to the whole family. It'll be up to all of us to take care of him."

"I know, Mommy," Mary said scornfully, already unfolding the new diaper and tucking it around Robbie's underside. "Wait'll you see," Mary assured her mother, closing the lid of the diaper pail. "You won't ever know he soiled his diaper. You won't even have to smell it. I am Chief Diaper Changer Mary Jenkins reporting for duty."

Pamela giggled and praised her daughter, mentally thanking Heaven that this was one task she wouldn't have to do. Her husband—dubbed "Big Rob" by his friends as soon as they'd picked the baby's name—had sworn to take on nighttime diapers and feedings. Unfortunately soon after Robbie was born he was forced to go out of state to work on a big contracting job. The work paid extremely well but forced him to live apart from the family for several days out of the week, and when he came back he was too tired to do anything. Little Robbie seemed to be keeping a mostly nocturnal schedule, requiring nighttime feedings but sleeping for most of the day. After the exhausting nights Pamela was extremely grateful to have Mary to help change Robbie's diapers in the afternoon while she got some much needed rest.

Seven-year-olds don't always keep their promises, but Mary was as good as her word, playing or watching TV near her brother and whisking him away to the changing blanket whenever it was necessary (and sometimes when it wasn't). "You won't ever know" was a bit of an overstatement, but Pamela rarely changed any diapers at all. On Saturday, Pamela's parents came over for dinner as they always did. An hour after Robbie was fed Mary gave him his evening changing. Her mother and grandma worked on dinner and Big Rob, who just returned home from a





month of work, watched TV with his father-in-law, who didn't even know how to turn on a stove. "Your mother tells me you're a great big sister, Mary," her grandma said. "I hope Robbie isn't too much trouble for you." Pamela rolled her eyes. Mary said quickly, "He's such a good baby, Grandma. He's so sweet, even his diapers smell sweet."

"Isn't she an angel," Pamela's mother cooed. Pamela smiled too and said, "That's pretty clever, Mary."

"What does clever mean again?"

"Um—well—in this case it means I think you made a good joke."

"It's not a joke. They really do. Not when he does number two, but his pee smells really sweet, like pancakes, and sometimes his skin does too. I think he might be magical."

"Like pancakes? Mary, is this something you saw on TV?"

"No!" Mary was getting perilously close to a tantrum. Why didn't grownups ever believe anything kids said? "Wait here, I'll go get his last diaper" A few minutes later she called out, "Okay, Mommy, smell," and held Robbie up for Pamela to take. Pamela hooked a finger in the back of the diaper, sniffed, and said, "I just smell poop, Mary. Nothing sweet."

"Let me." Mary took him back and sniffed too. "It doesn't smell like it now. But sometimes it does, especially when he hasn't been fed in a while." Noticing Pamela's expression, she shouted, "You think I'm making it up but I'm not!"

Pamela turned to her mother. "Ma, have you ever heard of anything like this?"

"No, dear," her mother said vaguely. "We'd better call the men in—the chick-en's just about ready."

Later that night, Pamela asked her husband, "Rob, have you noticed a weird smell coming from Robbie's diapers?"

Big Rob laughed. "That wouldn't be weird, honey."

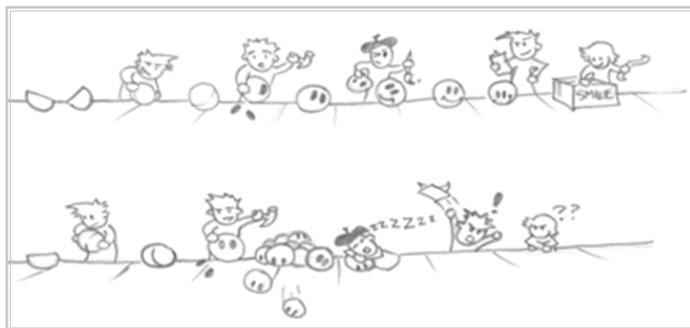
"I mean weird for a diaper. Like ... sweet."

"You think I smell them? Usually I'm doing my best not to smell them."

Pamela was strangely unsettled by Mary's observations and decided to do the afternoon changings herself from now on. Mary was an honest kid and not a particularly imaginative one; she always wanted to know how things really worked. Pamela's apprehension increased as the afternoon drew near. When it came time for Robbie's changing, Pamela nervously unsnapped Robbie's onesie and sniffed his diaper. A sweet smell met her nose. Had she somehow bought scented diapers by mistake? But this didn't smell like Fresh Linen or Spring Rain or any other marketing chemical; it smelled like maple syrup. "Pancakes," Pamela said out loud. Robbie gurgled. She thought, "Maybe it's nothing. Maybe lots of people's pee smells like syrup—how would I know? It just doesn't seem natural, though." She sat with Robbie a while, stroking his tiny hands. Then she unearthed her phone from the couch cushions and called the pediatrician.

"It's a good thing you came in. This sounds like it could be Maple Syrup Urine Disease," said Dr. Lillian Bit, putting a Band-Aid on Robbie's thigh where she had drawn blood.

Normal Metabolic Disease



“Mary’s the one who noticed it,” Pamela felt compelled to say, but added defensively, “I change his diapers too, but I didn’t notice this.”

“Hmm. Were you mostly changing him after feedings? If he has a mild version of the condition, and it seems like he does since his neurological exam is fine and the smell is not always present, the symptoms might not show up if he has been recently fed. The disease manifests when certain branched chain amino acids are burned to make energy, this can occur when an excess of them are ingested or during fasting when muscle proteins are broken down into amino acids for fuel. Since these branched chain amino acids are present in almost every protein the generalized break down of proteins into amino acids to be used for fuel could precipitate the signs of this disease. It is likely since his metabolism is through the roof that all amino acids in his diet would be used for protein synthesis and thus would not be used for energy production. As he slept all day he would be fasting and so the smell would be present in his evening diapers but absent from his morning diapers after he had been fed several times during the night.”

“So you’re saying this is an actual disease.”

“Oh yes, a silly yet descriptive name for a serious disease of amino acid metabolism that can cause permanent neurological damage and death. However, in more severe cases the smell is present more frequently as it is a sign of toxicity. Pamela, I’m 99% sure this blood I’ve drawn will confirm what I’ve just said. I’ll give you some handouts to take home, about how to set up a diet and a feeding schedule that will keep Robbie from going into this state, and we should schedule a checkup between now and his next appointment—say two weeks from now. The doctor smiled. “Good job, Mary. Maybe you have a future as a physician specializing in Metabolism and Genetics.”

Scientific Connection

Metabolic disease can be a complicated topic, but if you are capable of understanding the workings of an assembly line then you are more than capable of rationalizing the basis of metabolic disease. In a traditional assembly line, workers start with raw materials and each worker in the line does a specific job. As the product passes from worker to worker it is modified slightly until a complex product like an automobile is created. Assembly lines are as important to biology as they are to industry: proteins are the factory workers of biology and often work together exactly like this to convert one chemical, or several chemicals,

into an end product. Any chemical that has been processed in this way is considered to be “metabolized”. These chemical assembly lines are more properly called “metabolic pathways”, and proteins that participate in them typically get their names from the job they do. These names are usually highly descriptive but unfortunately instead of “riveter”, “roll turner” or “glass installer”, they are a little more unwieldy, like “pyruvate carboxylase”. However, just because someone has a job does not mean that they will be good at it.

If an assembly line worker is incompetent then partially assembled products will start to accumulate and back up, resulting in chaos.

A perfect example of this can be seen in this classic clip (<http://www.youtube.com/watch?v=4wp3m1vg06Q>) from I Love Lucy where Lucy and her friend Ethel work in a chocolate factory to disastrous ends. If a protein in a metabolic pathway is bad at its job or (even worse) not present at all, incompletely processed chemical intermediates will back up and accumulate until they reach toxic levels. Some metabolic diseases like Maple Syrup Urine Disease can be considered poisonings but instead of the poison coming from the outside world, it's made inside the person's body due to defects in a metabolic pathway. A person with a metabolic disorder can consume something non-toxic and because it cannot be completely processed its intermediates will accumulate and poison the individual. Another example of a metabolic disease is Hereditary Fructose Intolerance in which a simple glass of fruit juice can be lethal. Treatment usually consists of complete avoidance or minimal exposure to whatever it is that can't be metabolized. In a factory you can fire a bad employee and hire a new employee that will hopefully do a better job. In biology you aren't so lucky, because your body makes its own “worker” proteins based on the information contained in DNA. The segment of DNA that tells you how to make a specific protein is called a gene. In cases of metabolic disease, a gene of the affected individual has been altered or “mutated” so that the information on how to make a key protein is bad. This leads to the production of a protein that is horrible at the job it was originally designed to do. The sequence of genetic mutation, incompetent protein, and resulting disaster is the basis of metabolic disease.

In order for any nutrient (sugars, fats, amino acids) to participate in cellular respiration and be used to make vast amounts of ATP, it must first be converted into a Krebs cycle intermediate. In the case of poor little Robbie, Branched-chain α -ketoacid dehydrogenase complex—a key protein involved in the pathway that converts branched chain amino acids (valine, isoleucine, leucine) into Krebs cycle intermediates—is defective. This means that trouble is going to start whenever excess dietary protein is used to make ATP or when bodily protein is broken down for ATP generation during fasting states or illness. When any of these situations occur, incompletely processed intermediates that possess a sweet odor similar to maple syrup accumulate in the blood; when they reach

high enough levels they will be excreted in the sweat and urine of the affected individual, thereby producing the characteristic odor. The maple syrup smell is often the signal that someone has this disorder and is being poisoned (many disorders involving amino acid metabolism have distinctive odors associated with them, most of which are really bad: “boiled cabbage”, “mice”, “tomcat urine”). Maple Syrup Urine Disease is not one specific disorder but rather a collection of disorders that vary in severity based on how badly Branched-chain α -ketoacid dehydrogenase complex is doing its job. In the most extreme and more classic case, Branched-chain α -ketoacid dehydrogenase complex can't do anything at all. In this most severe form the smell is present within the first week of life and signs of nervous system toxicity like poor feeding, rigid muscular paralysis, seizures, coma, and death follow within a week or two. Robbie has one of the milder forms of the disease in which the smell is occasionally present after fasting, because while his α -ketoacid dehydrogenase complex can't work as well as most people's it does still retain some activity.

The treatment is to prevent amino acids from being used in cellular respiration and limit the amount of branched chain amino acids in the diet. It is good for an individual with this disorder to eat fairly regularly and avoid fasting. As long as this individual does not eat anything containing excessive amounts of protein production of toxic intermediates will be minimized, so bread is good and prime rib is not. Robert will have to avoid both excessive amounts of protein in his diet and prolonged fasting for the rest of his life to avoid toxicity. Thanks to the vigilance of his big sister and the suspicions of his mother, Robert's case was caught early enough to prevent neurological damage. Fortunately, in modern medical practice newborn screening is performed within the first week of life to identify metabolic disorders so that they can be caught and managed before they can do serious harm. Physicians specializing in Endocrinology, Metabolism and Genetics manage diseases like this one so if you find this case interesting it could be a possible career path for you.

↪ *Take Home Message* ◀

Nutrients have to be converted to any of the intermediates in the Krebs cycle in order to be used in cellular respiration. Metabolic pathways are responsible for this conversion and defects in them lead to diseases.

The Krebs Cycle

WILEY COYOTES

Death goes hand in hand with life on a livestock farm. Before he turned five, Ian Henderson had seen his dad kill the male lambs for the table. But staring out over his station—the grazing ground of South Australia, the farm that was his now—he dreaded what he knew he'd find: the bodies of the sheep that were his livelihood, their throats and bellies torn out, their meat and fleeces useless.

Packs of wild dingo dogs had arrived in the early spring and taken out the lambs first—this year's meat and next year's wool. Then they started in on the ewes whose fleeces he was planning to sell. Henderson and three of his hired hands guarded the night pasture with rifles in hand; but you can't keep sheep penned up in the daytime, and you can't be everywhere at once. He'd left out poisoned meat and even poisoned an already-killed sheep; the dingoes ignored it. He'd set spring-traps powerful enough to snap a human leg; the dingoes strolled around them. His own dogs were good at herding sheep but no match for the vicious packs. Every night one or two fewer sheep came in; every day he found another corpse.

What was to keep the wild dogs from coming back till every one of his sheep—each worth a thousand or more—was dead? He began going into town more often for a drink, and then for two drinks, and then for five. Grief and rage boiled up in him. He poured more whiskey on top of it. The man at the other end of the bar said, "You seem thirsty, mate," in a deep mild voice.

Henderson had always believed that a man doesn't talk about his troubles, but what did he have to lose? The stranger sipped his beer, silent till Henderson stopped talking. Then he reached into his pocket and pulled out a small card. DINGO DESTROYER, it said, and a phone number. "Call him," the stranger said, and took another sip of beer.

The Dingo Destroyer pulled up in a battered truck three days later at sundown: a short, scruffy, balding man with a dufflebag over his shoulder. Henderson's heart sank. The man waved away his explanations and followed Henderson to the night pasture, where he opened his bag and began fastening collars around the thick, woolly necks of the sheep. Henderson opened his mouth to speak. "Fluoroacetate," the Dingo Destroyer said. "Poison."

"I tried poison."

The Dingo Destroyer ignored him. When all the sheep had collars—they were long, wide plastic packets, made to fasten—he said, "You been keeping a guard at night?"

"What do you think?"

"Don't do it tonight. Leave them out."

"You're crazy. You're—" But the little man

