Lecithin, Intestinal Bacteria, and Disease

Kwashiorkor /kwɑːʃiˈɔːrkər/ is a form of severe protein–energy malnutrition in children characterized by edema, irritability, anorexia, ulcerating dermatoses, and an enlarged liver with fatty infiltrates. Sufficient calorie intake, but with insufficient protein consumption, distinguishes it from marasmus. Kwashiorkor cases occur in areas of famine or poor food supply.[1] Cases in the developed world are rare.[2]

Jamaican pediatrician Cicely Williams introduced the name into the medical community in a 1935 Lancet article, two years after she published the disease's first formal description in the Western medical literature.[3][4] The name is derived from the Ga language of coastal Ghana, translated as "the sickness the baby gets when the new baby comes" or **"the disease of the deposed child",[5] and reflecting the development of the condition in an older child who has been weaned from the breast when a younger sibling comes**.[6] Breast milk contains proteins and amino acids vital to a child's growth. In at-risk populations, kwashiorkor may develop after a mother weans her child from breast milk, replacing it with a diet high in carbohydrates, especially sugar, but deficient in protein.

Kwashiorkor: Not simply diet.

"You think of malnutrition in a simplistic way as having something to do with a deficiency in your diet, as something you're not eating," Manary said, "but the more we looked into this over 15 years, we thought this was not about what they were eating at all. They were eating the very same thing in the very same quantities in the very same places as children who weren't getting kwashiorkor. What else is in their environment that could be causing this condition?"

Trehan emailed Manary that same question after encountering a **set of twins where only one had kwashiorkor**. Trehan and Manary began to wonder if the condition might have something to do with gut bacteria and turned to their colleague Jeff Gordon at Washington University who had recently shown differences between the microbiomes of obese and non-obese women in the United States. “That’s a form of malnutrition too. Overnutrition is just as bad in many ways as malnutrition, so we took a look at the population that we knew, the malnourished kids,” Trehan said.

Working through diesel shortages, power outages, civil unrest, and washed out roads during the rainy season, Trehan and Manary regularly traveled to 20 clinics, collecting stool samples from 317 pairs of twins over a course of 3 years. Situations where both twins remained healthy or where one of the twins developed kwashiorkor were of particular interest, and those samples were flash frozen in liquid nitrogen and shipped to Gordon’s lab for 16S rRNA and multiplex shotgun sequencing.

Where's the Beef?

Back at the Cleveland Clinic Lerner Research Institute, Hazen's first volunteers ate hard boiled eggs or swallowed capsules containing deuterium-labeled phosphatidylcholine, allowing him to follow the labeled compound through metabolism. TMAO levels in the volunteers' plasma and urine before and after taking a broad spectrum antibiotic showed that the **sharp increases in TMAO seen after consuming eggs or phosphatidylcholine was dependent upon intestinal microbes.**

Those hours spent poring over mass spectrometry data would pay off for Hazen when he noticed that carnitine, a compound found in large quantities in red meat, was a significant hit in the original metabolomics data. Hazen didn't focus on it until he recognized that a portion of its chemical structure was identical to choline. "There is no question that a diet rich in red meat—at least epidemiologically—is associated with increased cardiovascular risk," Hazen said. He thought this bacteria-dependent metabolism just might provide a long sought after explanation for the connection.

Although it took eight months to find a vegan willing to eat a beef steak, several were willing to swallow labeled carnitine capsules. Hazen's team, to their surprise, found that not only were baseline levels of TMAO significantly lower in vegan and vegetarian volunteers, but those individuals also had a reduced capacity to synthesize TMAO from carnitine.

"Bacteria, whether they live in a Petri dish or in your intestines or in someone else's intestines or in the intestines of a mouse, they are still the same. If you feed them what they like, they will grow. If you don't feed them what they like, their proportions will be less," Hazen explained.