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00:06 Meagan Cantwell: Welcome to the Science Podcast for October 16, 2020. I'm Meagan Cantwell. Each week we feature the most interesting news and research published in Science and the sister journals. First up, I speak with Abigail Echo-Hawk a scientist fighting for Native Americans to be counted in COVID 19 data. Next, we have researcher Danielle Murashige. She speaks with Sarah Crespi about fuel use by the human heart and how it compares with the leg. The coronavirus pandemic underscores an issue Abigail Echo-Hawk the chief research officer of the Seattle Indian Health Board has been fighting her entire career, the exclusion of native people in public health data.

00:50 Abigail Echo-Hawk: We know that the data that is being collected across the United States isn't collecting race and ethnicity correctly, however, even with that incredible lack of data, the data that we do have shows an incredible disparity.

01:05 MC: Growing up in rural Alaska, Echo-Hawk was surrounded by examples of how a native community diligently cared for one another.

01:12 AE: I was raised amongst incredible people who were the very first public health practitioners I ever saw. If somebody needed fed, they fed them, if somebody needed a ride to a doctor, a five-hour trip to Anchorage, Alaska, they drove them. All of my scientific background comes from that space of understanding what it means to serve the community, and also the understanding, as an Indigenous person, I come from thousands of years of incredible Indigenous scientists.

01:40 MC: But after being stereotyped and mistreated while seeking prenatal care in Seattle, Washington, she knew how she could make an impact in her community.

01:48 AE: I had a medical assistant question me on how much I had been drinking, she pulled up my sleeves and then I realized she was checking my arms to see if I had track marks. It was really traumatizing to me as a young person, I was only 19 years old, and as a result of that experience, I didn't get prenatal care until I was in my second trimester. I became a grassroots advocate to ensure that native women were properly treated because we have some of the highest rates of infant mortality and maternal mortality within this country. And as I went through my college years, that turned into what I did my thesis on.

02:24 MC: She went on to study Health Policy at the University of Washington, but it wasn't easy navigating between western and Indigenous knowledge systems.

02:32 AE: It was hard to balance who I was as a native person versus what the Universities expected me to be and what western science wanted and almost insisted I had to be. It became another struggle to be seen as relevant, as smart, and as knowledgeable as the other people in the

room. And in fact, in the first year of my career, I would say that I did not actively practice Indigenous science. We come from thousands of years of data gatherers. In my communities, we know how to ensure that our corn grows, for example, in a time where there was complete droughts. I was called out by one of my elders in the fact that I no longer was representing or being an Indigenous person. He reminded me of who I was and that I would not make any difference in my community if I didn't go back to the knowledge that I knew was right, that I knew was ethical. I was able to incorporate that and not only see how western science has a lot of basis in Indigenous knowledge systems, but I also feel that western science needs to quit coming to Indigenous people because they think we have all of the problems, they need to come to us because we have all of the answers.

03:48 MC: Today, Echo-Hawk is the Director of the Urban Indian Health Institute, a Seattle-based organization seeking to de-colonize data by putting native people's priorities at the forefront of data collection. By being intimately involved in the collection of information, native people can shape the narratives told about their communities.

04:07 AE: Data in a western context has always been used against native people. It has been used to show how bad off we are, how high our suicide rates are, how high our diabetes is, how we don't achieve the same educational standards as western folks, that deficit narrative continues to build and support stereotypes of those communities as being less than, not as smart, of, they are responsible for their own health disparities, all of those things. As a result of that, many of our communities have protected themselves and have not participated actively in data gathering efforts across the United States and across the world. And that was absolutely the right thing for them to do, was to protect themselves. Tribal communities have a right to ensure that data gathered about them is used for their benefit and that they maintain ownership and control over that.

05:00 MC: Controlling the data also means making sure that Indigenous people are counted in federal and state data sets in the United States. A practice not always followed despite a treaty agreement between tribal nations and the United States government. The US Census didn't proactively count American Indians until 1860, and this dearth of data was used to settle on native people's land.

05:24 AE: One of the things that we actively are fighting against is that as a small population, people don't gather the data about us correctly, or they don't gather it at all. So very often I'll be at a presentation and we'll say a little asterisk that we were... American Indians and Alaska Natives were statistically insignificant. To me, that is one of two things either you did not actively try or didn't know how to connect with the community to gather the data you needed to, and the other is, is that when you eliminate us in the data, you are actively participating in the ongoing genocide of American Indians and Alaska Natives. And that seems really strong to say. And yes, it is, and I believe it 100%. So I ask people to question these practices that they're doing and recognize that, "Yes, I know they're not inherently individually racist but they're participating in a system that has been meant to eliminate my people."

06:16 MC: These data collection issues remain a major problem in the COVID 19 pandemic. Initially, Echo-Hawk was unable to access the CDC breakdown of race and ethnicity data. Once she saw the data, she was unimpressed with its quality and breadth.

06:32 AE: What we found in 23 States is that native people were 3.5 times more likely to be infected with COVID than non-Hispanic whites. Why did we only do 23 States in the country? Because the rest of the States simply hadn't gathered enough data for us to be able to analyze what was happening within their States. So only 23 States had gathered, 70% of their race and ethnicity data. Policymakers are trying to make data-driven decisions, how can they make data-driven decisions with bad data? By not gathering this data, the resources that we need are not being allocated in the right way because we don't know how to allocate them correctly.

07:14 MC: Echo-Hawk has provided training to universities and the state department about how to correctly collect race and ethnicity data, as well as how to restructure their database systems to better serve Indigenous people in all realms of public health.

07:29 AE: We know that there's about a 20% increase in domestic violence right now as a result of COVID and many folks who could leave their homes for work or school or things like that to get away from their abusers for an amount of time, no longer can do that. I'm deeply dedicated towards the safety of victims of sexual violence and domestic violence and other types of intimate partner violence. And so I am actively working with a large county here in Washington State, where we are changing their database system. And we are also going to assist them in working with the local tribal communities on what it means, once they collect that data, how that data is shared back to the tribal communities, how it's analyzed, and what kind of meaningful change can come from that.

08:16 MC: At the end of the day, the individual story behind the data guides Echo-Hawk's work...

08:21 AE: We are also listening to the stories of the community. The impact of a family who has lost both parents, the impact of a tribe where COVID 19 is just ravishing through their communities causing so much destruction. That qualitative data is just as important as the quantitative data... Simply because right now, we don't have enough of that quantitative data to get to those decision-makers so that they can make those data-driven decisions. Every single data point is a mother, is a grandfather, is an uncle, is an auntie, is a relative, we have a responsibility to the story and to the story-teller. To the story, we have a responsibility to ensure that it builds the strength of the community, it identifies gaps that we can then go in and work towards filling, that it also shows the strengths and the resiliencies and the answers that are held within our community. I hope for my great, great, great, great, great, great-grandchildren that they are not facing the same battles that I am facing. That we have an opportunity to come together now as allies within the scientific community, recognize where we have gone wrong and to see our path forward.

09:34 MC: This story was originally reported by Lizzie Wade as part of Science's Voices Of The Pandemic series. Stay tuned for Sarah Crespi's interview with Danielle Murashige about quantifying the heart's metabolism.

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09:53 Sarah Crespi: Every day your heart beats about 100,000 times on average. That's a lot of work and requires serious energy, but how much? Until now, we didn't know the precise needs of

the heart, Danielle Mursahige is here to talk about how to measure the fuel intake of healthy hearts and failing hearts. Hi, Danielle.

10:13 Danielle Mursahige: Hi, Sarah.

10:15 SC: Everybody has a hungry heart. I really wanted to incorporate that [chuckle] but how hungry? Why didn't we know before how much... What the metabolism of the heart was like?

10:25 DM: Much of what we know about cardiac metabolism and metabolite flux and substrate preference comes from almost a century of research in rodent models which have and continue to be the workhorse model in labs, but of course, they're imperfect, when we think about human physiology. Most obviously humans walk around upright, whereas rodents are on four legs, so our hearts have a lot more work to do to get blood all the way back up to our heads from our toes. In a mouse, the heart is responsible for about 3% of whole-body oxygen consumption, but in a human, that number is more like 10%, so it's more than a two-fold difference.

11:07 SC: You quantified metabolites from the heart, this is something called metabolomics. How did you do that? What is that?

11:14 DM: We used a liquid chromatographer coupled with mass spectrometry, which is an incredibly sensitive way of quantifying how much of a metabolite is present in human biofluid. So here we used human plasma.

11:28 SC: You talked about oxygen before, sometimes when I think about energy, I think about ATP, why is metabolites the thing that you looked at for quantifying what's going on with the heart?

11:39 DM: Cardiologists and cardiac researchers think about the heart as a pump, it's a pump that converts chemical energy in the form of metabolites into physical energy in the form of pumping blood around the body. And so we know that in heart failure, the heart is kind of like a pump that's run out of fuel. So if you look at the myocardium, it has lower stores of ATP and phosphocreatine, which are high energy phosphates for doing work. So the failing heart is kind of like an engine that's run out of fuel. And of course, the fuel is the chemical energy that's stored in the form of circulating metabolites.

12:20 SC: I realize reading this paper that I don't actually know much about the buffet of options that organs, cells in our bodies have to choose from when making energy. So there's not just, "Oh, here's some sugars." There's all different choices. Can you give us a rundown of that?

12:36 DM: Kind of what we all learn in school is that there's glucose, it goes through glycolysis, then we get some acetyl CoA and that's burned in the TCA cycle. Really, it's a little bit more nuanced. There's fats, so fats come with a lot of carbons, it takes many rounds of beta-oxidation to get acetyl CoA from them. There's carbohydrates of which we really think of glucose and lactate as the main sources to a cell and those circulate in the blood at pretty high concentrations. And then there's the ketone bodies, of which 3-hydroxybutyrate and acetoacetate are the main ones that are in relevant concentrations, however, acetone is also circulating in small concentrations. The last big

group that is worth mentioning are the amino acids. And most people, even biologists, think about amino acids in terms of protein synthesis and their role in making all of our proteins. However, amino acids are also burned, so we get ATP from burning amino acids as well.

13:43 SC: So you took this out of people somehow? Did you take their blood directly from their heart?

13:49 DM: We actually worked with interventional cardiologists that treat electrical problems in the heart. In certain types of procedures, they're able to access human arteries and the great cardiac vein, which is actually positioned on the back side of the heart and is not normally accessible. By this technique, we're able to sample all of the blood that's going into the heart and all of the blood that's coming back out of the heart.

14:17 SC: You also did this somehow with a leg. Why did you compare the nutrient used by the heart with a human leg?

14:24 DM: There's two reasons: One was we wanted to check ourselves, we wanted to check the technique, 'cause this hadn't really been done before on this scale. So we wanted to be able to compare two different organs and theoretically, two different organs should have two different metabolite uptake and release profiles. Furthermore, there was some available data from the human arm, so we were able to compare our leg data to the human arm to again, check ourselves.

14:52 SC: Looking at some of these figures, free fatty acids is different, lactate is different, but what does it mean that the heart is different than the leg?

15:00 DM: You kind of see that in the leg... The leg is releasing almost as much carbon as it's taking up. So these patients had actually been told to fast overnight for their procedure, so they hadn't eaten for maybe eight to 10 hours. They needed to be recruiting metabolites from their stores, much of which are actually stored in fat cells and muscle cells that are seen in the tissues like the human leg. Those metabolites and those fats and amino acids are then used by other tissues like the heart and the brain, which constantly have very high metabolic demands to meet their functional needs.

15:41 SC: Is it like there's a buffet [chuckle] circulating through the body and the organs can kind of pick and choose how they want their energy to be packaged, what they wanna break down to do their jobs?

15:52 DM: Towards the end of the paper, we wanted to start to ask that question. We wanted to know, is the heart a picky eater, is the leg a picky eater or is it just gonna eat whatever you give it.

16:06 SC: Yeah.

16:07 DM: And since... We couldn't really manipulate the amounts of fuels that were available, but what we did instead was we looked to see if there were any correlations between the amount of fuel that's available, so the amount of sugar, the amount of fat that's available in the arterial supply, and

then we asked, "Is that related to how much the heart takes up? Is that related to how much the leg takes up?" It looked like there really wasn't a relationship, within our window of looking, between most of the metabolites and the amount that they're taking up. But there were three metabolites that stood out.

16:50 SC: That suggests that for the most part, the diet of these organs is inherent to the organ but there were certain outliers in this too.

17:00 DM: Right, so there were three metabolites that stood out, that would be the ketone bodies, glutamate, and acetate. So for some reason, the more of these metabolites that's available to the heart and the leg, the more that they appear to take up.

17:14 SC: What about the failing heart, we talked a little bit about what the heart looks like when it runs out of fuel, that's something that people have known about, but when you quantified it, how did it look different than a healthy heart?

17:27 DM: Overall, we saw that both the non-failing and the failing heart, got most of their ATP from oxidizing fats. It dropped about 10% in the failing heart, so in the non-failing heart about 85% of ATP comes fat oxidation whereas, in the failing heart, that's about 75%. Really, the most striking differences were in the ketones and the amino acids. So we saw that the patients with heart failure, their ketone oxidation about tripled from roughly 6% up to over 15% of ATP coming from ketone oxidation.

18:06 SC: Why was that striking to you, what was it about ketone oxidation that might be important?

18:10 DM: Kind of the... The whole field of cardiac metabolism has gone through this resurgence lately, partially because of a trial in humans of the SGLT2 inhibitors, which result in a slight amount of ketogenesis and as part of the study, they found that there was a reduction in heart failure associated hospitalizations and all caused mortality. So the ketones have become a huge potential therapeutic target for heart failure directed therapies.

18:42 SC: So what were some of the other things that you learned about the heart that you... That people haven't been able to see before because they weren't able to access the inputs and outputs in such a comprehensive way?

18:52 DM: We were kind of originally excited when we saw that the heart seems to be releasing a lot of essential amino acids into the coronary sinus. And of course, essential amino acids can't be synthesized by human tissue, so the only way that they could be released is by breakdown of protein stores.

19:11 SC: So what does it mean if the heart is breaking down protein stores?

19:14 DM: What we think is going on is that the heart is breaking down the carbon that's stored in proteins that are within the myocardium and using the carbon as a fuel source. Which seems kind of

surprising because the heart has free access to all kinds of amino acids that are circulating through the plasma. Why this happens? We don't know. That will definitely require some more basic science.

19:42 SC: Yeah, this is just making me realize I have no idea what our organs do. [chuckle] To get energy, like I'm just like... I'm like, "Really?", "That's surprising." What are they supposed to be using?" [chuckle]

19:56 DM: Every time, even though we know that the human is the perfect model organism, it's still surprising.

[chuckle]

20:02 SC: We are the perfect model organism for ourselves, and yet...

20:06 DM: I know... And yet...

20:08 SC: What are you gonna do next? Are you gonna put more things in boxes, are you gonna put more people's hearts in boxes?

20:13 DM: There's really so much to do. In the lab, we've already started making some animal models to follow up on some of our peridialysis observations and then, in the humans we're definitely planning on following up these experiments with some slightly more involved studies. This was fairly straightforward in terms of methodology, but there are some pretty fancy things we would like to do involving some stable isotope tracing, probing different metabolic preparations and collecting other types of biospecimens.

20:46 SC: Is one of the goals of this type of research to be able to profile the metabolism of a person's heart and say, "Oh, this is going well... " "This is not going well... "?

20:56 DM: That is one of the goals. This could give us kind of an indication of when a heart is working well versus not working well.

21:04 SC: Alright, thank you so much, Danielle.

21:06 DM: Thank you, it was a pleasure.

21:08 SC: Danielle Murashige is a PhD student in the Arany lab at the University of Pennsylvania. You can find a link to her paper at sciencemag dot org slash podcast.

21:19 MC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions for the show, write to us at Science podcast at A-A-A-S dot O-R-G. You can listen to the show on the Science website at sciencemag dot org slash podcasts. On the site, you will find links to the research and news discussed in the episode, and of course, you can subscribe anywhere you get your podcasts. This show was edited and produced by Sarah Crespi and Meagan Cantwell

with production help from Podigy and Joel Goldberg. Jeffrey Cook composed the music. On behalf of Science Magazine and its publisher, AAAS, thanks for joining us.