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0:00:05.7 Sarah Crespi: This is the science podcast for January 28th, 2022. I'm Sarah Crespi. Each week we talk about the most interesting news and research from science and the sister journals, this week we're all about the microbiome.

First up, we have staff writer Kelly Servick. She has a story on putting the bacterial benefits of human feces in a pill, which can help avoid the use of fecal transplants to treat a tough hospital infection known as C. Diff.

After that, we have researcher Hannah Carey, we talk about the microbiome of hibernating squirrels and how this could help supply a key nutrient during times of scarcity.

Now we have staff writer, Kelly Servick. She's gonna talk about gut microbe. So welcome to microbiome week, Kelly.

0:00:56.2 Kelly Servick: Thank you, it's nice to be on microbiome week with you, Sarah. [laughs]

0:01:01.1 SC: We're gonna talk about fecal transplants, which they've been an option for recurrent infections of the gut for about a decade now, I've definitely talked about it on the podcast before. There's been interesting diagrams in the magazine, but not everyone is pleased with this treatment, they don't think it's optimal, what are some of the problems with giving stool from one person to another person?

0:01:24.3 KS: Yeah, so I should say that fecal microbiota transplants as they're called have been very successful at treating this really nasty bacterial infection called Clostridium difficile—C. Diff, and that's how people have been using it, like you said, for several years is sort of been part of mainstream medicine in a lot of places. C. Diff basically thrives in a gut with a disrupted microbiome, so for example, if you have to take antibiotics and they throw off the balance of healthy microbes in your gut, that environment becomes a friendlier place for this harmful bacterium, and you end up in these cycles of infection where it comes back and comes back and you keep fighting it with antibiotics.

0:02:01.1 SC: So fecal transplants are able to rid people of these recurrent C. Diff infections, probably through introducing helpful bacteria balancing what the body has left after all these bacteria have been killed off by antibiotics. This sounds holistic. Why is it not ideal?

0:02:19.5 KS: One big challenge is that it's quite hard to standardize this treatment, you are taking the feces from a healthy person and putting it into the intestines of someone with an infection, you're not giving every patient the exact same product, you're giving them something that changes in composition from person to person, and even within the same person over time as I think we all can attest. And so that leaves some uncertainty about what is working the magic here, and which stuff in the donor feces is helping and what's necessary, and meanwhile regulation in this field is pretty murky also, the US Food and Drug Administration classifies this as a drug, but so far it hasn't really required it to go through the formal drug approval process.

0:03:03.8 SC: Are there worries about, not exactly contamination, but giving somebody microbes that you don't want to give them?

0:03:10.7 KS: Yes, there have been some concerns about safety and these appear to be very rare situations, but there have been a few high-profile cases over the last few years where a donor who was not properly screened transmitted an infection to the recipient of the transplant, and in one case the patient died in a clinical trial after getting a transplant containing a strain of E. Coli bacteria.

0:03:34.8 SC: Wow.

0:03:35.9 KS: And to make matter worse, there's this pandemic.

0:03:37.7 SC: We know that wastewater is being monitored for COVID.

0:03:40.6 KS: Yes, we know that the virus can be in feces, We aren't certain that it could be transmitted in a transplant like this, but that's reason enough for FDA to amp up the screening requirements. And that has implications for the supply in this country of stool for transplant, so it's kind of this complicated situation where the screening has gotten harder, medical centers that process stool and do these transplants are having a harder time doing that and are sort of intimidated by the screening process and don't wanna do something wrong, and meanwhile, the biggest provider of feces for transplant in the US, the stool bank called OpenBiome is in the process of winding down its operations, so it just threatens to leave a little bit of a gap.

0:04:21.4 SC: Yeah, so there's a lot going on, and in this mix are companies that are trying to basically take the benefit of the bacteria from feces and put it in a pill form, Make it safer, make it more standardized. How is that going?

0:04:38.2 KS: It's coming along very quickly. There's this cohort of companies that are getting closer and closer to the finish line, from the perspective of a company, the ideal situation would be to have this more defined collection of microbes that might be eligible for a patent that you might be able to commercialize in a way that the natural product, you can't. The most recent development here, and what I wrote about this past week was a company called Seres Therapeutics that just published results from its phase three trial of a pill that is still derived from feces, but goes through processing and purification to make it more of a drug product.

0:05:14.7 SC: How does it compare with the full fecal transplant?

0:05:17.7 KS: That is the question that I think a lot of people in this field would really like to know in terms of just sort of the numbers in the trial, it performed quite well against the placebo, but we don't have a direct head-to-head comparison of the traditional fecal transplant and this drug, there is some skepticism that you can whittle down the set of microbes into the standardized therapy and get something that is as potent as the full spectrum product, the sort of complex blend that comes out of feces.

0:05:47.3 SC: And how do we know which microbes matter, is that something that they're trying to figure out to make this optimal mix?

0:05:53.9 KS: Yeah, that's something that a lot of researchers are working on and they know a lot, so this pill from Seres Therapeutics is based on the idea of narrowing down the microbes to bacteria in this phylum called Firmicutes. I've heard it pronounced, I think three different ways, but I prefer the cuties pronunciation. [laughter]

0:06:14.3 SC: I'll take cuties for this. [laughter]

0:06:16.4 KS: So in not approach, they're sort of applying ethanol to the stool product, killing off a bunch of stuff, leaving this Firmicutes group that can form spores and survive that treatment, and then those are a group of bacteria that researchers think competes with C. Diff in the gut and also seems to change the concentration of bile acids in a way that C. Diff really doesn't like. So that's the idea, is that you've got this very good set of fighters going into this pill.

0:06:46.4 SC: And what about the other companies that are working on this problem, are they using the same approach, the same clean up everybody, but one particular family, or are they doing different things?

0:06:56.4 KS: There's some variation, there's a company called Rebiotix that is also sort of filtering the stool product into something a little more refined and actually delivering that as an enema instead of a pill, there's the company called Finch that is freeze drying stool by this particular process and putting that in a pill, and then kind of a different approach, and one being taken by Vedanta Biosciences, I think among others, is creating a pill that has individually selected bacterial strains, not isolated from stool but grown in cell banks built from the bottom up.

0:07:28.6 SC: So that's very bespoke?

0:07:30.7 KS: Right.

0:07:31.7 SC: So the idea there would be to look at the profile of the person that has the illness and then supply them with what they need to conquer it?

0:07:38.8 KS: That's the idea. And I think for a lot of researchers in this field, that would be great if you could even on an individual level, look at a patient, analyze their microbiome and say, "This is the way that your microbiome is screwed up right now, and here's what we need to introduce to help you."

0:07:53.7 SC: We're going past C. Diff now to talk about more generally disturbances of the gut microbiome.

0:07:58.9 KS: Yeah, C. Diff happen to just work really well, and it was the first place where these microbiome-focused treatments could really succeed, but there are hopes for applying the same approach to other types of conditions, including inflammatory bowel disease and others, for that. A lot of people think we're probably gonna have to go back to the feces and look at the whole product and figure out what is useful.

0:08:18.4 SC: Mm-hmm. Alright, Kelly, crazy question for the day.

0:08:21.0 KS: Okay.

0:08:22.5 SC: Is this ever gonna be an over-the-counter drug?

0:08:26.1 KS: I don't know, it would surprise me, but I think it depends on what indications it ends up looking promising for. This sort of intersects with the whole probiotics world, which a lot of those products have a lot less evidence to support them.

0:08:38.9 SC: And less oversight.

0:08:40.0 KS: And less oversight than what we're talking about here, but I think there's a lot of optimism around various microbiota treatments, and it's a matter of really proving them in trials and teasing out what's effective.

0:08:51.7 SC: Alright, thank you so much, Kelly.

0:08:54.3 KS: Yeah, no problem, thanks for having me.

0:08:55.3 SC: Kelly Servick is the staff news writer at Science, you can find her link to the story we discussed at science.org/podcast. Don't touch that dial. Up next we have researcher Hannah Carey. We talk about how ground squirrels can survive for months at a time in a state of hibernation, and how their gut microbes provide a little helping hand.

[music]

0:09:23.6 SC: Hibernating animals enter the special state in order to survive during times of scarcity, but even with severely reduced temperatures, a slow metabolism, those kinds of things, the animal eventually gets low on the essentials like nitrogen, which is needed for the amino acids that make up proteins. Hannah Carey is a professor in the Department of Comparative biosciences at the University of Wisconsin-Madison. She and her colleagues published a paper this week in Science on how gut microbes might actually help hibernating squirrels with their supplies of nitrogen. Hi, Hannah.

0:09:58.6 Hannah Carey: Hi, Sarah.

0:10:00.8 SC: What exactly happens when an animal is hibernating, is it much different than sleeping?

0:10:06.3 HC: It is different, Sarah, when we go to sleep at night, we drop our body temperatures may be a degree or two, ground squirrels go into hibernation, the state of torpor actually is what we use, metabolic depression, they enter that state from deep sleep, but then they go full in, their metabolism starts to slow to very low levels, and that causes body temperature to fall by many, many more degrees than ours, but the Hibernators are in an unconscious state, just like we are during sleep, but after that, the differences are quite extreme.

0:10:46.7 SC: There's no eating during hibernation, they don't get to take an extra water or food when they're in this torpor state and things are really slow, but the animal could actually run low on nitrogen, where is it going and why is it a bad thing for that to happen?

0:11:02.3 HC: The hibernators that we study actually are called seasonal hibernators, and for the whole season of the winter hibernation period, they don't eat. Some hibernators periodically eat food that they cash in their burrows, but not these ground squirrels or animals like ground hogs and marmots and those sorts of animals and even bears, when they're at that very low body temperature and low metabolic rate, they have turned down their thermostats and they actually don't need that much energy and they're not using that much of their protein, but periodically during the winter, they'll turn on their metabolism without any external cues, they'll turn on their metabolic capacity and rise up to close to summer time body temperature and metabolism, and that is an energetically expensive process, and there's a lot of protein synthesis that goes on during those what we call inter-bout, in between the torpor bout arousals. So nitrogen in the body is used to synthesize new proteins during that time, these periods of high body temperature that occur every few days to every few weeks throughout the winter, it varies with species and temperature, but it lasts for about a half a day and a lot of the time they're sleeping, they're catching up on their sleep, but at high body temperature.

0:12:24.3 SC: Oh wow, so they're leaving a hibernation state just so they can catch up on their sleep and then go back to hibernating?

0:12:31.0 HC: Yes, that's why we like the word torpor, they leave the torpor state, they're still in hibernation, but they leave torpor, come up, do a lot of important biochemistry that we're all just still trying to figure out, and then they go back down into their torpor state but some of the nitrogen is used to make new protein, but no new nitrogen is taken in because they are fasting, no food intake.

0:12:53.1 SC: And so it's not good for them to run super low on nitrogen?

0:12:56.6 HC: That's right, but of course, they've evolved to do this very well, and evolution has led to seasonal cycles, such that they don't normally run out before the spring time comes, and they come out when they know they need to, their body tells them it's time to start eating again, and our study actually adds this little twist that involves the process that's well-known in ruminant animals of all things, so cattle and sheep and goats.

0:13:25.8 SC: And their microbes do some digesting for them, right?

0:13:28.6 HC: Absolutely. That's the crowning glory of what we call urea nitrogen salvage, where the waste product urea that all animals, vertebrates, even some invertebrate animals make to get rid of excess nitrogen that can be toxic to the body, we make urea and we usually... That comes out in our urine, but certain microbes, not all gut microbes, but certain microbes have the special enzyme, urease that's able to split the urea molecules, liberating that nitrogen molecule that's in this waste product and use it for their own purposes, and for ruminants this all happens in the rumen, which is the big part of the four stomach that occurs before the small intestine.

0:14:13.3 SC: What made you think that this might be happening in ground squirrels? That this might be a process that would be in place during hibernation?

0:14:22.5 HC: The question of whether non-ruminant animals, including humans, get some help from their gut microbes by liberating nitrogen from urea that they could eventually use, that question's been around for a long time, and there's been quite a bit of research in the past, including with humans to see if it really can contribute to our biology and help us, especially in times of protein, need low protein diets, for example, or even pregnancy where there's a lot of new growth in the body, and you need robust protein stores. So research has gone on on this process in non-ruminants and even in hibernation literature, people have studied hibernation for decades, have hypothesized really, that hibernators that go through the winter with no new nitrogen intake, maybe they're especially linked through symbiosis to their gut microbes, so that they can regain that nitrogen back from the urea molecule and recoup it back to their bodies, but there was very little evidence, good data that suggested this happened.

0:15:32.6 HC: So we asked whether the hibernators, first of all, if we could get evidence that urea nitrogen salvage, which involves the microbes using that nitrogen for their own purposes to get nitrogen so that they proliferate, but they release metabolites like ammonia, and even some of their own amino acids that they make for themselves. It's possible that some of those metabolites are coming back and absorbed across the gut wall and are available to the hibernators. So we ask, does it happen in squirrels, ground squirrels? Does it happen? Especially prominently in hibernation, and we went a step further and hypothesized that the longer they're fasting, the more important their symbiotic relationship with microbes might be.

0:16:21.1 SC: What did you do to track nitrogen, seeing if the microbes were contributing any to their host?

0:16:29.2 HC: We use technology known as stable isotope tracing or stable isotope tracking, and when I thought years ago about this project and how I could be able to track the microbial signature, if you will, you actually know that that nitrogen molecule in the ground squirrel tissues originated from their gut microbes. The way science goes is funny, I was at a graduate student lecture and I saw her talk about using stable isotope technology, tracking a stable isotope of carbon, carbon 13 instead of the more carbon 12, and using that technology in breath testing to see if you could pick up changes in metabolic state of an animal, then they used NMR, Nuclear Magnetic Resonance Spectroscopy, metabolomics, essentially, to actually look at that carbon isotope in the body of the animals. And I said, Wow, maybe that's it. Maybe if we could get a stable isotope of nitrogen in a urea molecule, which you can, you can purchase doubly labelled urea with carbon 13 and nitrogen 15, and then through these breath testing and metabolomic technologies, you could ask whether it would appear after injecting the doubly labelled urea into the body of the ground squirrel, could you pick it up later on, and by definition, this is key.

0:17:56.5 HC: Mammals, other vertebrates, even invertebrates, do not make the urease enzyme, you need to have that urease enzyme or this nitrogen will not be liberated from the urea molecule, but microbes, only certain microbes make urease and are able to do that. So we said, Well, perhaps this can be happening during hibernation with the help of these ureolytic microbes.

0:18:22.0 SC: Right. And so you're able to show that the microbes liberated it and passed it on to their squirrel host. Did you see, I don't know if you wanna say seasonality, but did you see it changing over time depending on where in hibernation this square was?

0:18:37.0 HC: Yes, we did, we did all our experiments with summer ground squirrels that weren't eating in winter that were fasting, and then we looked at our squirrels that we studied after just one month of fasting early in the hibernation season, and those three or four months or longer out closer to when they finally emerge in spring, and the two tissues we examined showed this time-dependent increase in the protein pool that had the nitrogen 15 in it. So as we thought when the animals needed the most, their bodies were incorporating the urea nitrogen that was originally released by their gut microbes into their tissues.

0:19:19.8 SC: Is this something that it's possible people are doing now that you pinned down how it might be happening in hibernating squirrels, is it more likely to be happening in people?

0:19:28.4 HC: The answer there is yes. As I've mentioned earlier, there have been studies with human subjects to examine this, so we know that from those studies, the machinery, if you will, to go through all the steps, and there are several steps along the way that are needed both in the microbes and the host to pull this off, that machinery, is there.

0:19:47.7 SC: What would it mean if this type of bacterial assistance was happening in people?

0:19:53.0 HC: We think there are some potentially and helpful or important implications of this work that could eventually make their way back to humans, there are diseases and pathological conditions where there is what's called muscle wasting, for example, people for example, who are bedridden because they're in a coma, when you don't use those muscles, especially put weight on them, muscles pretty quickly start to atrophy, start to lose mass and therefore function, and then if the person is able to once again resume low commotion, walking, it takes a while to rehab those muscles and get back up to speed again. So perhaps there may be a way through the microbiome, if we understood more in detail about what the microbes are doing functionally and the steps within the body that we also looked at in the ground squirrels, maybe understanding how to enhance those steps would help individuals that were in these situations.

0:20:54.2 SC: We have to go all the way to space travel here, we can't stop before we get to that application.

[laughter]]

0:21:00.8 HC: This one is kind of cool and actually is something that's on the plate of the first doctor of this paper, Matthew Regan, who was a postdoc on the project and as a young child, he's been fascinated with space travel, and the studies that he'll be continuing along these lines includes asking whether enhancing the symbiosis between gut microbes and their human hosts could be manipulated in a safe, beneficial way to enhance their ability to recoup their urea nitrogen during long distance, long duration space travel, like in deep space where you just can't put enough food on these space craft, right?

0:21:42.7 SC: Right. We'd have onboard recyclers.

0:21:45.8 HC: Humans and their buddies, their gut microbes. It's a symbiosis, for sure.

0:21:50.1 SC: Yeah, I thought you were gonna say working on human hibernation, like if we could induce hibernation in humans.

0:21:56.6 HC: That's part of the equation too, both European Space Agency and NASA are interested in this idea about inducing a safe and reversible metabolic depression, a torpor-like state, nothing is the extreme as the little ground squirrels do, but something more akin to bears. Actually, bears would be a good model 'cause of their body size and they don't drop their body temperatures nearly as low as the squirrels, but there's definitely interest there in terms of going through these periods so that they don't have to have so much food and oxygen, the other benefit is there are study supported by NASA in the '50s and '60s that suggests the torpor state protects against radiation damage.

0:22:37.1 SC: Oh wow.

0:22:38.5 HC: And that is one of the most important impediment to progress is the radiation burden that humans would take on with deep space travel, so there may be a double benefit there.

0:22:49.2 SC: Thank you so much, Hannah.

0:22:50.9 HC: Thank you, Sarah. This is always a joy for me to talk about hibernation and we're very excited about this project. So it was great talking to you.

0:22:58.0 SC: Hannah Carey is a professor in the Department of Comparative biosciences within the School of Veterinary Medicine at the University of Wisconsin-Madison. You can find her link to the paper we discussed and her related commentary piece at Science.org/podcast.

And that concludes this edition of the Science Podcast. If you have any comments or suggestions for the show, write to us at sciencepodcast@aaas.org. You could listen to the show on the Science website at science.org/podcast, you can subscribe on the site or anywhere you get your podcast. This show was edited and produced by Sarah Crespi with production help from Podigy, Megan Cantwell and Joel Goldberg. Transcripts are by Scribie. Jeffrey Cook composed the music on behalf of Science Magazine and its publisher, AAAS. Thanks for joining us.