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0:00:05.8 Sarah Crespi: This is the Science Podcast for April 26th, 2024. I'm Sarah Crespi. First on the show, Staff Editor, Kelly Servick, explores the science of loneliness. Is loneliness on the rise or just our awareness of it? How do we deal with the stigma of being lonely? How do we treat it? The Ex Producer, Ariana Remmel, talks with researcher Tim Schulte about making one of organic chemistry's oldest reaction, the Sandmeyer reaction, safer and more versatile. Finally, we kick off our 2024 book series with books editor Valerie Thompson and books host Angela Saini. They discussed this year's theme, "A Future to Look Forward to," and discuss some of the books that we'll be reading.

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0:00:53.3 Kelly Servick: "I am unhappy doing so many things alone. I have nobody to talk to. I feel as if nobody really understands me." These are items on a questionnaire that researchers use to formally measure loneliness. It's a complicated experience and it can be hard to study, but it's increasingly being recognized as a public health issue. Loneliness and social isolation have been linked to all kinds of health problems, and recently, the World Health Organization even launched a commission that will look at the evidence on how to build social connection. Governments around the world are paying a lot of attention to loneliness. I'm Kelly Servick. I'm a writer and editor at Science Magazine, and I wrote an article in this week's issue about researchers trying to understand and alleviate loneliness and isolation. It might be in the spotlight now, but the study of loneliness is not new. So I asked some of the experts that I spoke to for this story about the moment that we're in. As the public starts paying more attention, are there misconceptions that need clearing up? And what they told me was, "Yes, there are." And those start with basic definitions like, what exactly does the word loneliness mean?

0:02:11.3 Julianne Holt-Lunstad: The conversations I have, people are using the term loneliness as this catchall term for all forms of lacking social connection. But from a scientific standpoint, it means something a bit more narrow. My name is Julianne Holt-Lunstad and I'm a Professor of Psychology and Neuroscience at Brigham Young University.

0:02:35.9 KS: Julianne has been studying the role of social connection in health for more than two decades. Loneliness is one piece of that.

0:02:42.3 JH: I find it often easiest to define by distinguishing it from social isolation. Social isolation is more objectively being alone, having few relationships or infrequent social contact, whereas loneliness is more subjectively feeling alone, and it's a distressing feeling. So while, of course, being objectively alone can increase our risk for feeling alone, they don't always go together.

0:03:15.8 KS: But loneliness seems to be the word that politicians and journalists often choose as a shortcut for various issues around our social lives. And that makes sense because loneliness is something that we can acutely feel, and in fact, there's a good reason we feel it. As other researchers pointed out to me, loneliness has a purpose.

0:03:35.5 Laura Coll-Planas: It has been defined as a social pain that help us to react. So if I need more connection, then I look for more connection. So it belongs to this reaction that we need to be more adapted.

0:03:48.9 KS: Laura Coll-Planas is a medical doctor and public health researcher at the University of Vic Central University of Catalonia. She describes loneliness as a useful signal. If we feel tired,

we rest. If we feel physical pain, we might seek medical help. And if we feel lonely, we might seek out other people for support.

0:04:08.2 LC: It's a natural, unavoidable aspect of all our lives. That's how I see it. The tricky thing is when to understand that loneliness has to be alleviated.

0:04:20.3 KS: Because there is some point where loneliness is not helping anymore, where it becomes chronic and harmful. Julianne Holt-Lunstad has studied this harm including in a meta-analysis of mortality data from more than 3.4 million people. Her group found that loneliness was linked with a 26% increased risk of earlier death, and social isolation with a 29% increased risk.

0:04:45.8 JH: Data on mortality is consistent with a large and growing body of evidence on chronic health conditions including increased risk for cardiovascular disease, stroke, type 2 diabetes, depression, anxiety, addiction, suicidality, cognitive decline and dementia.

0:05:04.1 KS: All these risks are definitely alarming. But are they new? Are we getting more isolated? Are we getting more lonely? This is another place where the evidence is more complicated than some of the headlines. In the US, long running surveys do show some clear trends.

0:05:21.8 JH: Americans, over the past two decades, are spending significantly more time alone, significantly less time with family, both household and non-household family. We see declines in time spent with friends and time spent in companionship. This has been a pattern, right? First off, while, of course, it was exacerbated by the pandemic, but because these data started in 2003, we can see it did not begin there, and certainly that getting back to normal, the normal wasn't necessarily good to begin with.

0:05:58.0 KS: Those data tell us isolation has increased. When it comes to the subjective feeling of loneliness though, it's not so clear. Some experts told me, the evidence for a new epidemic of loneliness is just not there.

0:06:14.0 Samia Akhter-Khan: Headlines such as, "We Are Lonelier Than Ever," do not really represent findings from longitudinal cohort studies that we see where loneliness actually doesn't increase over time. Hi, I am Samia Akhter-Khan. I work at King's College London as a PhD candidate. It's probably been like five or six years that I've been working on the topic of loneliness.

0:06:32.1 KS: Samia has been studying loneliness outside of the wealthy western countries where a lot of the research data have been collected. She moved to Myanmar during her master's degree to study loneliness in older adults there.

0:06:44.7 SA: I think I was a bit naive in the sense that I expected a very socially embedded and close-knit society where people didn't feel lonely because they didn't live alone or were socially isolated. But then when I started doing research on this, we actually found, with the Myanmar Aging Survey that had over 4000 respondents from all over the country, that 32% of all the adults felt lonely in the past month.

0:07:05.9 KS: That's roughly on par with the rates found in some surveys of older adults in the US, for example.

0:07:11.6 SA: So it's quite surprising, but now I'm a wiser person now after doing this research.

0:07:18.3 KS: Interviews in Myanmar helped Samia and her colleagues develop a theory about the underlying causes of loneliness. A list of expectations that if they're not met can lead to loneliness.

One of those expectations she calls generativity.

0:07:32.2 SA: So contributing meaningfully to society or leaving a legacy.

0:07:35.9 KS: Another is respect.

0:07:38.3 SA: So feeling valued and appreciated maybe also for the care you provide.

0:07:44.2 KS: Those ideas informed a loneliness intervention that Samia and her colleagues tested in a small feasibility study. It included nine older adults from Myanmar who had migrated to northern Thailand. The team used a research method called Photovoice, where participants learned photography to capture their everyday experiences and highlight problems their communities face.

0:08:08.2 SA: So, I remember one photo of a woman. It was a self-portrait actually. She asked her grandchild to take a photo of herself cooking. So she's sitting on the floor squatting, and yeah, she's an older woman, so it's obviously not as comfortable for her anymore to squat on the floor and cook for her grandchildren. But she just says how she provides this kind of care every day and it's really hard work, but she doesn't feel appreciated and people don't really see how she's contributing.

0:08:38.2 KS: Participants in that small study did report reduced feelings of loneliness, and they decided to have an exhibition with their photos and messages.

0:08:47.3 SA: When the grandchildren, for example, saw this photo addressing them, they were pretty surprised but also in awe of older people. And I interviewed them as well, so people who came to the exhibition, and they just said that it completely changed how the way they saw older people in their community as really meaningful contributors to their lives and what kind of value they provide.

0:09:12.9 KS: Another thing that has emerged from Samia's work with older adults in Southeast Asia is a sense of how big structural factors can drive loneliness.

0:09:19.8 SA: Older people list reasons for feeling lonely that were related to their financial situation, such as food insecurity, not being able to buy medicine or not being able to contribute to community activities as a result of poverty. These factors, such as poverty, stigma, financial stress, are definitely risk factors for loneliness anywhere. It's just that maybe that the focus is not so much on these social determinants in research in higher income countries because poverty is just so much more prevalent in low and middle income countries by definition.

0:09:49.4 KS: This is another place where the public conversation about loneliness might be missing something.

0:09:56.8 SA: Some government initiatives sometimes position loneliness as the failure of an individual or community without considering the wider contextual factors.

0:10:04.7 KS: I heard that from multiple researchers I talked to. Loneliness is being treated like a personal problem, which contributes to stigma. As in, if you're lonely, this is a defect with you. You need to get out more. You need to socialize better. Julianne Holt-Lunstad told me, "We lack evidence on how policies might address loneliness at the level of communities or societies." She recently helped develop a map of the evidence we have so far for different interventions.

0:10:30.8 JH: The majority of these interventions are individually based. They are targeted to affect change at the individual level.

0:10:40.3 KS: That might mean organized social activities that a person can opt into, or a program where a volunteer provides companionship to someone who's isolated, or cognitive behavioral therapy to help someone who's lonely change their outlook. According to reviews of the evidence, Julianne says, "One approach doesn't seem to be way better than another."

0:11:00.9 JH: One doesn't rise to the surfaces as like this is the go-to gold standard in what we should be doing. Rather we see success across many different types. But I will caveat that with, the evidence also shows that the success is somewhat limited. These effect sizes are small to moderate, and these reviews and meta-analyses have shown that, in many cases, the quality of the evidence is quite low.

0:11:27.9 KS: Laura Coll-Planas and her colleagues are trying to build strong evidence for one loneliness intervention. It involves weekly group activities in urban green spaces to support people who may have been cut off from social connection for various reasons like unemployment, disability, chronic illness, discrimination.

0:11:47.9 LC: For some people, it can be unfair to be lonely. They can have more access to social support and social connection than they have. We can build social opportunities for people that can help people to feel better. So we should do that.

0:12:03.4 KS: In the study, which is taking place in six different countries, groups of participants do outdoor activities accompanied by trained facilitators.

0:12:12.8 LC: We build a group, we build a sense of belonging to the group, the commitment to the group, and the group choose which activities they would like to discover through a map that has been co-created where all these natural resources are identified and they know what's around me.

0:12:27.9 KS: Laura acted as one of the facilitators in Barcelona, and one group meeting stands out in her mind.

0:12:34.5 LC: That day we were going for a walk in one of the parks nearby. And it was a very sunny day and we thought about sitting in a cafe altogether, and we started talking there about very deep things, about how is life and the meaning of life. And that day, instead of two hours, we were like three hours together because it was such a deep conversation that we couldn't really stand up and say, "I have to go back to my work." These are conversations that are sometimes very hard to have or impossible to have with your best friends sometimes. It's so deep.

0:13:20.6 KS: Laura has been thinking about the consequences of all these public health campaigns against loneliness.

0:13:27.5 LC: We are in a very interesting moment globally with WHO creating this Commission on Social Connection to tackle loneliness. It's good there is this awareness on loneliness, the social awareness, political awareness. There's more money now to research on loneliness, but loneliness is not an epidemic. Loneliness is not an illness, but I think the majority of the society is understanding this message of loneliness kills. We have to end loneliness. So we have to make sure how this interesting moment doesn't go against us and simplifies too much and medicalize too much.

0:14:10.8 KS: That was Laura Coll-Planas. Also in this story were Julianne Holt-Lunstad and Samia Akhter-Khan. I'm Kelly Servick, and you can read the full article at science.org.

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0:14:28.4 SC: Stay tuned for a chat with producer Ariana Remmel and researcher Tim Schulte about making the Sandmeyer reaction safer.

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0:14:43.2 Ariana Remmel: When it comes to making complex carbon-based compounds from simple building blocks, chemists have an extensive toolkit of trusted reactions at their disposal. In fact, some of the most widely used reactions for synthesizing sophisticated molecules, like pharmaceuticals and fluorescent probes, trace their origins back to the 19th century. These methods have proved tried and true for more than 100 years, but some still come with the risk of explosive consequences. This week in Science, Tim Schulte and colleagues wrote about a new way to make one of organic chemistry's oldest reactions both safer and more versatile. Welcome to the Science Podcast, Tim.

0:15:24.1 Tim Schulte: Hey. Thank you very much.

0:15:25.0 AR: We are so excited to have you here talking with our listeners about this new chemistry that your team has developed. So, your research focused on a chemical reaction that's commonly called the Sandmeyer reaction. What does this reaction do and how is it used today?

0:15:41.2 TS: The Sandmeyer reaction is a very useful reaction in organic chemistry. It's based on diazonium salts. This is a very specific group of molecules that have dinitrogen as a leaving group attached to the molecule, which makes these molecules useful because you can just substitute that dinitrogen with a different functioning group, which means you can make a lot of different other molecules. And to understand that a bit better, I think it's nice to think about organic molecules in general as something that we want to assemble. Now, when you want to wanna assemble a very specific molecule, not all of these building blocks fit together super perfectly. So we have to try to find new ways to take the building block and basically change it or manipulate it into something that we can use in a more efficient way. And for Sandmeyer reaction basically takes one building block that's an aniline and transforms it into a building block, which is actually much more useful called diazonium salt. And it takes these diazonium salts and converts them into aryl halides.

0:16:33.5 AR: So just to be clear, an aniline is a kind of carbon ring that has a Nitrogen substituent, an amine, associated with it, right?

0:16:42.8 TS: Yeah, exactly. So you basically have a derivative of Benzene, which is the six member carbon ring, which is aromatic that is usually the flagship structure of organic chemistry. So when you google organic chemistry, the picture that comes up probably is a picture of Benzene, of an arene, and it's basically just an arene connected to a Nitrogen containing a functioning group.

0:17:01.3 AR: Okay. So the Sandmeyer reaction, it's using these diazonium salts as kind of an intermediate to make the original building block a little bit easier to stick onto the molecules that you're interested in building. Diazonium salts are highly reactive, which I guess make sense for why they're making these initial compounds easier to work with in terms of forming chemical bonds. Diazonium salts are also notoriously dangerous to work with. Can you tell me a little bit more about the safety concerns that chemists face when they're performing a Sandmeyer reaction or something else that's using diazonium compounds?

0:17:36.2 TS: So diazonium salts are actually compounds that are prepared quite routinely in labs, and every chemist in their career probably makes them a couple of times, but it's definitely not a reaction that you just do on the side while thinking about something else. And this Sandmeyer

reaction, the conversion of these anilines to the aryl halides, which we do in this paper, is actually only one kind of reaction of what you can do with diazonium salts. The diazonium compounds, as you already said, are super useful because they have a part in the molecule that can leave the molecule very easily, and in the case of diazonium salts, this is actually dinitrogen. So dinitrogen, as probably most of the people know, makes up 80% of the air that we breathe. And since this dinitrogen leaving group is so prone to leave the molecule, it's very easy to substitute it with something else, which makes this compound so useful.

0:18:24.5 TS: But as you can imagine, if there's dinitrogen in the molecule and just wants to go out of the molecule, sometimes this nitrogen release happens very, very fast, and sometimes it happens so fast that this happens in an explosive fashion. So you can say that these diazonium salts get their properties from dinitrogen leaving the molecule, but this also makes them very explosive and very dangerous. So usually you take a lot of precautions before you set up these reactions. So you wear your personal protective equipment, you probably also set up a blast shield. You always keep your fume hood set down. So it's just not something that you do while you're not concentrated. And actually there are some reports about people actually dying because of explosions that happen during the synthesis of the diazonium salts. And when I started working on the project, I was actually quite surprised on how many publications there are out there that report explosions of diazonium salts, and then you're even more surprised that people actually keep preparing them.

0:19:18.4 AR: Then this gets to your new work here. You describe a new way of doing this kind of Sandmeyer type chemistry. What makes your protocol different?

0:19:28.3 TS: So, what you usually do with diazonium chemistry is you make a two step reaction. So you always have the first preparation step of the diazonium salt. So you start from an aniline, you have to put in reagents and then you isolate or at least you accumulate. So you prepare a large quantity and solution of a diazonium salt. And then in the second step, you put your second part of reagents that then form your valuable product. And you always have to do that in two steps because usually the reagents that you use for the second step are not compatible with the reagents that you use in the first step. So for the synthesis of diazonium salts are usually quite harsh reagents. So this always forces you to make quite of a large quantity of diazonium salt if you want to make a valuable product out of it. And what we are doing conceptually different is we can do everything in one step. So we start from the aniline, which is the precursor for the diazonium salt, and we go in one step directly to the valuable product without making large quantities of the diazonium sodium salt in the middle. And that means now at no point you have a large quantity of the diazonium salt in your flask or in your reaction mixture, so therefore your reaction is much safer.

0:20:35.8 AR: So in the previous traditional way of doing this reaction that probably chemists who have done this are more familiar with, you've got two steps. The first step is to basically make a large enough quantity of the diazonium salt and then react that with the second thing that you're trying to bond together. But this version, you're still making the diazonium salt in the process, but it's a fleeting intermediate that's getting used up really quickly. Is that right?

0:21:00.0 TS: Yeah, that's exactly correct. We never actually observe a large quantity of the diazonium salt. So the quantity of diazonium salt that's formed at a time is lower than our detection limit, which basically means it's very, very low. So this was also part of the analysis of our work, is to actually understand if we even go through this diazonium salt. Because if you cannot observe it, then the question is do you even form it? We have some really cool experiments in the work that prove that the diazonium salt is formed, but as it gets converted so fast to the valuable product, you never actually see it.

0:21:30.3 AR: So why does this reaction work?

0:21:31.7 TS: This is a process that's called nitrate reduction that changes the oxidation state of our reagent. And the reagent that we are using is called nitrate. That's a very common reagent that's also used in the fertilizer industry. And the process we are doing is therefore called nitrate reduction. Nitrate reduction is a process that's very common in nature. So plants use nitrate production in their metabolism. So we take our starting material, we do the reaction that we know from nature. Now our starting materials and reagent fit together so we can form the diazonium salt, and then directly convert them into the valuable product that we want to have. So we are coupling nitrate reduction to the diazonium chemistry.

0:22:11.7 AR: So we talked about before, with risks of exploding reactions in the traditional method, you're using blast shields, face guards. What does it look like to do this reaction that y'all have developed now?

0:22:24.1 TS: So the setup is actually quite easy. The reagents, you can all weigh it under normal atmosphere. You don't have to take any precautions of getting a protective atmosphere over your reaction or in the reaction flask. That means you can just sit on the balance, you weigh in all the reactions because by themselves they're not dangerous at all, and then you can just take them to your fume hood. So we still take a lot of precautions and we still put the blast shield there, but it doesn't mean that you would actually need to be required to do that. It's just something that chemists are prone to do because you want to take every safety precaution you can, not the ones that you must.

0:22:56.9 AR: Yes, again, a solid message to our listeners, please always wear your personal protective equipment in the lab.

0:23:02.8 TS: Yeah, that's definitely important.

0:23:03.5 AR: So. There's clearly some safety benefits that have come from this new protocol, but how does its performance actually compare to the original Sandmeyer reaction protocols?

0:23:15.4 TS: So for a couple of molecules, and actually our reaction I believe performs the same, but then in some cases, it actually also performs better. So it seems like that this reaction is not only safer but sometimes even more efficient. There might be some substrates out there where the conventional Sandmeyer reaction still works much better than ours, which was not the case for the ones that we've tried, but you never know.

0:23:35.2 AR: You had also mentioned before that because the initial reaction conditions are not so harsh, that you can also use different starting materials to begin with. So, does that mean that this reaction is also allowing you to work with a broader set of materials than you could before?

0:23:49.3 SC: Yeah, exactly. We can now use drug molecules, which you can usually not easily functionalize with the diazonium salt. For example, if it's a drug or pharmaceutical molecule, it usually contains many different functioning groups. And if you have that, then each of these groups of molecules usually is sensitive to something else. And as I said, for the diazonium reaction, you use harsh conditions. So if you take these complex molecules with a lot of sensitive functioning groups, it's very easy that you decompose that molecule, which means you break it. And we've shown now that you can actually use a few, actually quite a few of these pharmaceutical molecules and do that chemistry with them without seeing decomposition. So we get a high yield, a high efficiency of converting them into even more valuable products. So yeah, this is something that you cannot do with conventional diazonium chemistry.

0:24:33.7 AR: The Sandmeyer reaction is like 140 years old. Why did it take so long to come up with this new and improved protocol to do this kind of chemistry?

0:24:43.9 TS: Yeah, that's actually a great question, and that's also a question that we asked ourselves while we worked on this. So the reagents and the complete conditions that we use to do this reaction, that's not something that you would usually come up with when you just think about how you would design this reaction. Some of the reagents are actually completely orthogonal to each other. So you would actually think, when you put these reagents together in one pot, they would directly react to each other so that you don't have a productive diazonium formation. So, we didn't actually design this reaction. I was working on a completely different topic during my PhD. So I actually managed to develop a new kind of catalysts that were able to functionalize arenes. Then I was lucky enough that a postdoc from our group who's called Xavier, he's also a good friend and he's the other equal contributing first author on that paper, he had very cool ideas, and one idea was to use these catalysts that usually functionalize arenes to functionalize anilines.

0:25:37.3 TS: So together we came up with some experiments, but none of the ideas actually worked. So all of the ideas that we had were completely useless. The catalyst was not doing anything. But we found that something is happening to the aniline, which was completely unexpected. And then we thought a bit about, and luckily we asked the questions at that time, what happens to the aniline? We did a control experiment without the catalyst and the reaction was still working, which means it had nothing to do with the catalytic reactions that we originally had in mind, but still we found that it goes through diazonium salt. And then we actually found that you can also do the Sandmeyer reaction with this protocol. Yeah, so it was an accidental discovery while working on a different project. And I think this is why probably no one has discovered that before. Yeah, because the reagents that you're mixing are not reagents that I would've designed on the whiteboard if I wanted to make this reaction work. You just have to find this kind of reaction.

0:26:27.2 AR: That is so interesting, and another great example of serendipitous discoveries as you're investigating these mechanisms. We love to see it. Diazonium salts, of course, they show up in reactions far beyond just the Sandmeyer reaction. I'm wondering if you can say anything about potential broader applications of this method that you've developed and the mechanisms that you were able to uncover and how they might be applied to other kinds of diazonium chemistry.

0:26:56.6 TS: Yeah, so diazonium chemistry in general is incredibly useful. These diazonium salts are intermediates that you can actually use for a lot of different reactions. And this Sandmeyer reaction, the conversion of these anilines to the aryl halides which we do in this paper, is actually only one kind of reaction of what you can do with diazonium salts. So what we also hope is that other people take our paper as an inspiration to develop other chemistry that you can do in one step from anilines that would usually rely on diazonium salts. And maybe, yeah, there's a lot more stuff that you can now do in this one-step protocol if you apply this strategy that we describe in our paper.

0:27:31.8 AR: This is such a fascinating story. Thank you so much for joining me on the podcast today, Tim.

0:27:36.4 SC: No worries. Yeah, it was good talking to you. And thank you very much for inviting me and having me here.

0:27:41.6 AR: Tim Schulte is a graduate student at the Max Planck Institute for Coal Research and RWTH Aachen University. Be sure to read the paper from Schulte and his colleagues in science this week. It's titled Nitrate Reduction Enables Safer Aerial Diazonium Chemistry. You can find a link at science.org/podcast.

0:28:01.8 SC: Don't touch that dial. Up next, we hear about books that look to the future and don't see doom and gloom. And this year we have all of our books already confirmed, so you can go to the episode page and read along with us month to month.

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0:28:21.4 SC: We are about to kick off the 2024 book series for the year. The theme can be summarized in a number of different ways; a future to look forward to, the optimist toolkit, how to have the best apocalypse for you. We have our books host Angela Saini and our books editor Valerie Thompson. They're gonna talk about the theme. Let's go with a future to look forward to and some of the books we're gonna hear about for the rest of the year. Here's Angela and Valerie.

0:28:48.5 Valerie Thompson: This was a tricky year, I think, for us. So the theme for everyone was kind of looking forward to the future or a future to look forward to, utopian writing, which was far trickier than you would think.

0:29:00.4 Angela Saini: Yeah. I mean, we've done some heavy topics in the past. We wanted to present some perspectives that are counter to the increasingly dystopian views of the future that are out there. Not to say that the concerns that people are raising about various subjects are not true concerns or that we shouldn't be worried about them, but just that there are some reasons for cautious optimism.

0:29:26.3 VT: Yeah, and it is very difficult, I think particularly this year, with so many elections happening, the rise of authoritarianism, these threats to democracy, the climate change threat just feels to be bearing down on us in ways that it didn't feel quite as... I mean, it always felt urgent. It almost feels that we're at kind of doomsday now in so many different areas, AI, everything. And it is quite difficult, I think, with the literature when you survey it to find hopeful looks forward or hopeful scientific ideas that could get us out of this. And sometimes it feels almost too optimistic that these are unrealistic, almost.

0:30:11.8 AS: Yeah, I know exactly what you mean. Like there's that type of science writing that I think of more as like science cheerleading that was a trend in writing for a while. But I feel like there's this new trend in media right now that I'm noticing with a lot of books and films that are trying to emphasize that in all these situations that are very difficult, dealing with climate change, ensuring that artificial intelligence is deployed properly, all these arenas where we feel out of control or we feel like it's happening without our agency, that we actually do have agency and that there are reasons to be cautiously optimistic about the future. And so that was something that we really wanted to make sure came through.

0:30:52.8 VT: Yeah. One of my favorite books, and I think it's from the 1960s, by Alvin Weinberg, looks at the technological fix. So that was an age in which everybody thought that technology could solve all our social problems. That if we just threw enough money at research and development, that somehow we could science our way towards a better world. This was the age of The Jetsons and these very optimistic ideas about the future. And I think we've evolved out of that. I don't think we take that approach anymore. But I have to say, with the list that we have, I do feel that there is a recognition that in certain disciplines, there are little tweaks and things that we can do to realign the way that societies work in such a way as to drive us through into a more optimistic future. So one of the books, for example, that we have on our list is Tokens by Rachel O'Dwyer, which looks at the future of money. And this may feel like a red flag to many people because you think of Bitcoin and crypto and you think that that can't be good. But our relationship with money is quite strained in capitalist democracies. We are struggling. So maybe there are more radical ways of thinking about

how we organize financial systems and money that can at least start to push us out of that.

0:32:10.4 AS: Yeah, I really like this one too because she's looking at this idea of how these new forms of currency are changing the balance of power between digital platforms and the state. And in some cases, that's really good, and in some ways, it's concerning. And so, balancing those two ideas and thinking about what this means moving forward is gonna be something really interesting, and I'm really looking forward to that discussion.

0:32:33.5 VT: And I think Climate Capitalism by Akshat Rashi, which is one of our books, which is going to be appearing in the summer, fits into that same vein, which is, how do we get capitalism to work for us? How can we use it to our advantage rather than it exacerbating inequality and environmental degradation? So he looks at all these different mechanisms and schemes out there that can harness the capitalist power that we have in order to improve the environment rather than destroy it.

0:33:07.9 AS: Another area that we're interested in and that we're planning to look at is how these things are gonna intersect with medicine. And in particular, one of the books we're gonna look at is looking at the future of reproductive technology. So Eve: The Disobedient Future of Birth is the name of the book, and this is written by a legal scholar, Claire Horn. It's kind of predicting this future where artificial wombs are gonna be a viable alternative to maternal gestation, which she's not wrong to extrapolate this. This is something that the work is progressing in animals. It's important to have these conversations now before the technology is a reality. But I'm really looking forward to her perspective on this as a legal scholar, because she's not really talking about how is this technology gonna work, it's more about how it's gonna be deployed. There's the potential for this to be a real game changer in terms of reducing gender inequality. But then there's also these questions of access and how it's going to affect things like reproductive rights that we also have to think about.

0:34:09.1 VT: And it's long been this feminist dream. I think Andrea Dworkin wrote about this many years ago, this idea that we can as a species get to a point where the burden of reproduction doesn't fall on women anymore, that it is evenly distributed in some way, and that possibly technology could provide an avenue towards that. We're very far away from it, but Eve does explore that possibility that we could one day have a world in which it's not women's job to think about reproduction and birth and childcare anymore. And I do think we're getting there slowly. I mean, there's another book coming out this year. It's not part of our lineup, but Fatherhood by Sarah Blaffer Hrdy, which looks at how much fatherhood has been underplayed as a really important evolutionary mechanism. Fathers are actually hugely important, but socially, we have moved towards that much more. And I do feel that so many things are happening at once. So not just reproductive technology, but also social change in the way that we parent that could create this revolution that feminists for a long time have dreamed of.

0:35:14.2 AS: Right. That book is not appearing in this series, but we do, we will have a review of that in the magazine.

0:35:19.9 VT: Right. That's good to hear. Yeah, we have a great lineup. I'm so excited about it. And it is very diverse. There is medical stuff in here. There is technology. There's, like I said, stuff about capitalism. And then at the very end of the series, we have this wonderful interview with Ruha Benjamin, who's a scholar who is very kind of visionary in the way that she imagines what the world could be like. And her latest book, Imagination, takes that a step further by asking how much different could life be if it wasn't just rich tech billionaires imagining these huge, big, radical futures and everybody got to do it? If it wasn't just Peter Thiel and Elon Musk dreaming that we might settle on the moon or on Mars or live forever, but that all of us got to have these radical visions

about the kind of future we might want.

0:36:13.2 AS: I feel like what she does really well is to ask whose vision of the future are we currently living in? Whose imagination should inform our next steps?

0:36:22.9 VT: Yeah, it is a really exciting book. I did actually reach out to a few friends of mine who either are scholars in this area or write sci-Fi, and they all struggled with finding a science fiction book that was genuinely utopian. So there's quite a few books that start off utopian and then disintegrate into dystopias, or dystopias in which there are a few utopian believers who then disappear or something terrible happens to them. There just genuinely isn't that much real utopian science fiction out there right now. And maybe that's a reflection of the time that we're in, that it's very hard to be hopeful in an era in which things are as bleak as they are. In fact, this year, I was asked to write a piece of speculative nonfiction, so this is kind of imagining that you are a few decades in the future, and I couldn't come up with anything utopian. The thing that I wrote was actually quite depressing by the end. It was just worse than what we have now.

0:37:21.5 AS: Oh, dear.

0:37:22.1 VT: It's just not out there. But I can understand why, fully.

0:37:26.5 AS: I mean, I think, in some ways too, it's just like, unfortunately, a dystopian story is just often just a better story. The utopian narrative is wonderful and I wish that we could all live that, but maybe we like to read about people that are undergoing struggles like we undergo struggles. We don't wanna read about someone who just feels like a perfect life. It sounds very interesting.

0:37:48.7 VT: No, I know. Yeah, you're absolutely right. We want to see our experience reflected back at us, and things are hard. I mean, frankly, they are hard for, still, for so many billions of people around the world, and that's the way life is. But I do hope, with the books that we have, that we can at least see the possibility of people being able to dream of something better.

0:38:10.6 AS: Yes. And I think a nice thing too is that all of these authors are very cognizant of the perils of these technologies that they're talking about, thinking about how this is going to affect other social systems.

0:38:24.2 VT: Yeah you're right. I mean, none of this is blind optimism. It's definitely tempered with reality and they're very much rooted in the real world, each of these authors.

0:38:32.7 AS: Okay. Well, we talked about most of the books here, but there are a few more that we haven't been able to talk about. So, you're going to hear about them in the upcoming series, and there will be a blog post that is accompanying this intro as well that will go into more detail. So we look forward to bringing you these stories.

0:38:51.1 SC: That was editor Valerie Thompson and host Angela Saini taking us through some of the 2024 books. We're gonna see six over the course of the year. They come out the last episode of each month, starting with a kickoff in April. The first book will be May. You can check them out on the site, science.org/podcast, and actually see the full list and read along this year. We have every book confirmed and the dates are set. So yeah, go to science.org/podcast and look at this episode page and you will see a full list of what we're reading for the year.

[music]

0:39:26.7 SC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at sciencepodcast@aaas.org. To find us on podcasting apps, search for Science Magazine, or you can listen on our website, science.org/podcast. This show was edited by me, Sarah Crespi and Kevin McLean. Special thanks to Kelly Servick and Ariana Remmel for all their work on some fantastic stories, and a big welcome back to Angela Saini as we kick off the 2024 book series. We also had production help from Megan Tuck at Prodigy. Jeffrey Cook composed the music. On behalf of Science and its publisher, AAAS, thanks for joining us.

[music]

0:00:04.7 Sarah Crespi: This is the Science Podcast for April 19th, 2024. I'm Sarah Crespi. First up on the show, staff writer Paul Vossen is here to talk about how reductions in air pollution may lead to a warmer planet. Next, I'm joined by contributing correspondent Andrew Curry. We're gonna discuss what appear to be ritual killings carried out in Neolithic Europe. We talk about how these gruesome deaths actually resemble some modern-day mafia killings. Finally, we have researcher Eric Nelson to talk about how cholera is fighting a war on two fronts. Actually, this is the cholera bacteria, which can be killed by antibiotics, but it's also hunted inside the gut by a bacteria-killing virus. It turns out the dynamics between the virus, the bacteria, and antibiotics are important to understanding the course of the disease. This past year, 2023, was the hottest on record, and these high temps support the idea that global warming, climate change, is accelerating at an unexpected rate. This week in science, staff writer Paul Vossen wrote about a possible contributing factor, cleaner skies leading to more absorption of solar energy at the surface. Hi, Paul.

0:01:21.1 Paul Vossen: Hi.

0:01:22.4 SC: Welcome back to the podcast.

0:01:23.4 PV: Thank you.

0:01:24.6 SC: I found this a little confusing the first time I heard about it. You know, isn't absorbing radiation from the sun kind of the main driver for global warming? How is what we're talking about today something different?

0:01:34.6 PV: There's this thing called the albedo of the Earth, and that's the amount of light that we reflect back into space. And over the past couple of decades, there's these instruments in space that have been monitoring. They look at both the energy being reflected and then the kind of heat being given off by the planet. Tally those together compared to the energy we know that's coming from the sun, and you get the amount of excess energy in the planet. And over this time, especially in the last decade, the planet has been getting less reflective. So, more sun is not being reflected off before it hits the surface of the earth. So, at the ground level, essentially, it's getting sunnier.

0:02:14.7 SC: This is something I've heard about before when we talk about shrinking of the ice caps, that means we'll have less reflectance. But this is a more general process like over the whole surface of the planet.

0:02:23.7 PV: There are a lot of different things that can contribute. It's not just cleaner skies, it's clearer skies, really. One big part of this is atmospheric pollution, a decline in atmospheric pollution that would otherwise be reflecting light. But that's not necessarily the whole story of this. There's a lot of this that right now is just a big mystery. Climate scientists don't understand why it's beginning less reflective. It could be other changes with the clouds that are not tied to pollution or it could be shifting circulation like air, ocean circulations, things like this that are just not quite understood yet.

0:02:55.7 SC: Pollutants would have contributed to darker skies or less clear skies because there's like particulates and aerosols and that shines light back into the sun.

0:03:05.1 PV: One of the primary things here is sulfate aerosols. So, you have sulfur dioxide comes out of power plants, dirty power plants and create these little reflective aerosols that shoot light back. They also interact with clouds and cause clouds to get brighter and give them little cloud nuclei to make them more reflective or last longer in the atmosphere. Just how powerful both of these are is another big uncertainty in climate.

0:03:30.7 SC: And what about the timing? You said this is something that's been observed a lot more in the last decade, but we've been cleaning up the atmosphere for some time in various parts of the planet, not regularly around the whole sphere.

0:03:42.7 PV: In some ways, this is expected, at least part of it, not unexpected. We've known that curbing pollution, which is a good thing, you know, causes lots of deaths. You don't want to keep pollution just to limit warming. Like that's far worse a problem than warming, right? Yeah, this is built into climate models to extent that declining pollution will see warming ramp up. And even in the predictions, though climate models warming does ramp up, accelerate some because these aerosols are going down. Now, this happened in the '70s and going onward. There's also work that suggests that when you clean up that pollution, especially in kind of really dirty places, it can take a couple of decades to actually really make a difference, which is somewhat counterintuitive. You think, oh, they stopped the pollution, then things should change right away. But some clouds are most sensitive to the first bits of pollution they get to. As you're ramping down the pollution, the clouds might not necessarily be changing that much until you really get low. Some of this, what we're seeing now could be tied to reductions from the 1990s, really.

0:04:46.6 SC: There's kind of a lot of unknowns here. But one thing that I was wondering about is, we're talking about this increased energy absorption by the planet. How does that compare to what anthropogenic gases are doing like the global warming part of what's happening? I'm really trying to tease apart this difference between what we're talking about here like clearer skies, this increased absorption, and anthropogenic climate change from greenhouse gases? Like how do these things compare to each other?

0:05:13.9 PV: It can be potentially large for the short term. Global warming keeps getting bigger year after year. That's the kind of inexorable CO2 rising in the atmosphere. It becomes more and more powerful. But over, say, this past 20 years, this modeling study looked at the increased energy in the system over that time. So, from 2000 to 2019, you have X amount of energy, new energy in the system. Maybe 40% of that it came from a decline in reflectivity and potentially driven by this reduction in pollution. The other part would be increasing greenhouse gases mostly.

0:05:50.6 SC: Oh, wow. Okay. Do we expect this increase in energy absorption to kind of level out or be reversed while the greenhouse gas effect just keeps ramping up?

0:06:00.5 PV: This is one of the big questions. This is like a big, difficult to grasp question in climate science because if this is just driven by declining pollution, right? Then okay, we get there. And then it's not going to keep happening, right? You can only get so clean. It would be lovely to have clear, clean skies, right? It's a short-term thing. It's really unveiling some of the warming that we've blocked before. But if there's something else going on, which climate models can't really explain everything, it seems right now like if some clouds are changing in some ways, that could continue. And it's just totally not understood. There are reasons to think. But there is something else going on because what these instruments in space called Ceres, they see the reflectivity of the planet declining in both hemispheres like northern, southern hemisphere, whereas pollution has really dropped in the northern hemisphere. So, like what's going on down in the southern hemisphere, right? It's a big question.

0:06:54.7 SC: The climate models only go up through 2019. So, something different might have been happening in the past few years and we wouldn't be able to tell.

0:07:02.5 PV: Yeah. Climate models projections obviously go out for hundreds of years.

0:07:06.6 SC: Yeah, I was going to say... [chuckle]

0:07:07.6 PV: But when you are trying to use real-world data to constrain what they're doing or understand kind of near-term, you do things like you put in the actual sea surface temperatures that were experienced over that time so you can kind of recreate the weather a bit more closely or use real-world data for how much pollution there was. And that can help you actually figure out what's going on versus it just going freely and creating some Earth that's kind of like the Earth but not quite like the Earth. There's this big bureaucracy to climate modeling that revolves around the UN climate reports. So, they put the plans together. The latest generation was finalized in 2017, the plans for it. And it just takes time to get the new data and update all this. But one thing is people are pushing that we need to do this more frequently to understand near-term mysteries that might arise.

0:07:56.9 SC: Speaking of continuing modeling, continuing measuring, these Ceres satellites, these instruments up on the satellites, they're not going to be around forever. Are we going to be able to keep observing this change in energy on the Earth's surface?

0:08:10.3 PV: It's quite possible there could be a big gap. So, right now if there are six total instruments, four of them are on these workhorse, amazing satellites that have been up for 20 years, or more than 20 years, but their orbits are now drifting, and they're going to go kaput in a couple more years. Even now it's not getting the same type of data because their orbits are drifting. So, they're essentially not that useful for the climate record. Fifth satellite, it's a weather satellite that's going to go out of service likely in the next few years. And so the last instrument is on kind of a flagship weather satellite for the US. And it should keep going until the successor comes up in maybe 2028, but it's a single point of failure. So, some bit goes wrong or it gets struck by radiation, and then that record goes silent. And these are such small, so the amount of energy coming in and leaving the planet is huge. And global warming is, you know, 1% signal within that. So, you need to have this trend continuing to be able to like ease out anything. So, a gap here is more damaging than some other satellite records, I'd say.

0:09:15.8 SC: Thanks so much for talking with me, Paul.

0:09:17.8 PV: Oh, yeah, no problem.

0:09:18.3 SC: Paul Vossen is a staff writer for Science. You can find links to the stories we discussed at science.org/podcast. Stay tuned for a chat with me and Andrew Curry about human sacrifice in Neolithic Europe.

[music]

0:09:38.4 SC: Okay. Just a quick warning for our listeners that might be sensitive to descriptions of violence. This is going to be a little bit graphic. We're going to talk about a way of murdering people. The story is about what looks like ritualistic killings of people in Neolithic Europe in an unusual and gruesome manner. Andrew Curry is a contributing correspondent for Science. He wrote about why it might be sacrifice, why it might be part of a ritual, and why we think these deaths are connected. Hi, Andrew. Welcome back to the podcast.

0:10:07.2 Andrew Curry: Hi, thank you.

0:10:08.6 SC: So, how this paper got started or how someone decided to take a closer look at these deaths is kind of an unusual story as well. Can we start there?

0:10:17.7 AC: Sure. The lead author on the paper is a forensic anthropologist in France who 40

years ago as a younger forensic anthropologist in France was excavating a site that was built about 3500 BC. And he found three really unusually placed bodies in what looked like a grain storage pit. The two of them were in a bizarre position. And at the time, he sort of wrote it off as unique or just something odd. And then later, just a few years ago, he told me he was reading a paper about Italian mafia killings. And he recognized the position of the bodies from this Neolithic grave he had excavated 40 years before. And he took the opportunity to look through the literature and he found a number of other similar positions at similar sites all across Europe from around the same time.

0:11:19.3 SC: Wow. Let's get into what exactly this method of killing was that he suspected was going on so far in the past.

0:11:26.6 AC: Yeah, I have to say, I read a lot of archaeology papers and this one was a hard read. Basically, a rope is tied around the throat. And then the other end of the rope is tied around your ankles. Victims are placed on their stomach, and the weight of your legs strangles you over the course of a few minutes. You can't hold that position for too long. And yeah, so it's sort of a torturous way to die that I guess is used by the Italian mafia when they really want to make a statement.

0:11:57.2 SC: I was going to say, we might suspect why the mafia would do this, but what do researchers think might have been the reason for doing this 5500 BCE?

0:12:05.9 AC: It's hard to say why this particular position or why they needed to subject people to this. The author and his co-authors suggested that societies at the time, these are all farmers. These are some of the first farmers in Europe. And something common to farming societies is sacrificing to the gods because these are sort of forces that you depend on completely, the rain and the sun, the weather. And so sacrificing something important, animals or even people, might be a way to try and get those forces on your side. But it's hard to know why that style of killing was a more powerful symbol or was so common. Another archaeologist I talked to said it's a little hard to say that it was symbolic. It might have been, there's a limited number of ways of killing people. There are other kinds of human sacrifice that also take place at the time it is striking.

0:13:02.2 SC: How many sites are we talking about here?

0:13:03.9 AC: They found 15 sites where they were sure that this asphyxiation or strangulation was involved. And I think 20 bodies. And the sites range from Bohemia, so sort of modern day Czech Republic, all the way to northern Spain. And on the one hand, that seems like a lot. But on the other hand, 15 over 2,000 years, yeah, it's hard to say that that's a universal phenomenon.

0:13:30.2 SC: Are there any suggestions for why it might have lasted so long or been spread so far?

0:13:36.4 AC: The authors think that there was a common belief system that incorporated this position or this kind of sacrifice into it. The comparison he made was that in the Middle Ages, you have all kinds of different cultures in Europe who speak different languages and eat different foods and live in different places over the course of hundreds or even thousand years. But they all would have recognized the significance of the crucifix. So, maybe this is something symbolic that different cultures share, and we just can't see exactly what it meant to them.

0:14:10.7 SC: Yeah, there's a lot of pieces that need to be filled in because right now we have body position, and it's not easy to tell if these people even died from this, right? Because they could have... Could they have been positioned this way after their death?

0:14:25.3 AC: It's super interesting. This is something that comes up in the mafia killings too.

Sometimes people are killed before and then put in this position. And because it's strangulation, it doesn't leave any marks on the bones like other forms of violence where your skull is crushed or your bones are nicked by arrowheads. So, really all we have to go on is the position, and it's hard to know what happened in those last moments or if they were indeed alive.

0:14:54.1 SC: I guess the next step is to look for, not necessarily more deaths like this, but maybe some kind of other evidence that this was ritualistic or it was a sacrifice. Or what kind of underpins the connection between the different sites?

0:15:08.4 AC: Yeah, and they try to find sites that it's not just the position of the bodies, but also are there other sites where it's clear that there was a larger ceremony taking place? Or at some of these sites, there was a ditch with openings oriented towards the solstice. So, are there also across cultures commonalities that go beyond the position of the bodies, also some sort of common element in the rest of the ceremony. Because it is 2000 years, although oral traditions do survive that long, it's a very long time and it is a huge span of geography.

0:15:46.6 SC: So, the way you end the story is great. So, whatever was happening here, it basically, as far as we know, went out of style right around the emergence of things like Stonehenge.

0:15:57.0 AC: Yes. So, sort of 3500 BC. People start doing something else. They organize society differently. They're still farming, but instead of these sacrifice sites or whatever they may be, they start getting people together to move big stones and make tombs and monuments and henges across France and eventually England. And they leave this kind of sacrifice behind, thankfully.

[chuckle]

0:16:27.5 SC: For real. I feel like the henges are still pretty mysterious and we have known about them for a lot longer. So, I mean, it's not a surprise that this sacrifice might leave us with some unanswered questions for quite a long time.

0:16:41.2 AC: Yeah, these aren't dramatic sites to look at. There are pits in the ground with a few people in them. And it takes a really careful excavation to record the positions of the bones in enough detail that forensic anthropologists can reconstruct the death many millennia later.

0:16:58.5 SC: All right. Thank you so much, Andrew.

0:17:00.8 AC: Thank you.

0:17:01.1 SC: Andrew Curry is a contributing correspondent based in Germany. You can find a link to the story and a related Science Advances article in science.org/podcast. Don't touch that dial. Up next, I talk with researcher Eric Nelson about how viruses hunt bacteria in our guts like lions hunt gazelles on the Savannah.

[music]

0:17:27.1 SC: In areas without access to clean water, cholera can become a problem. The bacteria that causes disease gets into people from contaminated water. Cholera affects over 1 million people a year, killing more than 100,000. It kills through, we'll just say, severe dehydration. Most people are able to recover through hydration therapies, but not always. And antibiotics are sometimes needed. Like most bacterial infections, there's a risk that the cholera bacteria will evolve defenses against antibiotics over time and become more difficult to treat. But the cholera bacteria is actually fighting a war on two fronts against the antibiotics used to treat it and against a virus that infects

and kills the bacteria inside the human body. This week in science, Eric Nelson and colleagues write about this balance between bacteria, antibiotics, and a virus. Hi, Eric. Welcome to the Science Podcast.

0:18:27.0 Eric Nelson: Nice to be here. Thank you.

0:18:28.2 SC: Great. So, this virus that attacks the cholera bacteria, it's called a phage. These are the viruses that specifically target bacteria, and it's been known about for a really long time. I saw in your paper a reference to people tried to use this phage to cure cholera like 100 years ago.

0:18:47.1 EN: That's correct. And many of the discoveries that were made back then were kind of left in some ways incomplete because they didn't have the technologies and skills and insights that we have today. And sometimes I feel like I'm just writing on the coattails of work that was done 100 years ago.

0:19:03.1 SC: That's pretty amazing. I guess they weren't sequencing the genomes of these different bacteria and phage and trying to figure out how they've changed over time. But we can do that now. There's a few ways to treat cholera, as I mentioned, hydration, antibiotics. But the phage is not one of them at this point. This is not something where you can go get like a phage treatment.

0:19:21.2 EN: It's not currently available. But like we said, there were, I don't know if you say proto or some of the original kind of randomized control trials run back in the '20s and early '30s that showed 50% reductions in mortality when you treated a patient with acute cholera, with a phage cocktail. That predated the discovery of penicillin. And at that time it was amazing. You could have a bacterial infection that you could treat with something that would mitigate morbidity and mortality. And then as antibiotics came on board, it kind of dropped away. And teams have tried to keep that idea alive. And then I think in the era of antimicrobial resistance, it's come back in the vogue.

0:20:00.5 SC: Yeah. How do you know someone has cholera? Is it hard to test for this?

0:20:04.7 EN: Well, it depends. And I'll just say that I am very humbled today because I'm representing two other teams. You have a group of clinical trialists in Bangladesh led by Dr. Khan at the International Center for entire real disease research. And then you have Jesse Shapiro and Naima Madi at McGill. They're the computationalists. And I kind of sit in the in-betweens as a microbiologist. You know, I can play the hat of the pediatrician or the microbiologist or the clinical trialist, but you would think that in this era you could identify someone with cholera straight off.

0:20:33.7 SC: Yeah.

0:20:34.0 EN: But actually it depends. If you're in a place where people are immunologically naive to color like they were in 2010 in Haiti or in Zimbabwe in 2008, the symptoms are not subtle [laughter] It's perfuse watery diarrhea that can kill, you know, in 18, 24 hours after consumption of bad water. If you're in a place like Bangladesh that's endemic for the disease, the population has a lot of immunological memory. And the number of patients that are symptomatic versus asymptomatic might be very dramatic. And actually in that context, it might be quite hard to diagnose because there might be very subtle findings.

0:21:10.9 SC: So, then do you have to go to a biochemical test or some kind of culture?

0:21:14.5 EN: Well, in practice, cholera hits some of the most kind of vulnerable poorest populations in the world. And so access to a laboratory or even a rapid diagnostic test can be really

hard to come by.

0:21:23.0 SC: Yeah.

0:21:24.8 EN: And so often it's just a clinical acumen, knowing your epidemiologic context in that space. You know, not on this paper is a discussion around why do rapid diagnostic tests are kind of lateral flow cell kinda like pregnancy tests, but in this case for cholera, why do they work sometimes really well? And other times they fail terribly. We get at that question of sometimes phages, sometimes antibiotics make those tests less effective. So, in practice it's often just clinical acumen.

0:21:51.3 SC: Let's move over to the clinical trial portion of this. So, your partners in Bangladesh, they collected data from, I guess, we'll say potential cholera patients. What were they looking for? You know, who do they recruit and what kind of data do they collect?

0:22:05.7 EN: It began as a really a clinical question. This is one of these kind of like instead of being bench to bedside, this is one of these bedside to bench stories.

0:22:11.8 SC: Yeah.

0:22:12.8 EN: Where a good friend and colleague of mine, Dr. Kahn and I, we ran this cluster randomized control trial at 10 different government hospitals across Bangladesh. And in that study we are asking if we built digital tools to help doctors better assess dehydration, could we look at decreased rates of antibiotic usage and improved rehydration? And so Dr. Kahn collected samples in these sites. And I'll just say that one of the things that we focus on is how the samples are collected. Because where we work often there's no electricity and upwards of 10% of like a phage genome is nucleases. So, they shred the host microbe very quickly. And so you might have false negatives in your research. So, we actually preserve the samples with the reagent that doesn't require cold chain. So, then downstream the research could find things that maybe other teams might have missed.

0:23:01.5 SC: So, you're saying that if the bacteria was infected with a phage, that it would destroy the bacteria in such a way that you wouldn't even really be able to tell it had been there?

0:23:09.2 EN: Yeah, I mean for the microbiologist listening, it's hard to believe that a phage could nuke the host bacterial genome in such a way that even PCR couldn't find it.

0:23:17.0 SC: Yeah.

0:23:18.3 EN: But that's what we've kind of found over the years. So, like going back to your question of diagnosis, we have these situations where a patient looks like they have cholera, you do culture, you do rapid tests, you do PCR or the pathogen, you can't find it. And then if you switch around and look for the virus, it's eating the pathogen, you can find the disease.

0:23:36.6 SC: How common is this phage? Does everybody who you looked at in Bangladesh, did they have this phage? And in those places where you said where it kind of was a naive population, like in Haiti, did they also have this phage?

0:23:49.1 EN: I'll do the second one first. So, [laughter], I know it's political, but the evidence is very strong that a UM peacekeeper from Southeast Asia flew to Haiti with cholera and contaminated a river, north of Port-au-Prince. But what that person forgot to bring on their trip was the primary phage we're setting in this paper. Whereas if you look at, it depends on when an outbreak you're looking, but generally you find about half the patients have these phages and half

don't and that ratio is gonna change over the arc of an outbreak.

0:24:20.8 SC: You're gonna see an increase in phage 'cause they're like yum food and they're just gonna get more and more phage.

0:24:26.1 EN: There's like this idea that outbreaks spark and spread exponentially because cholera is coming outta the patient, hyper infectious. And then they're expanding at a rapid rate. And then the phage, like you said, are kind of viewing the cholera as food and they're gonna begin expanding later in the outbreak. And one idea is that the outbreaks actually collapse because of phages finally get ahead of its food source being the Cholera.

0:24:50.2 SC: That's starting to sound like what I hear about, you know, happening in the ocean where there are all these ocean microbes being killed on the daily by phage.

0:24:58.3 EN: So, it's actually my background is marine microbiology and whenever the clinicians are struggling with the literature on the human side, I point them towards the marine micro side because that literature is so strong.

0:25:10.3 SC: It's such an important cycle for the ocean, for food webs, for global carbon. It's really just amazing that it's happening on this microscale, I guess, in the human body.

0:25:20.3 EN: The math coming from that literature is at play in our guts with cholera and phages. And there's much more similarity than difference. It's just in the human infectious disease space, especially in the GI space, there's just been less opportunities to study it at scale. And it's just that cholera is such a scaled organism. Like at our center in Dhaka, we have 1,000 to 2,000 cholera patients admitted per day. It's very hard to manage clinically. But from a scientific perspective, there's an incredible amount of science be done in a short time that you can't do with other diseases.

0:25:56.4 SC: Like you talked about the phage destroying the bacteria, making it hard to detect. But you also had a lot of concerns about covert antibiotic use. So, it wasn't prescribed to people, but there was a chance that they also had that going on when they came in.

0:26:12.1 EN: So, sadly, we're a polluted world when it comes to antibiotics and if you ask our average patient in Bangladesh when they come in, did they take a drug? Maybe half of them will say yes. But if you do mass spec, nearly all of them have drug and usually it's two or more. And we haven't built that into our experiments historically.

0:26:30.9 SC: Yeah.

0:26:31.5 EN: And now in this paper we're pulling in phages, which historically were forgotten a bit. We're pulling in truth on antibiotic exposure with mass spec. And then, you know, I think of this as almost like the Swedish chef where you put it all in the pot and you see what you get at the end of the day.

0:26:47.6 SC: So, you wanted to know how much bacteria they have, how much phage they have, and then if they have taken antibiotics and then you can sort out and kind of see the fate of their dehydration or their like clinical progress based on those variables. Is that what you were looking at?

0:27:01.0 EN: Yeah, that was the kind of grand hypothesis, which is if you look at two patients that seemingly are identical, why is one in shock without a distal pulse? And why is one having mild dehydration sitting upright, eating a banana and watching TV? What's biologically going on there?

So, in this experiment we're asking are phages a determinant of that? Are antibiotics a determinant of that? And what's the interaction of those?

0:27:24.6 SC: Say you have a patient that has antibiotics and phage, are they even better? Are they the the sitting up eating a banana people or is it more fine grain than that?

0:27:34.0 EN: It's always more complicated.

0:27:35.7 SC: Yeah.

0:27:36.0 EN: This is a hypothesis that was on the table about 10 years ago when we started these clinical trials, and I thought it would be like a drug detected yes, no. A phage detected, yes, no. And what was the correlation with severe disease? And after, I don't know, it was like six months to a year of analysis of was it detected or not. We didn't really find anything [laughter], the hypothesis weren't sorting themselves out. And then I read back into some older literature from some of my heroes, and there's some work that was done that said, don't just think about was it detected or not, what is the relationship between predator and prey as almost like a biomarker of a readout. And so we began looking at the data in terms of ratio, and we had this idea of thinking about effective predation was if you have a lot of predator being the phage with not a lot of prey being the vibrio cholerae, if that ratio is high effective predation, was that the correlate with mild dehydration? And then if it was ineffective predation being the opposite, were those patients severe? And once we flipped that question into a ratio and a biomarker question, then the analysis kind of jumped off the page within a day. It was pretty exciting.

0:28:48.1 SC: That is, it's very much like an ecological perspective on what's happening. Like thinking about predator and prey ratios. That's not usually something you think about happening in the gut, right? You think about it out there on the savanna.

[laughter]

0:29:00.8 EN: Be it Darwin's finches or gazelle's and lions on the savanna, or like you said, phytoplankton in the ocean. The math is the same.

0:29:08.5 SC: Yeah.

0:29:09.2 EN: And we think about 10 to 100 bacterial cells in our gut compared to our own us cells, but then the phages have 10 to 100 on top of the bacterial cells. So, that biology isn't super well understood, but it's happening right now as I chat with you.

0:29:24.0 SC: So, you did see this correlation then between your ratio of predator to prey and dehydration state. Once you were be able to get that number or that ratio out, you were able to kind of make predictions or better understand people's cases.

0:29:37.8 EN: That's correct. So, that was kind of the first discovery, which was once we looked at things with ratios, we could draw clear lines to disease severity. And even if you don't go beyond that first discovery, it's really important because you can use that discovery to think about confounding in clinical trials, how to think about not just building diagnostics, but also true positive versus false positives. True negative versus false negatives on the diagnostic side. And also epidemiologically like the numbers you gave on disease burden are probably huge underestimation of true collar burden. And it's just that we can build these things into our either current suite of diagnostics or we can think about a future where metagenomics can not only identify the pathogen, but they can actually predict the disease severity now and in the future. And then I think we're

gonna get to a place where you can actually use the profile from the metagenome to say, look, there's probably a antibiotic in this patient that you don't know about correct for that factor so that your clinical decision and epidemiology is more spot on.

0:30:41.0 SC: I also wanna get to, you know, as I mentioned before, this arms race idea that antibiotics, you're worried about microbes getting more and more resistant to them. There's also a similar thing that can happen with the phage where the bacteria can evolve and basically protect itself from this virus. What did you find out about that process in your study?

0:31:04.9 EN: That's super exciting. So, I'll just let the listeners know that the whole phage evolutionary piece came after we submitted the paper.

[laughter]

0:31:13.7 SC: Was it from a helpful reviewer, perhaps.

[laughter]

0:31:16.0 EN: It was partly from the reviewer, but also Naima Madi the first author. She's brilliant and usually you don't wanna go beyond what the reviewers ask you to do, but she went beyond and we debated like, do we include this in the paper or not? And we just went for it. And for those kind of evolutionary biology nerds out there, there's someone named Van Valen, not Van Halen [laughter] And van Valen has this old theory from like 1973 around something called the Red Queen Hypothesis, which is both the predator and prey have to run just to stay in the same place. And while the first part of the story was if you have effective predation in which you put the squeeze on the pathogen by the phages, and you have that ineffective predation, you have mild disease, does the pathogen have increased genetic diversity? That was kind of where we started. And then Naima kind of flipped that around and said, will it happen if the predation is ineffective? Will the squeeze beyond the phage particles and you'll have increased genetic diversity? That's the part that came actually after we submitted the paper and she showed it. And so you really close that loop in the Red Queen Hypothesis in a way that hasn't been shown very often in human medicine.

0:32:30.8 SC: Wow.

0:32:31.0 EN: One thing that you kind of started with was that this is real in the global task force for cholera control, which is at the WHO. That team there is dealing with nearly 30 countries that are battling large scale collar outbreaks and a whole long list of people of studied collar for all these years. And you would think that in this day and age we would be doing a better job. But if you have these gaps in the science, gaps in the clinical approach, and then challenges with economics and leadership and war that make this problem very real and present. There's also like a clinical piece, which is, does anyone in the US or developed world care about cholera?

0:33:09.5 SC: Yeah, we should.

0:33:11.1 EN: Yeah. So, like, you know, my paycheck is from the US taxpayers, why should the US taxpayer care about cholera in Haiti or many other places? And I would say we have a humanitarian obligation there, but you could also make a case that if you have a urinary tract infection and you're on University of Florida campus in our hospital, everything that we've just chatted about, it's probably at play in your bladder when you're taking a drug. When you have E coli in your bladder and when phages may or not be there. And if a patient says, oh, were you gonna look at those drug concentrations and the phage dynamics? I'll say, well, that's not even on the table in terms of how we train clinicians or how we approach these clinically, but it should be now in the future.

0:33:55.5 SC: So, there might be all kinds of common infections where the bacteria we are testing for it, but it turns out there are also phage that are targeting those bacteria, battling it out inside of our bodies. And we are not trying to detect that. And, as you mentioned, if there's a phage involved, there could be, this could be a confounder in all kinds of infectious disease trials, you know, not just for cholera, but for other kinds of infections.

0:34:22.2 EN: Trials are really expensive to run.

0:34:24.1 SC: Yeah.

0:34:24.4 EN: Wouldn't it be a bummer if you get one of those kind of 0.09 p-value studies and you're like it sort of worked, but then if you assayed for these phages and then you went on the look for these ratios and you did some mass spec and suddenly you found a much more meaningful finding, that's important. And as we try to come with better suites of antibiotic regimens, we need to build this into our standard of practice.

0:34:49.6 SC: Thank you so much, Eric.

0:34:50.8 EN: Thank you for your time.

0:34:51.8 SC: Eric Nelson is an associate professor in the departments of Pediatrics and Environmental and Global Health and in the Emerging Pathogens Institute at University of Florida. You can find a link to the paper we discussed at science.org/podcast. And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at sciencepodcast at aas.org to find us on podcasting apps, search for Science magazine, or you can listen on our website science.org/podcast. This show was edited by me, Sarah Crespi and Kevin McClain with production help from Megan Tuck at Prodigy. Jeffrey Cook composed the music on behalf of science and its publisher AAS. Thanks for joining us.

0:00:05.7 Sarah Crespi: This is the Science podcast for April 12th, 2024. I'm Sarah Crespi. First up on the show, researchers are testing drugs and antibodies against Long COVID. Producer Megan Cantwell is joined by staff writer Jennifer Couzin-Frankel, some researchers and a patient to discuss the difficulties of studying and treating this debilitating disease. Next, move over mitochondria. A new organelle called the Nitroplast is here. I talk with researcher Tyler Cole about what exactly makes an organelle an organelle, and why it would be nice to have something that can fix nitrogen just living in your cells.

0:00:48.6 Shelly Hayden: Well, I'm sitting here in the parking garage at UCSF. I got here really early, and I got the really good parking and I'm pretty excited about that. I'm looking for all those signs that maybe I'm gonna be getting the actual infusion of monoclonal antibodies today and not the placebo. I just passed my three-year date for when I got COVID in 2020. I've been living with this for a really long time, and last year, I had some really, really dark days, where I had to face. What would I do if I was never gonna get better? What would I do if I really couldn't take care of myself? I was very frustrated that these trials were taking so, so long to get approved. And I knew that I was just one of millions around the world who was in a similar situation, but this weekend, it hit me. The time has come. Here we are. I'm actually getting to do something. I really had no idea how much patience it took in order to move medicine forward. Okay, I'm excited. Let's see what happens.

0:02:00.3 SC: Shelly Hayden was one of the first of her friends and family to get COVID in the summer of 2020. In the wake of her initial illness, she's been grappling with a syndrome known as Long COVID. Long COVID can last for months or even years like in Shelly's case. It has a wide range of symptoms from extreme exhaustion to shortness of breath, and difficulty thinking. Shelly recorded what you just heard before she began participating in a clinical trial, seeking to find a treatment for the debilitating condition. Our reporter, Jennifer Couzin-Frankel took a look at the different trials on the table to treat Long COVID. Jennifer, this is not the first Long COVID story you've written. You've been following this for quite some time now. Why did it feel like this was the right time to start looking into these clinical trials?

0:02:47.9 Jennifer Couzin-Frankel: We're starting to see trials that aren't just targeting symptoms, which of course is important, but we're seeing trials that are trying to get at the roots of this syndrome. What is actually going wrong biologically, and how can we correct that? So, I was really interested to see still a relatively small number of trials, but a non-zero number of trials now starting up or running that are testing that often in a very rigorous way. There's been a real desperate need for treatments to help people who have the syndrome, and we don't have any approved proven treatments right now for Long COVID.

0:03:28.7 SC: To become an expert in her own disease, Shelly has found community online. Without any approved treatments, she's tried to find any way to improve her symptoms, from supplements to off-label medications and significant lifestyle alterations.

0:03:43.0 SH: I don't think I really admitted how bad it was until more than a year after I had COVID. I had a really bad crash. I had like signs of neuropathy, and one of my legs wouldn't work. I really couldn't talk. I could barely move. I had to really face the music. There's no just pretending like this isn't serious. We've gotta figure out a way to manage this, live with this. At that point, I had become part of the patient community and we're self experimenting on ourself all the time. We're all constantly evolving what we're taking. That's what we have access to right now. I wanna be clear, if you go to a Long COVID clinic, or you go to your doctor, they will run some tests. They'll probably be normal because they're not running the tests that are gonna pick up these things that are happening in Long COVID. And they will say, yeah, I don't have much for you. And you might then say, well, I've heard that, and name some things that might help and they may or may not be

comfortable prescribing, because they're gonna be off label. I just took ownership that that's what it was gonna take, because treatments I knew were a long way away.

0:05:00.4 SC: Jennifer, the trials that you're focusing on in this story are aiming to clear the lingering virus that's within the body. Why do researchers think that that could be driving Long COVID in the first place?

0:05:10.1 JC: The one I focus on here is what's called the viral persistence theory. SARS-CoV-2 is the virus that they get and then that causes COVID-19, which is the illness. Most of us, we get COVID and we get better and we clear the virus as far as we know. There's a theory that at least a subset of people with Long COVID for reasons we don't understand, aren't able to fully clear that virus. So they're still testing negative on a nasal swab, but they may have virus that's hiding in different parts of their body or maybe just fragments of virus. It may not be the whole virus. There are a couple other important theories as well. One of the big ones is that there's immune dysfunction in patients. So, their immune system is kind of behaving in ways that it shouldn't be, and that's causing a lot of symptoms. And that also kind of interlocks with the virus theory, because the lingering virus could cause an immune reaction and that in turn could cause other symptoms. I chose to focus on the viral persistence piece of it, mainly because those trials for the most part are the farthest along.

0:06:11.7 SC: In terms of who's eligible for these trials, is it only people who have detectable amounts of virus in their body?

0:06:16.7 JC: The trials that are testing this theory of is viral persistence causing symptoms are not limiting enrollment to people with detectable virus, and that may seem a little strange. The reason is, that there's still so much we don't understand, so we don't even really know how to find virus and people. Our technologies can only detect a certain amount of fragments or a virus, and so we might be missing it. And then there's also a large subset of people with Long COVID who haven't been found to have detectable virus.

0:06:45.4 SC: Since it's hard to find detectable virus in all Long COVID patients, how are clinicians measuring whether or not a treatment is successful?

0:06:55.5 JC: The trials are looking at symptoms, but then the those studying virus are looking at a whole bunch of other measures. We're still trying to understand like immune cells, there's other markers in the blood to try and see if there's any correlation between how someone responds to a drug or doesn't respond, and then what's happening biologically. We don't right now have kind of agreed upon objective measures by which we can assess disease. So if you think of like a trial, testing a cancer drug, you're looking at the tumor shrinking or disappearing, and we can literally go in there with an imaging, study and measure the tumor and see how it changes before and after giving a drug. With Long COVID, we don't have measures like that.

0:07:38.2 Sara Cherry: I really worry that we're missing something by not having more direct biomarkers for the trials.

0:07:43.4 SC: Sara Cherry, a virologist at the University of Pennsylvania has been studying how the virus interacts with different tissues in the body since the beginning of the pandemic. Now, she's looking for biomarkers, molecules, or other substances in the body that largely show up in people with Long COVID. If virus or antigens, viral fragments can be detected, they could help clinicians better track how well treatments work.

0:08:08.7 SC: You don't detect like virus in the blood, and you don't even detect viral antigens by

the standard approaches in the blood. Not surprising, the virus is not replicating in the blood. But with very sensitive technologies, some groups have been able to detect the viral spike, so what those antibodies would be recognizing. What we've also been trying to do is look in stool samples from Long COVID patients to see if we can continue to detect viral antigen, and if so, that will give us lots of information. Potentially, we can use that as a biomarker for treatments, watching to see if that goes away. There are other strategies being looked at to try to find remnants of the virus in various accessible tissues. Maybe then, we can be more careful or more thoughtful about which clinical trials we enroll, which patients in to potentially have a better efficacy.

0:09:07.5 SC: Even without biomarkers, trials are still pushing ahead, and most are starting out pretty small.

0:09:15.8 Michael Peluso: There are different philosophies around clinical trials and there are different types of clinical trials.

0:09:19.2 SC: Michael Peluso, an infectious disease specialist at the University of California, San Francisco is running one of these Long COVID trials.

0:09:27.1 MP: There are large registrational trials meant to get a drug approved, and then there are also trials like the types that we do, which are really meant to probe the biology to figure out whether the mechanism that we think is at play is really at play. And those trials in my mind, which are often smaller and more intense are equally important.

0:09:48.6 SC: Jennifer, what are the major approaches that clinical trials are taking right now?

0:09:53.9 JC: There are several tactics that people are trying. One that I think is probably the farthest along is testing the drug Paxlovid in people with Long COVID. Paxlovid is the drug that's approved for acute COVID-19. You take it for five days, and it typically can help you clear the virus more quickly. One potential challenge with Paxlovid is that it's designed to target virus that's rapidly replicating, but we don't really know what the virus might be doing in people with Long COVID. So, is it replicating? Is it just fragments of virus that are kind of sitting there and making the immune system unhappy? We're not sure. So it's possible that people could have persistent virus, but Paxlovid might not work to treat them and that doesn't mean that the viral persistence theory is kaput. There's some other approaches too. There's a group that's testing antivirals that are currently approved to treat HIV infection and they don't necessarily need rapidly replicating virus to work. There are a couple of trials that have started or are going to start looking at monoclonal antibodies.

0:10:55.7 MP: I had actually wanted to do a study of a monoclonal antibody for Long COVID basically from the moment that we identified that at least some people had these viral remnants. And a subset of people, we think that these remnants are intermittently present in blood, and if that's the case, they could almost act sort of like as a toxin. Setting off an immune response.

0:11:17.7 SC: Monoclonal antibodies could eliminate lingering virus by binding to the spiky protein, SARS-COV 2 to two uses to attach to cells.

0:11:25.0 MP: It was really intuitive to me that you'd want to sort of neutralize that potential toxin. We know that in addition to being able to neutralize a viral particle, some of these antibodies can also kind of recalibrate the immune response. Monoclonals were a really critical part of our response to COVID, especially in the first couple of years. Unfortunately, the virus has continued to evolve to the point that there are no currently available monoclonals. The monoclonal that we're using in this study was one of the last that would've been standing, but it doesn't work against currently circulating variants. That's why we focused on people with Long COVID attributed to a

susceptible variant with a theory that a reservoir of that variant is what's driving the condition.

0:12:09.1 SC: Shelly is one of 30 people enrolled in Michael's clinical trial. She doesn't know yet whether she received the placebo or experimental treatment, and has avoided sharing her personal experience during the trial to make sure to maintain its integrity.

0:12:24.9 SH: I would walk through fire and chew glass to protect this trial. It's small, but there are people around the world right now who are putting off end of life decisions, because of the severity of the disease. Waiting for the results of some trials. They're desperately wanting to know if there's some hope out there, and so I feel really responsible to them to get it right.

0:12:54.0 SC: Of the trials that you look into for your story, when can we expect to hear results?

0:13:00.8 JC: I think the hope is that we will see results from some of these small trials. By the end of this year, it's gonna be important to be thoughtful about how we interpret the results.

0:13:10.4 MP: What I am really worried about is that, if the top line result of any of these studies is not a home run, that the message will be, that it was a failure. That is the wrong attitude for these studies. It would be absolutely great if someone hit a home run. The likelihood of that happening is very, very low. It may be that lots of people benefit from the antibody, but it may be that there are five people that really benefit. And understanding what makes those five people different from the other 15 or so, would be a huge win. It would be a huge tragedy if a few negative studies sort of reported out this year and then people determined that this was an insurmountable problem and walked away from it. We really need to be keeping up the momentum that we've built up so far.

0:14:00.9 SC: Jennifer, would you say that funding is picking up right now for Long COVID research? Can we expect to see even more treatments and approaches in the future?

0:14:09.2 JC: There's been quite a lot of funding into Long COVID. I think there's been a fair amount of acrimony and debate about where that funding has gone, and whether it's gone in the right direction. These are risky trials, not with the patients necessarily, but risky in that we don't know what the answer is going to be. I think there's hope not just for more money, but for more innovative thinking and kind of openness to innovation and to risk taking in the science that many folks in the field would love to see.

0:14:38.5 MP: We need clinical trials focused on all of these different mechanisms. Once we do start to see signal in some of these trials, we may move to thinking about how these pathways are interrelated and combination treatments to intervene on multiple pathways.

0:14:54.5 SH: In the meanwhile, people need support, and that looks like financial support, that looks like caregiving support, that looks like better training for Long COVID doctors. There needs to be some kind of immediate action to get some education in place so that people have better access to care until we do have treatments. There's not a day that goes by that I don't think about what this is like for the people who don't have family to support them or help them if they aren't able to support themselves anymore.

0:15:26.1 SC: While patients like Shelly wait for answers, researchers also hope that what we learn from these trials can be used to better understand other chronic conditions that people develop after viral infections.

0:15:38.6 MP: There may be several overlapping mechanisms including viral persistence of course, of a different virus. The proof of concept of viral persistence for Long COVID could go back and

inform a lot of these other conditions.

0:15:53.7 Megan Cantwell: Part of why we know so much about Long COVID is that the whole world got infected around the same time, and so we're tracking like a huge cohort that is sort of synchronous. For these other viruses, they're sort of asynchronous, so it's much harder to tell what drove that syndrome that someone may be presenting with. So if we understand the mechanisms that drive Long COVID, we may then really be able to understand these other syndromes that we really knew very little about.

0:16:21.9 SC: That was producer Megan Cantwell and staff writer Jennifer Couzin Frankel. Also appearing in the segment were Shelly Hayden, Sara Cherry and Michael Peluso. You can read more about the Long COVID trials and read Jennifer's story at science.org/podcast. Stay tuned for a chat with me and Tyler Cole about a new-ish like a hundred thousand years old organelle called the Nitroplast.

0:16:55.2 SC: Deepen our history way back at our single cell days, eukaryotes like us, the cells with a nucleus and membrane-bound organelles had to get those organelles from somewhere. Basically, they started out in symbiosis with a tiny Prokaria, a bacteria that eventually became something like the mitochondria, which we all know does some very useful work for our cells. Similarly, chloroplast started as a helpful symbiotic bacteria, and ended up doing important work on a full-time basis for photosynthesizing cells. And these are billion year relationships at this point. It's been a long time since a new organelle has joined the team, but this week in Science, Tyler Cole and colleagues write about what might be the onboarding of a new organelle in a marine algae that does important work in the nitrogen fixing business, creating what we might be calling a Nitroplast. Hi Tyler, welcome to the Science podcast.

0:17:54.8 Tyler Cole: Thanks for having me here.

0:17:56.3 SC: So the big question that this paper brings to mind is what is an organelle? When is it an organelle, and not just a symbiotic friend that trades with the host for the benefit of both?

0:18:09.5 TC: This is a question that has been debated in the literature extensively, and it's ultimately an artificial distinction. There's no lying you're gonna cross. We're on a spectrum here, but there are criteria. There are criteria that scientists have thought deeply about and laid out in the literature, and we feel that this organelle meets those criteria such as protein import from the host that supports the functioning of this organelle genome reduction, and a process of cell division by which these structures are vertically inherited and transmitted to the future generations.

0:18:48.2 SC: Basically, one of the clues that this might be an organelle is that it doesn't have all the genes it needs anymore to survive on its own. It's offloaded some of them to the host cell. The host then makes those proteins and supplies them into the organelle. It's imported. And then these things divide at the same time. The organelle and the host cell, it's all synchronized.

0:19:08.4 TC: That's right.

0:19:08.5 SC: Okay.

0:19:08.6 TC: One of the major findings of this study was generated by my colleague, Dr. Valentina Loconte working at Lawrence Berkeley National Labs. And she was able to use soft x-ray tomography to image these cells in the process of cell division and reveal this beautiful synchrony between the host and the symbiont.

0:19:29.0 SC: Isn't it so interesting that sometimes you just need to watch and see.

0:19:32.1 TC: Absolutely.

0:19:34.4 SC: What happens. It's so amazing.

0:19:35.4 TC: Yeah. We did not know what we were gonna find, but we knew we had to look at these things and just see. And so, yeah. Watching cell division, you can see that all the organelles divide prior to cell division, and the Nitroplast is no exception. It fits right in line with all these other organelles. So that's a striking piece of evidence, but it's not all the work that we did.

0:19:57.4 SC: Well, let's take a little side trip here to talk about what this Nitroplast does. Up and down the family tree, all of us eukaryotes have to rely on bacterial friends to do nitrogen fixing for us. So taking this nitrogen, which is all around us in the air, we're breathing it constantly, but it's not something we can access without help. We need to be able to do chemistry with it. So why has this been so hard for us eukaryotes and so easy for bacteria? Why do we keep having to go to them to get help for that?

0:20:26.2 TC: That's a difficult question. Then there's a lot of different answers to it, different strategies that are used in different environments. In the marine environment, fixed nitrogen is very limiting. And so organisms that can perform this process of taking atmospheric nitrogen, converting it into a usable form, they can really influence ocean ecosystems and exert bottom-up control on the phytoplankton communities that we see out there. And that's kind of why we study nitrogen fixation in the marine environment, is to better understand ocean ecosystems. But yeah, the process itself of using the Nitrogenase enzyme to convert dinitrogen gas into ammonium requires very specific chemical conditions. It's very sensitive to oxygen. And this is why these organisms that perform this usually inhabit low oxygen environments. And it requires a lot of energy too. So it can be metabolically taxing on the cell.

0:21:28.7 SC: I kind of see where you're going with this. So sometimes, let's see, if a bacteria is doing it, it doesn't have to also control a multicellular body. For example, doesn't have a lot of other jobs to do.

0:21:37.4 TC: Yes. In terrestrial systems, such as the nodules of legume plants, these bacteria are coddled in little micro environments that are just right for them. And then they can perform this process and actually produce more nitrogen than they would solely for their own use. But organisms such as unicellular cyanobacteria that do it in the marine environment oftentimes don't have a lot of just produce as much as they need and don't devote extra energy to this process because it's difficult.

0:22:09.6 SC: This has been the job of bacterial helpers in the past, as you say, on the roots of plants or in the ocean. But it would be pretty amazing if eukaryote could suddenly start fixing nitrogen. Is that why you were interested in this? Because you found a cell out there in the ocean that was doing it and you were a little bit surprised that it had that function?

0:22:29.1 TC: Not exactly. So we were studying... The process of nitrogen fixation in the ocean, the microbes that carry it out. And so we'd known about this thing that was out there. We'd actually sequenced the genome of this Nitroplast at the point when we assumed it was a symbiont and realized that it had these gaps in its metabolism. When we sequenced the genome, we could tell immediately that it's streamlined or what we called streamlined. It's really broken. It's missing genes that should be essential. And therefore, it should not be able to survive on its own. Things like amino acid and nucleotide biosynthesis pathways, for example, they're incomplete. Glycolysis is incomplete. We really wanted to know how these cells survive with these major gaps in their

metabolic capabilities. That was kind of why we were interested in studying this, was to figure out how these gaps were filled actually and how we could use them to help us survive. Actually how it works. More from a perspective of an ocean ecologist, 'cause that's kind of what we are honed in our lab. Then this story turned into something bigger when we realized just how tightly coupled this Nitroplast is to the eukaryotic cell.

0:23:48.4 SC: Besides figuring out that the division was synchronized, like we talked about earlier, you also had to figure out a couple other important things that were happening. And this hasn't been discovered before, haven't been analyzed before because it was really difficult to culture this organism. So, what happened there? Why was it so tough? And what changed?

0:24:07.3 TC: The oceans are full of a diversity of microbiology that is uncultured and will never be cultured because it's very difficult. And we were fortunate enough to work with Dr. Kyoko Hagino of Kochi University. She spent over a decade developing the techniques to culture this marine alga containing this nitrogen fixer inside of it. So this involved hundreds of trips to the ocean, collecting water samples, individually picking thousands of cells, and then through trial and error kind of determining how to grow them. I think it really speaks to this. Unknown diversity of microbiology in the oceans that it just takes a labor of love to really study these things.

0:24:51.9 SC: Yeah. Between understanding how the organelle got the proteins that it needed and that it had this vertical inheritance, what else did you see that indicated to you that it was on its way or already at the state of organelle?

0:25:05.2 TC: I would say another important point is in the sequences, the amino acid sequences of these imported proteins, we see evidence of protein translocation machinery. So we see conserved sequence attached to all these different types of proteins that at this point we assume is part of the mechanism by which these proteins are imported. And this is analogous to mechanisms that are present in the chloroplast and mitochondria. So it's a targeting sequence. And that is one of these criteria that people talk about in making that distinction between organelles and symbionts. It's the presence of a targeting system for proteins. So that was a big one. Besides that, we have kind of circumstantial evidence such as, we can't grow these Nitroplasts on their own. We've tried many different ways and if you separate them, they do not survive.

0:26:01.2 SC: Do we know how long this relationship has been forming? How long it's been going on?

0:26:05.9 TC: We do have some evidence about this timescale here and it turns out this association began roughly 100 million years ago.

0:26:15.2 SC: Okay.

0:26:15.8 TC: Which sounds like a lot, but, like as you mentioned, the chloroplast and mitochondria are 10 times that or more. And so it's much more recent. And you can see that in things like the targeting sequence that we've uncovered here, it's really long. It looks like it's in the process of being optimized.

0:26:34.5 SC: That's so interesting. I don't wanna skip this, but it really came home to me when I was like kind of looking into like the history of organelles and their billion year relationship with chloroplasts and mitochondria. Is that they do such important work for the cell. They're making energy, they're working with the sun, like, and then this Nitroplast, same deal. So it does seem kind of like a major benefit for the cell. What does the organelle get? Why is it to the advantage of the organelle to like join forces like this?

0:27:08.8 TC: The initial symbiotic relationship, as far as we can tell, is kind of a simple exchange of carbon for nitrogen. So the symbiont received fixed carbon in exchange for fixed nitrogen. The metabolism of this Nitroplast is different than a lot of cyanobacteria in that it's missing the genes for carbon fixation. So it's lost the main carbon fixation gene, Rubisco, it's lost parts of its photosystem, so it can't make carbon. And we don't know exactly when that occurred during its evolution or the evolution of this relationship, but that seems to be the basis of the exchange between these partners.

0:27:48.5 SC: Okay. And what about the bacteria that turned into the organelle? Do we know anything about its heritage or its close relatives?

0:27:56.4 TC: Yeah, we do. We have examples of pretty closely related relatives of the Nitroplast, which are free living, and they are cyanobacteria that are photosynthetic. Meaning they retain carbon fixation capabilities, but they also perform nitrogen fixation. So, they're able to survive by doing both. Our Nitroplast has lost a lot of those genes. It's streamlined, as we say, but it's clearly related to these types of cyanobacteria.

0:28:27.4 SC: Do you feel like there is something that you've learned from this work that suggests that we should look harder for Nascent organelles more broadly, either in the ocean or anywhere in the world? Should we be like, there's probably some more organelles in the works. So we just need to know what to look for. And this will help us look for them.

0:28:48.6 TC: Absolutely. I think there's this untold biodiversity of microbes, not just in the oceans, but in all environments. And undoubtedly, there are more occurrences of this, what we call primary Endosymbiosis that have occurred or are occurring as we speak.

0:29:06.5 SC: Can this help us make organelles for other purposes? What if I wanted to put Nitroplast in corn? Could we use this as a guide for that?

0:29:16.6 TC: Yeah. I would say for many years, there's been interest in learning how to engineer nitrogen fixation capabilities into agricultural plants. And now we have this first example of a nitrogen fixing organelle inside of a eukaryotic cell. And we've shown that it's really coupled to the energy metabolism of the eukaryote. It's optimized to fulfill the entire nitrogen demand of this larger cell. And so certainly this would be of interest to scientists who are attempting to engineer synthetic Nitroplasts.

0:29:49.8 SC: Thanks so much for coming on the show, Tyler.

0:29:51.7 TC: Thank you, Sarah. It's been fun.

0:29:53.3 SC: Tyler Cole is a postdoctoral scholar in the Ocean Sciences Department at the University of California, Santa Cruz. You can find a link to the paper we discussed at science.org/pod.

0:30:05.5 SC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at sciencepodcast@aaas.org. To find us on podcasting apps, search for Science Magazine. And this is a reminder, Google Podcasts is going away, so please check out some of the other options on our website, science.org/podcast. This show was edited by me, Sarah Crespi, Kevin McLean, and Megan Cantwell, with production help from Megan Tuck at Podigy. Jeffrey Cook composed the music on behalf of Science and its publisher, AAAS. Thanks for joining us.

[music]

0:00:05.2 Sarah Crespi: This is the Science Podcast for April 5th, 2024. I'm Sarah Crespi. First on the show, did rats come over with Columbus? European colonists were not alone on their ships when they came to the uninfested shores of the Americas. Researcher Eric Guiry joins me to discuss how tiny pieces of bone from early colonial sites and shipwrecks can tell us when these pesky rodents arrived. Next, producer Meagan Cantwell talks with contributing correspondent Ann Gibbons about Lucy's Golden Jubilee anniversary. Lucy was a likely human ancestor that lived 2.9-3.3 million years ago and was found 50 years ago. They talk about what we've learned about her species and her place in the family tree in those 50 years. The Americas were not only colonized by Europeans, I guess, the middle of the last millennium. Hidden aboard their ships amongst their worldly goods were rats.

0:01:09.8 SC: Black and brown rats both traveled across the Atlantic and established themselves up and down the eastern coast along with pilgrims and pirates. But despite the omnipresence of their bones at many archaeological sites, when these rats came to the Americas has actually been a little tough to pin down. This week in Science Advances, Eric Guiry and colleagues trace the ratting of the Americas using bones, isotopes, and a few shipwrecks. Hi, Eric. Welcome to the Science Podcast.

0:01:40.0 Eric Guiry: Hi, Sarah. Thanks for having me.

0:01:41.7 SC: Sure. Yeah, this is such an interesting question. I had pet rats, so I'm interested in that. Obviously, they're an important lab animal, but this is more looking at them as an invasive species, how they got to where they are, and how they spread. So what made you interested in this question of their arrival and their spread?

0:02:00.2 EG: It traces back to an earlier paper we did in 2018, and I think it was Proceedings B. We discovered that rats had very different behaviors based on where they were. In rural settings, they had quite a different suite of things they were doing compared to urban settings. And this paper was an exploration of those patterns more generally. Ultimately, I was quite interested in animals at the marginality of archaeology, so thinking about things archaeologists tend to overlook. I was doing other projects and noticed often in these historic sites, there was a bag just labeled small mammals. Sometimes it hadn't been analyzed, but it was chock full of rat bones. I noticed this across many sites and thought, hmm, there's something here. There's animals that are kind of overlooked and they'll have a story to tell.

0:02:49.6 SC: So you looked at two types of rats in this paper, the black rat and the brown rat?

0:02:53.8 EG: That's right.

0:02:54.3 SC: Which one are we most likely to see these days in the United States?

0:02:58.0 EG: Actually, that's very complicated.

[laughter]

0:03:00.6 EG: There's not a lot of literature on that. I think you can still see both in many places. So for instance, in Vancouver, near where I am, both are present. Generally speaking, the brown rat is thought to outcompete its smaller cousin, the black rat, across much of its range in temperate areas, but black rats do still show up.

0:03:22.5 SC: So there's some environmental stuff, whether or not humans are there, all that can affect which rat is present or dominating?

0:03:29.2 EG: Yes. And it's kind of confusing because there are conditions and places in the world where we know that black rats can dominate. For instance, there are areas in the Southern Hemisphere, for instance in New Zealand, where the black rats have the upper hand over brown rats. It's not that one is inherently going to always outcompete the other. There are lots of factors at play, and we actually don't understand those terribly well, considering that both species can do similar things. But they might have different tendencies, like black rats are more arboreal and brown rats are more fossorial, maybe living in the ground. They can actually do the same range of things. Their ecologies can overlap fairly completely.

0:04:12.7 SC: And so in this paper, you looked deep into the past of their presence here on this continent, and you wanted to know when they got here and then how they vied for power over time. It sounds like rat wars, but you know what I mean. In your method, you mostly worked with rat bones, as we discussed, from various sites up and down the eastern coast. How did you pick these sites? I was a little bit sad that I didn't see Philadelphia in here. How did you decide where to specifically look at the rat bones from early colonial days?

0:04:45.6 EG: To some extent, I picked places that I'd heard or read had rat bones. As I mentioned, these bones often end up in auxiliary bags in these faunal assemblage collections, so it's not always easy to find them. They're not always featured in the publications where people write up about the animal bones they found at archaeological sites. So some of it was hearsay. Somebody I'd met would say, "Oh, this site's chock full of rat bones. Why don't you look there?" And that might lead to somebody else saying, "Oh, that one's full of them too". So to some extent, it was just being able to locate them, which is sort of directing where it was. That said, I'm fairly certain that rat bones will be a presence in most historical archaeological assemblages that have had the excavation techniques that can actually recover them. So you need to do sieving. You need to pay closer attention to the excavation in a way that would recover the small bones.

0:05:36.5 SC: If you go back in time far enough, some of these archaeological sites are not gonna have rat bones 'cause rats weren't here yet. Do we know when the first, I guess it was black rats got here first? Do we know when they first came?

0:05:48.7 EG: Supposedly, they were on Columbus's first voyage. So 1492.

0:05:52.7 SC: Oh gosh. [laughter] So specific. Amazing.

0:05:54.3 EG: Yeah. Yeah, yeah. It's one of those times where you can really tell, like, okay, yeah, that was the sort of advent of this whole giant process that followed of rats colonizing the Americas. It's pretty clear when black rats arrived, but brown rats, it's not at all clear. There are a lot of stories in the literature that get retold and rehashed. They're not well-founded, and it's not clear when they arrived in Europe either. It's generally thought North America, for instance, that it was around the time of the American independence, so 1775, but we can be fairly sure based on the results of this study that they were here earlier.

0:06:31.7 SC: How can you tell from the bones from these sites that it's a black rat or a brown rat?

0:06:35.7 EG: So the morphology and shape of the bones can differ between the two species, but those are difficult to tell. If you have, like, a complete skull, then you can more easily establish which it is. But often, archaeologically, we're just finding small fragments. So we used a peptide fingerprinting technique that can allow you to differentiate the two. It's based on tiny differences

between the sequence of amino acids that are present in the collagen of the two species, so slight differences allow you to differentiate them.

0:07:04.7 SC: So you can tell which ones are which, and you try to tell the age of them with a couple of different methods? It turns out that radiocarbon is not gonna do a great job for this time period and so you went to archaeology, but there are also some bumps on that road.

0:07:22.0 EG: Yeah, it's very difficult. We weren't really able to date things in a radiocarbon sense. We were relying on archaeological context information. And because brown rats can burrow, when we find them in early context, it's always a bit of a question mark going, "Well, could they have just gotten there on their own? Were they intrusive and not actually reflecting the date of that deposit?" So one of the ways we got around this was to look at rats in shipwrecks.

0:07:47.8 SC: Oh, this is great. Yeah.

0:07:48.9 EG: Yeah, we know when that ship was built. We know when it sank. We often even know where it's been. And rats are unlikely to be swimming down into those shipwreck sites and burrowing in and dying there for us to find later. So it's a pretty ironclad way of looking at chronology. So some of those shipwreck dates, well, one of them in particular was really useful in giving us a super firm date, latest possible date of arrival for the brown rats, which was about 1760.

0:08:16.7 SC: A little bit before Declaration of Independence, but still in that 1700s, mid-1700s. A rat being on a ship, is it leaving this continent? Is that why you know it's from here as opposed to coming from somewhere else?

0:08:29.3 EG: I think we could be fairly sure that when rats are on ships that are going to ports, that they're going to get out. It's quite clear from some of the earliest literature, the letters back from colonists in different places. Some of the first things they ask for is rat spaying or various things that can help them deal with the rat.

0:08:47.7 SC: Oh my goodness.

0:08:48.5 EG: The rat infestation. So because we find it in a ship doesn't 100% mean that it was also in the port that that ship had gone to, but it's fairly likely. But we're being super conservative with that perspective. We do have archaeological contexts that seem fairly secure, that date well before that. As early as say 1720-1740, we had a context in New Orleans with a brown rat. So we take those a little bit more cautiously, but there are enough of them that a pattern starts to emerge where it's fairly clear they were there before 1760. So through some modeling, we were able to suggest tentative early arrival of say 1730s. So while that's tentative, I would suspect that if we were to expand these analyses considerably, we would find earlier evidence.

0:09:36.5 SC: They just go where people go, it sounds like.

0:09:38.1 EG: Absolutely, yeah.

0:09:39.4 SC: You talked a little bit about how as soon as colonists got here, there were rats here, and they were like, "Oh, these rats, we have to do something about them". Is there anything we can learn from your results here or your earlier study for today's rats?

0:09:53.1 EG: Black rats and brown rats do seem to have an affinity or a preference for higher animal protein diets. So that makes a preferred habitat for them is likely access to these kinds of foods. So to the extent that it's possible to control that access and to limit it, you'd be limiting the

availability of preferable habitat for them.

0:10:17.1 SC: I lived in Washington DC for a long time. I saw plenty of rats. I saw them on the train tracks. I saw them outside, you know, on patios at restaurants. They're kind of all around us, but it's still kind of difficult to study them.

0:10:28.4 EG: I'm not a contemporary ecologist studying urban environments, but I understand from the literature that it is quite a challenge to study rats in current urban places. And that has to do with sort of jurisdiction and accessing all the places that a rat might go. A rat doesn't care that it's leaving your study area or moving amongst different areas. It's actually quite challenging, costly and sort of time consuming to do research in these areas on rats.

0:10:55.0 SC: Part of it is because it's a populated area. You have to go into all these spaces that are limited against people coming in, but rats have managed to finagle their way in there.

0:11:04.5 EG: That's right. Rats aren't like wandering around, you know, to be seen. They're doing their own thing. And that often involves places that's sort of the margins of society. It's kind of difficult to observe them. And one of the interesting things about archaeology and what I think we could think a lot more about in terms of archaeological fauna remains is that we have this massive trove of animals that represent human-animal relationships over hundreds or even thousands of years, depending on where you are. And those human-animal relationships could tell us a lot about how we might relate to animals in the future, particularly in the context of sort of urban planning.

0:11:36.5 SC: You've mentioned you're in Vancouver, you're on the West Coast. You have rats there, I'm sure, are those rats descendants from the early colonial rats, or are they their own thing?

0:11:48.1 EG: One of the interesting things, there was something called the Manila trade in the mid... Starting in the mid-16th century, so the 1560s, where it was a direct trade route between the Philippines and the West Coast of North America. So they could have come directly across the Pacific as well. Our study wasn't able to sort of look at that. You need to do genetic work and a lot more sampling in that region, but it's quite possible that there's a much more complex picture at play here.

0:12:17.1 SC: So it might not be the case that they came to the Eastern Coast and then traveled across the continent and started colonizing the West Coast. They had their own separate delivery of rats over there on the West Side?

0:12:29.4 EG: It's possible.

0:12:30.1 SC: Yeah.

0:12:30.6 EG: It's equally possible that they came across once the railways were through, or they traveled with the 49ers or whoever else was moving up and down the coast with ships infested with rats.

0:12:41.7 SC: Yeah. What else do you wanna learn about early rat populations in the United States, or where do you wanna... What are you going to study next?

0:12:48.3 EG: Well, right now, I'm actually part of a UKRI funded project based out of the University of York in the UK, and we're looking at the spread of rats in Europe. To some extent, we'll include some information from the state, so we're gonna do some genetic studies to look at relationships between different rat communities in those early years. So that's something that we'll

be moving along hopefully soon.

0:13:11.4 SC: That sounds amazing. Thank you so much, Eric.

0:13:13.4 EG: Thank you very much. It's been a pleasure.

0:13:15.1 SC: Eric Guiry is a research associate in the Trent Environmental Archaeology Lab at Trent University. You can find a link to the Science Advances article we discussed at science.org/podcast. Stay tuned for a chat about Lucy at 50 with producer Meagan Cantwell, and contributing correspondent Ann Gibbons.

[music]

0:13:43.1 Meagan Cantwell: After paleoanthropologist Donald Johanson defended his graduate thesis, a member of his committee asked him what he was going to do now that he graduated. He told him, "I'm going to Africa, and I'm going to find something really good". That same year, on a hot day in November of 1974, Johanson glanced over his right shoulder and saw a fossil, specifically the part of the elbow that lets you flex and extend your arm. Over the next two weeks, researchers uncovered more and more pieces to a skeleton that all belonged to one specimen, who they named Lucy, after the Beatles song, Lucy in the Sky with Diamonds. For the 50th anniversary of Lucy's discovery, contributing correspondent Ann Gibbons took a look at her legacy and how much our understanding of the human family tree has changed since then. Thank you so much for joining me, Ann.

0:14:28.2 Ann Gibbons: Happy to be here.

0:14:30.1 MC: Could you set the scene for what exactly we knew about our ancestors before we discovered Lucy?

0:14:35.7 AG: So before we discovered Lucy, there had been fossils discovered in the East Africa in the 1950s and '60s that showed us that members of our genus, Homo, showed up around two million years ago or so. And it had been a long time coming because Darwin had predicted back in the 1870s that members of the human family arose in Africa rather than in Asia. But fossils weren't discovered until the 1920s in South Africa that showed that Africa was probably the place where human ancestors arose. And there was still a great deal of debate about that until the 1950s. The big question is, what came earlier before two million years ago? And so, when Lucy was found at 3.1 million, the feeling at the time was that if you reached back a little bit further, you would get an ancestor we shared with chimpanzees.

0:15:25.5 MC: What about her discovery stood out? How was she different than the previous finds they had had in other areas of Africa?

0:15:32.1 AG: So Lucy was interesting because she showed that upright walking came before a big brain. Her brain is only a little bit larger than the size of an ape's. What was most exciting is her partial skeleton. We have 40% of her skeleton, showed that she walked upright. It's very clear. We had known from earlier fossils from South Africa that upright walking probably came before the big brain, but Lucy confirmed that. Before that, researchers had thought maybe that upright walking and the big brain and tool use all came together.

0:16:01.7 MC: It seemed like it was kind of a curveball discovering Lucy first since she was so tiny. She was only three feet tall. And that made researchers think, "Oh, all these early humans are probably tiny little things". But then as they discovered more of her species, Australopithecus

afarensis, they found out, oh no, there's actually a lot of diversity. Is that diversity in her species unique when you compare it to other early humans that have been found?

0:16:21.7 AG: No, it's not unique. But what we have from A. Afarensis, which is her species, is a remarkable number of well-preserved individuals. In addition to Lucy, we have the first family, a whole group of individuals that died suddenly that include children, males, and then other individuals found not only at Hadar, but A. Afarensis has been found in Tanzania. A number of members have been found fossils throughout Africa, East Africa, including Kenya, possibly in Cameroon. Her species lasted for a very long time, maybe as early as 3.8-3.85 million, that's a little bit debatable, all the way down to 2.9 million years. Interestingly, by having so many individuals, we also learned that the males are quite a bit bigger than the females. Now, Lucy's still a small female, she's unusually small, but the males were quite a bit larger, which suggests they were competing quite fiercely for female mates. We can also see, for example, how afarensis adapted to different habitats over time.

0:17:21.1 MC: It was quite a while, right, that Lucy kind of sat and had the crown as the oldest ancestor of ours, but she's been dethroned in recent years. You actually joined a lot of these people on their expeditions in the '90s to try to find these older specimens. There were multiple research groups that were competing to try to find something older. What ended up coming of those expeditions?

0:17:43.4 AG: Yes, so the big, big question after the discovery of Lucy and members of her species is what came before her? Well, lo and behold, the big surprise was, no, she wasn't that primitive, that if she was at 3.2 million, there was two to three million years of human evolution before her. One of the first discoveries was a fossil called Australopithecus anamensis that dates to about 4.2 million years in East Africa. The wonderful thing about Australopithecus anamensis is that she looks like a more primitive version of Lucy in many ways. That pushes back Australopithecus to about 4.2 million. But then, several teams, including two teams that bet each other, Tim White of Berkeley and Michel Brunet of Frenchman, they would find the earliest member of the human family. Tim White's team found this fossil Australopithecus ramidus that dates to 4.4 million years, a partial skeleton that is what they call the root ape. It's much more primitive than anamensis and afarensis. They were still spending a lot of time in the trees, but not walking upright like a modern human. And this thing would look more like an ape than a modern human if you saw it.

0:18:48.3 AG: Tim likes to say you wouldn't invite Australopithecus ramidus to dinner. Then, in addition to finding Australopithecus ramidus, Yohannes Haile-Selassie found something that was 5.8 million years old called Australopithecus kadabba. It's an earlier ancestor of Australopithecus ramidus. And then the biggest and oldest, probably more controversial fossil was Michel Brunet found a beautiful skull in the Djurab desert of Chad, dating between six and seven million years, that is of an ancient, ancient member of the human family that Michel Brunet claims walked upright based on the angle at which the skull sat atop the spine. It shows several traits that suggest it was also walking upright, would make it a hominin rather than ancestor of another ape. We'd love to find more fossils to prove that.

0:19:32.7 MC: With all these discoveries of earlier human ancestors, how did that change our understanding of how the traits that define us as humans evolved over time, like upright walking, brain size?

0:19:43.6 AG: Yes, so first of all, it doubles the time back of the human family from Lucy's age of 3.2 to six to seven million. Probably one of the very first things that started us down the road toward the path of becoming human rather than another kind of ape was upright walking. Then we begin to see some changes in the teeth, which show perhaps a little less aggression, maybe less competition

for mates, maybe because we're upright walking, the males are helping females get food, because if they're carrying a baby and walking upright, it's hard to gather as much food as you would need. So maybe we're seeing some social changes that start to make us more human-like, more cooperation. Then later after Lucy, we begin to see tool use. That has now been pushed back to probably 3.3 million years ago. There's nothing that says that Lucy wasn't capable of making primitive tools, but no one has ever found stone tools at the sites where Lucy's species were found. Tool use and then later the big brain starts to take off around 1.8 to 1.6 million years ago, and at that point we're fully in the carnivore guild hunting and competing with carnivores for meat.

0:20:49.7 MC: We talked about how Lucy's been dethroned as our oldest ancestor, but there's also a lot of other species that probably shared the same landscape with her during her time. What other species might have existed, and how might they have interacted with Afarensis?

0:21:03.0 AG: Yeah, so what's really exciting is that when Lucy was found, she was the queen of all the hominins. Lucy was seen as the direct ancestor of our genus Homo, and also of Australopithecus africanus, which is in South Africa, and also perhaps of this other more robust genus of hominins, a whole group called Paranthropus. But then starting in '90s researchers began to find some other fossils that were around at the same time as Lucy, the first one was Kenyanthropus platyops, which showed up at about 3.5 million years ago, perhaps persisting to 3.3 million years. Then, only 30 kilometers away from Hadar, Yohannes Haile-Selassie found another species called A. Deyiremeda, which dates from about 3.3-3.5 million years as well. It's found at a site where Lucy's species is also found at roughly the same time, and A. Anamensis shows up there also at about the same time. You have those three specimens, and then a foot. It's a very primitive foot that looks a little bit more like an earlier hominin. So you have four species all around at about the same time, between 3.3 and 3.5 million years ago. Are any of those ancestors of early Homo? Nobody is as good a contender as Lucy at this point.

0:22:20.5 AG: She's still the best fossil that's most like early Homo to be the ancestor of our lineage, but the fact that there are other kinds of hominins around that we've found suggests that we're only seeing part of what was there. So it's not this neat, simple story of just Lucy giving rise to early Homo in a straight, neat lineage. It's a more complicated picture now.

0:22:43.3 MC: We've touched on the major discoveries that have been made since Lucy was discovered in 1974, and there hasn't been much progress necessarily in hunting for these fossils, right? It's just still kind of mainly the same technique to look for these?

0:22:57.0 AG: Well, I think the way people look is very similar, although they use satellite imagery more now to look for areas of erosion, which help them zero in on where to go, look for fossils. But I would say the biggest change has been the number of specialists that come to a site now and try to reconstruct what the ancient landscape was like, what was the ancient weather? What kind of ancient plants were there? What was the habitat that Lucy was living in? How did that change over time? What did she eat? Also, how do you date the sites? The dating revolution has really gotten precise. We can fingerprint actual specific volcanic eruptions and get much more precise dates and tie different sites across the landscape together. So we know a whole lot more about the world that Lucy lived in. That has been reconstructed now. Every fossil site, researchers are able to do this to reconstruct the ancient worlds. It's not enough anymore just to discover the fossils. You've got to put the hominins in the context. What was their habitat? And how do they adapt to it? How did their habitat change over time? When Lucy first emerges, she's living in a more wooded landscape.

0:23:58.0 AG: By the end, she's living in a much more varied, dry habitat. So she's adapted. She's more flexible than most other hominins that we've seen before her. She's able to range across different landscapes and survive, which is a hallmark of being a member of our genus Homo, that

we are able to adapt to a lot of different habitats.

0:24:15.6 MC: In terms of other advancements within the field, what would you say stand out to you besides understanding the paleoenvironment?

0:24:21.8 AG: We also are really good at analyzing the fossils now. The 3D morphometrics revolution has meant that we can really compare with statistical confidence different jaws, different teeth, different skulls, different bones, and see how they really vary. Also, genetics have come in. We are now studying ancient DNA, not back to Lucy's time. We can't get DNA that old, but it has revolutionized the way we study members of our species, early Homo sapiens, and our encounters with Neanderthals and other species that we interbred with. There's a revolution going on underway in studying ancient proteins. And those are going back in time to studying fossils that are as early as almost 500,000 years and earlier. So we're beginning to use ancient proteins to differentiate fossils to see if they belonged to different species, and maybe even to get at things like their diet and how they lived on the landscape, ancient diseases. That hasn't happened yet, but we're beginning to get there.

0:25:17.6 MC: The reason we're putting out this story now instead of in November when Lucy was actually discovered is because there's a big celebration of Lucy's legacy and recent research that is happening at the Institute of Human Origins this week. And you're attending and also speaking at that celebration. What do you think will come of the discussions from there? What kind of new research is on the cutting edge right now?

0:25:39.5 AG: So there will be talks about the fossils and the new fossils. Yohannes Haile-Selassie will talk about the diversity in the new fossils that have been discovered. Other people are going to talk about the kind of animals that lived with her and the changes in understanding of her habitat. Now, there are as many as 50 PhDs working on some of these sites with different specialties. And so there are projects drilling the ancient lake sediments to try to reconstruct how climate changed and the conditions over time in which hominins developed. And can we say things like how changes in the climate, did that drive speciation? Did it drive new births of new species because suddenly in dire times, different hominins had to adapt? Also, I'm hoping we'll hear a little bit more about the animal herself. It's interesting to find out how did she live? What was she like? Not only what did she look like, but what was doing on the landscape? And how does that reveal why members of the human family survived? How we became human and what came after her?

0:26:39.9 MC: It's an anniversary like this is also a good time to reflect, look forward to how things might work in the future. Yohannes Haile-Selassie, an Ethiopian paleoanthropologist who you mentioned before, has found a lot of amazing fossils. He's helping to lead a workshop on how to build up the infrastructure in African countries to support local scholars to contribute to this important work. In the past few decades, how have more Ethiopians and Kenyans become involved in this research that initially was really led by mostly white people?

0:27:10.9 AG: Yeah, so when I first started covering this in the early '90s, that was the beginning of training Africans like Yohannes Haile-Selassie. Some of those paleo-anthropologists like Yohannes Haile-Selassie, Zeresenay Alemseged, are now leading major expeditions that have found major fossils in East Africa. The same in Kenya, Chalamont and in South Africa. But very few of them get to actually work in Africa because there isn't still the infrastructure, other than at the museums, where researchers can get the kind of funding to do the research and be based in East Africa. There's a lot of work going on. These paleo-anthropologists that are African that work in East Africa have formed an organization where they encourage the training and development and sharing of scientific results, but a lot more needs to be done there. Lucy's, I think, helped open that up, as did other fossils found in Kenya. Her legacy, though, if it leads to training more Africans, that's

fantastic.

0:28:05.8 MC: Yeah. Thank you so much, Ann, for joining me. I really appreciate it.

0:28:08.7 AG: You're welcome. It's my pleasure.

0:28:10.3 MC: Ann Gibbons is a contributing correspondent for Science. You can find a link to her story at science.org/podcasts.

0:28:18.9 SC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at sciencepodcasts@AAAS.org. To find us on podcasting apps, search for Science Magazine. Don't forget, Google's podcasting app is going away, so make sure you subscribe somewhere else. Or you can listen on our website, science.org/podcast. This show was edited by me, Sarah Crespi, and Kevin McLean, with production help from Megan Tuck at Podigy. Special thanks to Meagan Cantwell, for making a podcast segment while she was making a video about Lucy's 50th. Jeffrey Cook composed the music on behalf of Science and its publisher, AAAS, thanks for joining us.

[music]

0:00:04.7 Sarah Crespi: This is the Science Podcast for March 29th, 2024. I'm Sarah Crespi. First on this show, a robot that can predict your smile. Researcher Hod Lipson joins me to discuss how mirrors can help robots learn to make believable facial expressions, and eventually improve human-robot nonverbal communication. After that, we have researcher Margaret Handley with a letter she wrote to science about how her past, her family, and a rare musical instrument all relate to her current focus on public health and homelessness. Letters editor Jennifer Sills also weighs in with the different kinds of letters people write into the magazine.

0:00:48.2 SC: Picture this, you're in a meeting. Something slightly off-kilter happens. Maybe a cat comes into view on someone's screen. You make eye contact with a co-worker and you realize you're both kind of slightly smiling. Silliness is confirmed. You're sharing a little joy. It's lightening up the day, the meeting. This is an example of nonverbal communication, and it's just one of an enormous repertoire of gestures and expressions that we humans keep on hand, or on face, and now robots want to get in on the game. In the world of words, machines are definitely catching up. Think ChatGPT, think audio transcription. But in nonverbal communication, there's definitely a lag. This week in Science Robotics, Hod Lipson and colleagues write about robots that can anticipate your smile and time theirs with it., for bonding. Hi, Hod. Welcome to the Science Podcast.

0:01:44.1 Hod Lipson: My pleasure.

0:01:44.4 SC: Why is it a good thing? Why is this something we should try to do, to have robots engage in nonverbal communication?

0:01:52.5 HL: Well, I think it's very similar to the reason we want robots and AI to learn to communicate in verbal communication, we just want to connect with these machines, we want to allow them to communicate with us better, to convey information, and that's an incredible channel that we're missing right now.

0:02:09.6 SC: Right.

0:02:10.7 HL: Machines can communicate incredibly well, both in video, and in text, verbally, if you like. But when it comes to facial expressions and nonverbal communication, they're less than a one-year-old child, they can't even smile. So we're trying to catch up, a lot to catch up there. These are things that we take for granted, but are very, very important. In fact, some people say that humans communicate with each other more through nonverbal communication than they do through verbal communication. So it's a really, really important channel that we've been neglecting.

0:02:41.3 SC: They have a much smaller bandwidth if you think about it that way. If humans are communicating on all these levels, the robots are only picking up on a certain level and also only expressing on a certain level.

0:02:51.1 HL: Exactly.

0:02:51.9 SC: We're also talking about anticipating the expression or the gesture, how is that different than just reacting?

0:03:00.3 HL: Right, so there's a lot of things that go into nonverbal communication, and these are actually things that sort of are very difficult to quantify, if you think about it, the reason we need to say cheese when we take a photo is because actually smiling on demand is actually pretty hard. And you're trying to explain to a child how to smile, it's actually very, very difficult. You can talk about

verbal communication pretty well, but how to do all these other things, these non-verbal communication is really challenging in part because it's, there's a lot of motion involved, there's a lot of channels within the facial communication, a lot of muscles involved, it's not just a channel of words. But also there's a timing issue, which you refer to. All right, so smiling at the wrong time could backfire. If even by a few milliseconds you smile a little bit too late, it feels like you're pandering maybe or you're... We humans are very, very good at picking up incorrect smiles, smiles that are awkward, smiles that are badly timed, so getting the robots to do all these things at the right time, in addition to the right way, is really, really challenging. That's what we're trying to do.

0:04:07.0 SC: You actually have these robot faces, these heads, looking in the mirror, to make expressions. Why do they need to do that? Like what, how does that train them better than say, typing in, "Next smile after five milliseconds."?

0:04:23.6 HL: Turns out, first of all, making a face, a robot face like that can smile was incredibly challenging from a mechanical point of view, it's harder than making a robotic hand.

0:04:33.6 SC: Yeah.

0:04:35.2 HL: Or a robotic leg, there's so many muscles, and the more muscles we put into the soft face, it was never enough, it couldn't quite smile all the way, it... So there's a lot going on mechanically. But then on top of that, it's very difficult to control. It's very difficult to know how to exactly pull all these muscles to create a smile that's authentic. And again, we're very good at spotting inauthentic smiles. So we're very, very sensitive to that. So if you look at most robotic systems out there, none of them smile, first of all, almost, and I haven't seen any robot that can smile. And even those that can talk on stage and do all these fancy things, they barely smile. They're very cold, they...

0:05:11.0 SC: Very stoic, yeah.

0:05:12.9 HL: Yeah, and they have these Muppet mouths that open and close, but don't really, they don't lip sync in any deep place. So it's really, really hard to do. So we resorted to this idea of machine learning, which is what we do with everything else. Forget about trying to program these robots to smile, just let them learn. And how do you learn? You watch people. This is how babies learn. This is how kids learn. This is how adults learn, and this is what these robots do. They just watch people smile and make other facial expressions, and they pick it up.

0:05:43.0 SC: Yeah, so this is taking advantage of machine learning and also, how good we are with computer vision now so...

0:05:49.4 HL: Exactly.

0:05:50.6 SC: The robot can see itself, and interpret that, and then turn it into motion. It's quite a number of steps in order to train a robot, to look in the mirror, make expressions, but then also you trained it to look at people, and see what their expressions are with the hope of gaining mimicry. So how does this all come together? Like, how do they predict? As you say, you want them to smile at the same time. How do they predict when someone is going to smile?

0:06:16.6 HL: So it turns out that before you smile, so the robot is learning to smile and get it all right in the right timing, but it picks up on cues that we humans, I don't know if maybe subconsciously we pick up on these things, but if you could slow-mo what your face looks like before you smile, before you smile, like, 300 milliseconds before you smile, I haven't actually looked at it, but there's probably some... That we squint our eyes, and, I don't know, nostrils expand,

I don't know, there's probably some minute gestures that we make just about as we're thinking of smiling. And this is probably what the robot picks up on, I don't know what it is, but it's pretty reliably...

0:06:56.5 SC: One of those mysteries of machine learning at this point.

0:06:58.8 HL: One of these mysteries, exactly, but it's, I can tell you, I'm a jaded roboticist. I don't smile at machines, but when this robot smiles at me, I smile back.

0:07:07.3 SC: I was going to ask you, yeah.

0:07:08.3 HL: I can't hold back. We are so... This is so deep in us to connect with things that smile, and when the robot can smile genuinely, it's very, very endearing. It's a whole new level of communication, but there's one more thing I wanted to say, which is a little bit behind the scenes, but it's really important. Is that the robot spends a lot of time modeling itself. This is something that we spend a lot of time in our lab, we call it Self Modeling, the machines that learn about themselves. And when it's smiling in front of the mirror, it's sort of like learning how its face will look as it pulls all these muscles, it creates a sort of self-image, just like you can close your eyes and you know that when you make a certain facial expressions, you kind of know what you look like. This is how you can communicate, you know what you sound like and you know what you look like. The robot knows what it's going to look like when it's going to do certain things, and that self-image, if you like, allows it to react and anticipate and make gestures that it hasn't made before even.

0:08:08.7 SC: When I first read the paper, I was like, oh, is this also tuning in to, say, a conversation or emotional tenor? Is it picking up on other cues or is it just looking at people's faces and mimicking? And is that something that you'd be interested in doing?

0:08:26.1 HL: Yeah, that's a really great point. So no, the robot is not picking up on all this extra stuff. So that's absolutely important. It's not even something that we can get away without doing. So this is our... All right, our robot is now literally like a baby that just learned to smile. Okay? It doesn't understand anything about context, smiles every time that they see their parent or, and at the wrong time, possibly. But this is where we're at. So there's a lot more to go. And understanding these cues and when to smile and what context, and sometimes facial mimicry is okay, like smiling. But sometimes frowning is not a good facial mimicry. If somebody frowns, the last thing you want to do is frown back.

0:09:07.7 SC: Yeah. [laughter]

0:09:08.8 HL: Maybe you want it to smile back, right? So there's a lot more to it.

0:09:10.4 SC: Yeah, you don't want to get in a fight.

0:09:11.2 HL: Exactly, so there's absolutely, we're not even close to mastering nonverbal communication, but it's the first step, and I think it's an important one because, it's one of those things that we humans don't even appreciate how well we do.

0:09:25.8 SC: Yeah.

0:09:26.8 HL: Moving your face, moving these 300 muscles, in concert, it's a beautiful symphony to... Making a good smile is a symphony that comes together in a beautiful way. Very, very hard for robots. Robots can write a poem, and they can write a technical report in no time, but smiling, that's

a whole different story.

0:09:44.4 SC: Yeah. I feel like... I don't know where I read it, but the idea that the face is like a pool of water and it's just like a tiny ripple moves across it and everybody else can read that.

0:09:52.9 HL: It's exactly that. It's exactly that. So we're just beginning to realize how difficult it is. We have this thing in engineering that you don't really understand something until you build it. And I think this is for us the first time we really are diving into the complexity of a smile.

0:10:10.8 SC: When I looked at these videos, I felt all the emotions, I was like, "Okay, this is creepy." And then I was like, "Oh, but it's learning to smile. Yeah, I kind of appreciate that. Like, that's nice." And then I eventually started to feel that, like, "Oh, this is not creepy. This is a smiley guy." And I did kind of come around after watching the videos. But I wonder, why are some of these robot faces blue?

0:10:33.5 HL: We wanted to step away or outside this uncanny valley, as it's called, this idea that if it's, it looks like a human, but it's not a human, and this looks like a corpse or, whatever, it's... It's not quite there, it's kind of disgusting. So we said, "Okay, let's just make them blue, and we're not even trying to make them human." And we had green versions and purple versions and all kinds and...

0:10:53.3 SC: Interesting.

0:10:54.3 HL: So we really want to sort of step away from making it trying to look like a human. But then, if you put a wig and lipstick and all kinds of things on it, it really begins to get a personality, let's put it that way. And that personality actually adds. So I think it's inescapable, that eventually these robots are going to start looking like humans, and we're going to have to... We're going to start to bond with them whether we like it or not.

0:11:19.5 SC: Is there a concern that as they become more anthropomorphic, that people will use these robots to play on people's emotions and to manipulate them into doing things? If you can form a bond, you can take advantage of that bond.

0:11:32.2 HL: Right. Absolutely. That's a serious concern. Not just for manipulation. I think, yes, people just like AI technology, as it gets better, you can do good things and you can do bad things with it. That's the conundrum of AI ethics, I think, in general. So yes, this is a... It could be a very powerful technology, but I think just to add to that, it's not only malicious actors, it could be even that for good reasons, if we, people will feel could potentially connect to a robot more than they connect to a human friend, and at that point, there's a loss involved in that. So I worry about these things. On the other hand, the potential, for example, to communicate better, to communicate faster, more easily, more effectively is enormous, so we're going to have to find that balance.

0:12:22.0 SC: Yeah, absolutely.

0:12:24.2 HL: Yeah. Our next thing is to work on lip sync. The lip sync, while the robot is talking, is very, very hard as well, but all these...

0:12:32.5 SC: Oh, so while it's producing sound, when you say lip sync, I thought immediately, "Is it going to be doing karaoke?" But you mean...

0:12:39.2 HL: Talking.

0:12:39.3 SC: To its own voice.

0:12:39.9 HL: Yeah, to its own voice. So when it's going to say, "Hello," it's actually going to move its lips in the right way.

0:12:46.5 SC: Oh my gosh.

0:12:47.9 HL: And this is, again, you haven't seen robots do that.

0:12:48.7 SC: No.

0:12:48.8 HL: It takes it to a whole different level. If you think that engaging with ChatGPT is interesting, just wait until these things become physical and all bets are off.

0:13:00.3 SC: Definitely. All right, thank you so much, Hod.

0:13:02.2 HL: Thank you.

0:13:02.9 SC: Hod Lipson is a roboticist who works in the areas of artificial intelligence and digital manufacturing, and he's a professor at Columbia University. You can find a link to the science robotics paper we discussed at science.org/podcast.

0:13:18.7 SC: Stay tuned for a chat with researcher and letter writer Margaret Handley, about how her past was a prologue to her science career.

[music]

0:13:33.2 SC: We have a different kind of segment this week. We're actually going to have a letter writer read the letter that they published in Science. This is going to be from Margaret Handley. She's going to read her letter about an important musical instrument that influenced her life in science. So we're going to have a letter writer read their letter, but first we have Jennifer Sills, our letters editor. She's going to talk about the kinds of letters that come into science. The letter for today is part of a series called Past as Prologue. Letters editor Jennifer Sills explains this type of letter and the other kinds we have.

0:14:09.9 Jennifer Sills: This letter did come in, I believe, as a Past as Prologue feature, which is focused on how does your background or your childhood or your family influence your scientific or career decisions?

0:14:25.5 SC: Yeah, so you said it was called a feature. It's a feature, but it's in letters.

0:14:31.6 JS: Yeah, so a standard letter has to fit a certain format. It shouldn't be anecdotal. It should be connected to a current event. It should be a call to action. There are certain things that we look for in a standard letter, but that doesn't give us the flexibility to really look into who are scientists, and who is this community that we're representing in the letters pages. And so we have a few different features which provide that... We have some other features, like A Life in Science is a feature that describes just a funny or a quirky or an interesting situation that you could say only a scientist would have that experience. They often have to do with fieldwork or animals, but not always. And we also have a feature called Outside the Tower that focuses on scientists' advocacy experiences. And that gives us a chance to say, what are scientists doing to bring their science to children, to prisoners, to people in far-flung places who don't have access to all the information that we have. And so all of these features, their purpose is to kind of give a more well-rounded idea of

who is the scientific community.

0:15:57.3 SC: So to you, this story of the Fern Mandolin really fit in with all these other past examples?

0:16:03.0 JS: Well, I wouldn't say that they have to fit in. I would say that it provided a new avenue of what it looks like to take your family history and apply it to your career decisions. And I think part of this work is always about combating the stereotypes of scientists. And I think each of these pieces in their own way really makes you think. Well, scientists are just a community like any community, and every scientist is different and has a different story. And every, even scientists in the same field, come to that field from completely different places for different reasons with different goals. And I think having something in letters that makes that point is important for our readers.

0:16:56.8 SC: Yeah. Absolutely. All right, Jennifer, that was super interesting. Thanks so much for talking with me.

0:17:00.0 JS: Thank you.

0:17:01.8 SC: That was our letters editor, Jennifer Sills. Now we're going to hear from researcher Margaret Handley. In her letter, Margaret writes about the resurfacing of a relic from her childhood, what she remembers about it in the past, how she feels about seeing it now, and she reflects on the influence it had on her work today with unhoused people. After we hear the letter, Margaret's going to stick around and talk a little bit with us about what she wrote.

[music]

0:17:32.5 Margaret Handley: My dad's prized possession was a Gibson 1920s Fern Mandolin. Inlaid with mother of pearl, the handmade instrument made a marvelous sound, perfect for playing traditional bluegrass melodies. As kids, my brother and I would visit the Fern Mandolin in our dad's storage locker, the type with a big pull-up door. In hindsight, the unique, delicate piece seemed out of place in the vast industrial storage park landscape. But the locker was my dad's only permanent address. He couch-surfed, rented rooms, sometimes lived out of his car. People sometimes called him a drifter, but when he played the Fern Mandolin and sang, his captivating grin filled the space. There was so much promise in that locker. In his youth, my dad had played in a Bluegrass band. He often sang songs that reflected his rural background, growing up in Texas and his experience moving to California during the Dust Bowl in the 1930s. The folk song, Freight Train, about the lonesome life of riding on the cross-country freight trains, was also one of his favorites.

0:18:41.7 MH: When I was in my early 20s and just starting my studies to become an epidemiologist, my dad disappeared. My brother and I searched for him at his most recent address and at local flea markets, where he liked to go to trade guitar and bicycle parts. We never found him. Now, I work with an interdisciplinary team of investigators and clinicians focusing on understanding and preventing homelessness. We've explored when stays with family members do and don't work out. We've worked with a cohort of unhoused people as they age, to learn about how their needs change, and how they care for each other. The idea of helping people stay in housing, improving their lives as they revolve around the uncertainty of a storage locker existence, keeps me going on my research-weary days. I often remember how natural it seemed to spend time with my dad at his locker, and how unimportant it was to me that he didn't always have an address. Belongings in lockers, on the street, or seized during evictions reveal people's complex inner lives, histories, and talents. I want our society to appreciate, as I try to, the richness of the lives of those who are unhoused or marginally housed. We never knew what happened to my dad's storage locker.

But a few years ago, the Fern Mandolin resurfaced at a rare instrument auction. My brother and I went to see it. It was still beautiful.

0:20:18.0 SC: So do you play music?

0:20:18.1 MH: I like to sing, but I don't play myself.

0:20:22.6 SC: The song that we heard with your letter, I know your daughter and her friend composed and performed it for us, but is it Bluegrass?

0:20:29.5 MH: It's kind of inspired by Bluegrass, but I wouldn't call it that per se, it doesn't have a mandolin itself in it, but it's sort of in the style of, I think, building off of a Blues tradition and a Bluegrass tradition.

0:20:42.2 SC: Yeah. So your daughter plays some of these instruments?

0:20:44.1 MH: Yeah. She plays guitar. Her siblings play as well, horn instruments and guitar, piano. They all play piano, and my husband plays guitar.

0:20:53.0 SC: So how do you know that when you went to the rare instrument auction, how do you know that that was the same Fern Mandolin?

0:21:01.2 MH: It's not like a hundred percent sure, but there were only a couple of them ever made in that particular style. And the case itself, and it was this particular color, this bright green, it hadn't faded, as if it hadn't been used a lot. And there were these packets of extra strings, and they were tied together with a particular kind of string that my brother and I recognized from when our dad made kites. It was a special kind of string. So when we were looking at it, thinking about the rareness of this mandolin, that it was found in San Jose, where our dad last had lived, and that there were strings that were tied together with a special kind of kite string, we thought it was our dad's.

0:21:44.4 SC: You're pretty sure that this was your dad's mandolin, that was put up for auction, why didn't you or someone in your family try to buy it?

0:21:52.3 MH: Yeah, we didn't try to buy it, it was really very expensive. And I think for us, it was nice to see that it was highly valued still, the rareness of it, the beauty of the instrument. It was going to be purchased in the community of people who are playing the mandolin. And while my brother plays guitar, he doesn't play the mandolin in particular. And so neither of us thought we needed to have it.

0:22:18.3 SC: Needed to be with a musician who would appreciate it.

0:22:21.7 MH: Yeah.

0:22:22.3 SC: And just seeing it is kind of amazing, right? Just knowing that it's around.

0:22:25.0 MH: Seeing it was amazing, and knowing that it had sort of been maybe quietly waiting for its next life, that it was found and part of a mandolin community was an exciting component for us. There's a lot of interest in these beautiful old mandolins. And so on one level, it was bittersweet to see it for my brother and I sort of out of range in a way, but also it was nice that it was in a community that could appreciate its specialness.

0:22:57.2 SC: Absolutely. Now how did you end up writing a letter about this to Science?

0:23:01.5 MH: I work with a training program and we try to help people tell their stories in different kinds of ways. It's an NIH career development program, and our program is called the RISE Program, for Research in Implementation Science for Equity. And a lot of people in our program have had pretty interesting experiences about how they came to do research on health equity. So I was looking for places to, basically ideas to share with our group. And I saw that and I thought, " You know I kind of have this story I've written," kind of written for myself after we visited the mandolin. And I thought, "Well, maybe this would be something to... To give an example of how to do this, just even if it didn't get accepted."

0:23:48.6 SC: Yeah. So you saw a prompt, the prompt Past as Prologue.

0:23:51.1 MH: Yeah. So a colleague and I were both looking around to find things where they could write sort of personal essays in their work in healthcare or in public health. And so I came across that and said, "And you think this would be good for our group?" I'll sort of test the waters and submit this story that I'd actually written. I'd written it in a slightly kind of different way, more for my family. And I rewrote it also. I mean, I've shared the story with people I work with, and they know my story and I told them about it, when it happened.

0:24:26.6 SC: And how much of an influence do you feel like your father's situation had on you deciding to focus so much on homelessness?

0:24:33.2 MH: It's not that it was that direct in a way, because I didn't really see him as a person who was homeless. So I think that you can look at that and say that is part of his life experience. Obviously very significant part of my life experience. But I wouldn't necessarily say that I think of him in that particular way. And I think that's part of the point.

0:25:00.2 SC: Yeah, it is, it surprises you when you look back at your youth and say, "Oh, well, that probably had something to do with where I am today but never been front of mind," right?

0:25:09.1 MH: Yeah, I think the larger sort of focus on people who fall through the cracks is sort of a consistent component of how I've approached public health training and what I've ended up doing. And I think that you can link, whether it's things that happened in my life or just observations I made in the moments in time that I lived through history, that I gravitated to things like that. So this is just one of those stories.

0:25:32.4 SC: And music is also, had stayed as part of your life?

0:25:34.5 MH: I'm a huge music fan, I listen to music a lot and I love all kinds of Blues-influenced music.

0:25:41.0 SC: Very cool. Yeah, I would love it if my family made music around me, I am not a musician, but like everybody else knows how to play stuff, and I just want them to like... I just want to be living that life, but I don't get to.

0:25:53.1 MH: I know, and I thought I would learn when my children were learning music and they had piano lessons, but I was kind of doing other stuff. I had a job. I really do like how much they play music all around me. And for example, we have music night at our house often. So I'm part of that and I sing, but I'm not the best. But I like to sing.

0:26:12.6 SC: We're not going to make you sing.

[music]

0:26:17.6 SC: Margaret Handley is a professor in the Department of Epidemiology and Biostatistics and Medicine at the University of California, San Francisco, and co-director of PRISE, Partnerships for Research in Implementation Science for Equity. As well as a faculty member for Vulnerable Populations at the Benioff Housing and Homelessness Initiative. Special thanks to our guest musicians, they created and played a piece of music for this segment, Kate Rose and Josephine Haas. Jennifer Sills is the letters editor for Science. I'm going to put a link to some of these Past as Prologue pieces in the episode text so you can check them out at science.org/podcast.

[music]

0:27:00.6 SC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at sciencepodcast@aaas.org. To find us on a podcasting app, search for Science Magazine. Or you can listen on our website, science.org/podcast. This show was edited by me, Sarah Crespi, and Kevin McLean, with production help from Megan Tuck at Podigy. Special thanks to the creators of our letters music this week, Kate Rose and Josephine Haas. Jeffrey Cook composed the rest of the music on behalf of Science and its publisher, AAAS. Thanks for joining us.

0:00:05.6 Sarah Crespi: This is the Science podcast for May 22nd, 2024. I'm Sarah Crespi. First up, hope in the field of deadly prion diseases. Prions are these misfolded proteins that clump together and chew holes in the brain. The misfolding of these normal proteins can be switched on in a number of ways, genetics, spontaneous folding and infection with a misfolded prion from another animal or person. Staff writer Meredith Wadman walks me through new potential treatments for these always fatal neurodegenerative diseases. Next up on the show producer, Katherine Irving talks with researcher Ashley Larsen about the effects of organic farms on their neighbors. If there are very few organic farms, conventional farms actually tend to increase their pesticide use. But if organic farms are a cluster together, the pesticide use goes down for everyone.

0:01:02.3 SC: Prion diseases have a very strange mechanism. Prion start as a normal protein with a normal function in the brain. These prions can mis-fold or adopt another shape and then cause other prion proteins to also mis-fold. These misfolded proteins accumulate and slowly, surely destroy the brain. Neurodegenerative prion Diseases like Creutzfeldt-Jakob in humans and Bovine Spongiform encephalitis in cows can actually infect others in certain circumstances. Like you might have to eat part of the cow. And there are also certain ways for humans to pass this to another, no matter which way you get it, it's also genetic versions. It's a hundred percent fatal. Attempts to find treatments for prion diseases have really been stymied since the discovery of these mechanisms in the 1980s. But this week in science staff writer Meredith Wadman, wrote about new tactics to take on prion diseases that are giving hope to researchers and patients. Hi Meredith. Welcome back to the podcast.

0:02:05.4 Meredith Wadman: Hi Sarah. I'm glad to be here.

0:02:07.5 SC: Yeah, I'm happy to have you. Although this is a pretty intense story. You have a lot of people that you talk to that are either had this disease, are studying this disease because they have family or enrolled in the trials. It's an impactful piece for sure. In fact, I first heard of this story on the science Slack channel four months ago. You wrote on there, my friend is having these really weird symptoms. He's in the hospital. Do you want me to read your slack message? Would that be weird?

0:02:36.6 MW: Sure, yeah. No.

0:02:36.9 SC: Okay. Do you wanna read it or do you want me to read it?

0:02:40.2 MW: Go ahead. You can read it.

0:02:40.3 SC: Okay. So I see the slack message from you on the... On one of the new slack channels, for any of you disease sleuths out there. A personal question. We have a good friend, 67 years old in Arlington Hospital since Sunday with progressively worsening confusion, now hallucinating. He has left-sided weakness. His MRI shows something going on in the right temporal lobe, no recent travel. His last travel was to England in March. In a stretch, the STOMP doctors are testing for CJD. They have also just requested a neuro consult from the Mayo Clinic. I asked if they have tested him for eastern equine encephalitis, WNV, Rocky Mountain spotted fever, herpes simplex, cryptococcus. Is there anything I'm missing? I didn't ask about malaria. There was recently a case in Maryland. So this is you reaching out to our science new staffers who have explored all aspects of disease and biology and saying, who can help me figure out what's going on with my friend? And of course, it turns out it was the super unlikely CJD, which is a prion disease.

0:03:44.0 MW: It was... And I've gotta correct myself, my slack message in two elements. Number one, Charlie was 70, not 67.

0:03:52.1 SC: Yeah.

0:03:53.0 MW: And number two, my sort of know it all-ish saying in a stretch they're thinking about CJD. And of course you think about what you know, and even as a medical student years ago, CJD was so rare, like it is rare as a physician that you will see a case in your life.

0:04:11.6 SC: Yeah.

0:04:12.2 MW: So I was kind of like, what?

0:04:15.6 SC: It's not easy to diagnose. Right? Creutzfeldt-Jakob disease. What we're talking about, it's a prion disease. It's the human... One of the human forms. It's not easy to diagnose. It's very rare. Like people are not coming down with this. And the only way to tell often is in aftermath. Right?

0:04:27.3 MW: Oh. The only definitive diagnosis is from a pathology in a brain autopsy. So yeah, that's the for sure method. Although there are some very good diagnostic tools, one in particular now that give a lot of certainty, but that's not gonna change the course of the disease, which in almost all cases is very rapidly progressive. Our friend Charlie died about five weeks after he showed the very first symptoms.

0:04:52.1 SC: Yeah. Was that what made you decide to write this story?

0:04:56.0 MW: Certainly got it on my radar. And then in discussing with one of our editors, John Travis, what was going on, because this has been a uniformly bleak field for having treatments. There are none. He and I kind of came across several potential treatments that are progressing.

0:05:13.3 SC: Yeah.

0:05:13.9 MW: And one just happened to be launching the first clinical trial in more than a dozen years, started in January. So it seemed like an auspicious time to be writing about this.

0:05:23.5 SC: There are different sources of prion diseases. So for example, I mentioned the cow form was transferred to people through diet in England during this huge outbreak. But nowadays, how are people getting prion diseases? How can someone end up with this kind of misfolding protein accumulating in their brain?

0:05:43.6 MW: Right. So if you think about all prion disease as pie, there's a tiny sliver, less than 1% that is acquired by eating contaminated meat or by having a surgery, a neurosurgery in which a contaminated instrument was used. Something external to your body comes into it.

0:06:03.6 SC: The case we heard about a researcher in France in the last couple of years who had a needle stick from, you know, working with prion proteins.

0:06:12.5 MW: Right? Exactly.

0:06:13.6 SC: Super rare.

0:06:15.1 MW: The whole pie is ultra rare is a bunch of ultra rare diseases or super rare.

0:06:18.1 SC: Yeah.

0:06:18.8 MW: And the acquired kind is like less than 1%. So, and just to put it in context, in the

US there have been four cases of acquired from infected cattle disease ever since the British outbreak. And three of those had traveled abroad.

0:06:37.4 SC: Yeah.

0:06:38.6 MW: And one of them possibly had traveled, they had picked it up traveling. So this is not something homegrown where you gotta look at US cattle say and say, "Ooh, I better not."

0:06:47.5 SC: Right. So what do we have left in this pie?

0:06:48.5 MW: So 10 to 15% of the pie is genetically acquired prion disease. That's where you inherit a mutation. And these are dominant mutations, which means that if your parent is carrying the mutation, you have a 50% chance of getting it from them. And then if you do inherit it, you have a 100% chance of developing the disease. It's not a matter of if, but when. Then finally you have these 85% or 90% of people who just develop it. They call it sporadically. Consider it spontaneously. This protein goes rogue. That's much more likely to be in people over 60. So related with aging, perhaps it's not well understood why these proteins, regular normal Prion proteins, which inhabit all of our brains suddenly just mis-fold and go berserk and basically chew holes in the brain.

0:07:46.3 SC: How easy is it to study interventions in this population? You know, you have your people who have the spontaneous form, you have your very small slice of genetically predisposed. How do you enroll people in a clinical trial if they're already kind of on their way in a short-term disease to death?

0:08:05.1 MW: Right. So that is a key hurdle. One clinical trial that just launched in January, the first one in more than a dozen years, that is randomly assigned very carefully controlled the kind of trial that produces evidence that FDA would look at and say, yes, we'll prove this or not. It's the first stage. But the company Ionis that developed this drug hopes to be able to win an FDA approval. But they're testing it in people with acute disease at this time. And so they have a small window to find these people. People bounce around from doctor to doctor, no one knows what's happening. The symptoms look odd. Doctors haven't seen this by and large. And it's really tricky to diagnose. So by the time there's a presumptive diagnosis, there may be only weeks left for that patient to live. And so you've gotta get them enrolled in that trial very quickly. The medium survival time for Creutzfeldt-Jakob disease, the most common of these prion diseases is four to six months.

0:09:02.0 SC: So the clinical trial that we're talking about here that's kicking off is using basically the fact that this is starting as DNA going to mRNA and then going to protein and trying to interfere in that process by introducing an Antisense oligonucleotide. So a little little strip of DNA that will go and find the RNA before it gets turned into the protein?

0:09:28.2 MW: That's exactly it. Antisense oligonucleotide ASO for short.

0:09:32.8 SC: And how does it get into the brain?

0:09:35.3 MW: It is injected into the spinal fluid near the base of the spine. And that fluid is contiguous with the brain. It bathes it and it goes into systems inside the brain and then it... The ASO is believed to track along the small arteries and get into the brain tissue. There's a question about how deep and distribution is one of the challenges actually with this approach.

0:09:56.5 SC: Is it a one and done or do you have to keep injecting people with this?

0:10:00.7 MW: They need repeated injections at intervals of weeks. That's what this trial is set up to do. This stage, which is a first in human trial, they're testing for safety and for how the drug is metabolized in the body to get to appropriate dosing levels.

0:10:13.4 SC: Are they also looking at some other endpoints? Are they looking to see if they can decrease disease markers or something?

0:10:19.8 MW: There is a biomarker in the cerebral spinal fluid that can be followed by collecting it at regular intervals, which I believe this trial will do. And the biomarkers, basically the normal human prion protein. Because what this ASO intends to do is shut down production of normal protein because without normal protein then the misfolding can't happen.

0:10:42.6 SC: Are people okay if they don't have any of the normal protein?

0:10:48.1 MW: Several animal species have been engineered to completely lack prion protein. And even though it's abundant in the brain and serves lots of different functions, it's thought these animals have been fine. There's one issue in some of the older mice with a peripheral neuropathy that develops with time. But you know, the risk benefit ratio for humans is pretty clear.

0:11:12.3 SC: What about in people? Are there people who have had like none of this?

0:11:14.6 MW: No, but there are a few adults who have been found who had only half the regular allotment. In other words, one of their genes wasn't functional for normal prion protein and they were found in late middle age or as elderly people and they had had kids and they didn't seem to have any problems.

0:11:33.6 SC: Yeah. So that's one approach that's being tried and it's moved into clinical trials. There's also these other approaches you talk about like zinc fingers.

0:11:42.0 MW: Yeah.

0:11:42.8 SC: That's something I know interlocks with DNA, but that's all I got. How does that work?

0:11:47.2 MW: Yeah. If you picture the sort of progression of prion disease, starting with the DNA being transcribed to make messenger RNA, so the DNA is the first step. That's where zinc fingers attack. And they are naturally occurring proteins that a company Sangamo has tailored to attack specifically prion DNA and prevent it from ever being turned into mRNA so that you're way upstream of the protein actually being produced. Now it needs to be said Sangamo is in animals still. They're not in the clinic like Ionis is with their ASO. So then if you move to the right along this timeline of protein production, you get the mRNA and that's where Ionis is antisense oligonucleotide attacks. And then if you move just a little further along to where the polypeptide chain of the protein is being made by a ribosome that's glued to the endoplasmic reticulate, more final protein assembly steps happen. That's where yet another approach works being made by gait bioscience, which would be a pill to take to block those final steps of production of the Prion protein. Again, all three approaches are trying to just zero out Prion protein because without it you cannot have misfolding.

0:13:00.7 SC: That is a question though, like when this intervention would be ideal, any one of these blocking the production of Prion proteins, would you want it if someone had genetic testing and saw that they had or a prion protein mutation that was gonna lead to misfolding, would you wanna do it super early?

0:13:16.7 MW: Oh yes. And that's something I meant to circle back to when you asked about the very different approaches to the clinical trials. This is not a prevention trial that's currently going on, but that is the aim of Ionis is to get to where you can identify people carrying the genetic mutations who have a certainty of developing Prion disease and treat them years or decades ahead of the disease developing. And one of the biggest advocates and real workers in the trenches to make this kind of trial happen is Sonia Vallabh at the Broad Institute whose mother died of a prion disease at age 52, and who herself has inherited the mutation that caused that disease. And she is working feverishly with her husband, Eric Minikel and lots of other collaborators to get to a point where you could have a therapy that would zero out Prion protein production given preventively to people who are bound to develop the disease but do not yet have symptoms.

0:14:17.0 SC: And just to reiterate what you said, these people change their careers because they realized that she had a prion disease, they went and got PhDs and they became part of the research community. And they are a big motivator behind a lot of the work that's being done and driving some of the funding. Because this is a super rare disease. It's a very hard target to hit. It's fast moving. And yet here we're seeing, you know, a real forward momentum in the field that you kind of would think would be pretty abandoned or orphaned.

0:14:49.0 MW: Yeah. And a lot of that is to Sonia and Eric's credit and of course to the Prion research community more broadly, who have really rallied and worked with them and been very, I think moved by Sonia and Eric's motivation. And Sonia and Eric are involved, not only, you know, they did preclinical work for Ionis to get the current trial launched, but they're also working with Sangamo to test the zinc fingers. And they're working with this company Gate Bioscience, which is developing that pill I alluded to that would shut down the final stages of Prion protein production. So they got fingers in lots of pies and they are just wickedly smart and so motivated. They're really extraordinary people.

0:15:34.5 SC: We talked about some of the hurdles, getting patients, getting these materials into the brain is always a challenge. And then also zeroing out prion, there's just a lot to overcome to make this work. Have we seen any success in other diseases with some of the approaches that you're talking about today that are being tried for prion diseases?

0:15:54.0 MW: Yeah, so Ionis, the company that made the ASO that's now in a clinical trial has had mixed success developing ASOs for a number of neurological diseases. They had one for Huntington's. That was a big disappointment. But they had one that they developed for a very small portion of ALS patients that got approved by FDA last year. And perhaps most noticeably, they had an ASO approved in 2016 for spinal muscular atrophy, this rare inherited disease that cripples kids from the very earliest days of life. And that is being widely used. So there have been some successes.

0:16:32.0 SC: That's great.

0:16:34.8 MW: They are also a... Work on one for Alzheimer's, so stay tuned.

0:16:38.9 SC: Yeah. I was gonna say that's a really good segue. This brings up something that I think came up in your story. The idea that, you know, this is a rare disease is very specific mechanism at the beginning, but you know, the formation of aggregates is common to other neurodegenerative diseases that we know about. Is Alzheimer's a disease that might benefit from our understanding of prion diseases?

0:17:00.0 MW: Absolutely. And also Parkinson's. I mean, there's misfolding of proteins that then

form aggregates that then do brain damage in both those diseases, which particularly Alzheimer's clearly much, much more common. And Parkinson's is not uncommon either. The learnings and the applications of what's learned in this trial and in prion disease approaches generally definitely could have relevance to these commoner neurodegenerative diseases.

0:17:29.7 SC: Okay. Meredith, before I let you go, I just wanted to circle back to kind of what we started talking about, which is your friend Charlie. He was a journalist. He was writing a weekly column about the community that he lives in. And then he's hit with this like slew of strange symptoms. And even to the last, you know he did not survive very long past when he was diagnosed. He still continued to show how much he cares and contributes to the community around him. And this just really comes across in the way you write about him.

0:18:05.6 MW: Yes. Charlie, when the doctor diagnosed him, this was like eight or 12 days before he died, he reached out and shook his hand and told the doctor Congratulations for solving the mystery. And then within a few days he made very clear that he wanted to donate his brain for research. And the one place that collects all the brains of people who died with suspected prion disease in the United States is the National Prion Disease Pathology Surveillance Center at Case Western Reserve University. And that's where Charlie's brain is.

0:18:37.5 SC: Oh, wow.

0:18:37.6 MW: And in fact, that is also the first trial site in the current trial. So I was able to go out and meet Brian Appleby, who directs the surveillance center and also is the main investigator on the clinical trial. And it just so happened that the day I was there, he got the results from Charlie's brain that showed that Charlie had not had a mutation that he might have passed to his daughters, that it was sporadic.

0:19:01.7 SC: Oh, wow.

0:19:02.6 MW: And that he'd had a certain gene variation that made it very rapidly progressive and it was really moving. And Brian said to me after talking to Charlie's wife, Ellen, that he had learned that Charlie was a journalist and wow, what a great final contribution this was to be part of this story.

0:19:19.6 SC: Amazing. Meredith Wadman is a staff writer for science. You can find a link to the story we discussed at science.org/podcast. Stay tuned for our producer Katherine Irving and researcher Ashley Larsen. They chat about the spillover effects of organic agriculture.

[music]

0:19:36.3 Katherine Irving: I think most of us have heard of organic agriculture, but what we probably don't know is that what happens on an organic farm doesn't necessarily stay on that organic farm. What goes on on an organic farm could actually affect how surrounding farms take care of their crops. This week in science, Ashley Larsen and her colleagues report a discovery about the spillover effect of organic farms onto non-Organic Farms. Hi Ashley, welcome to the podcast.

0:20:10.2 Ashley Larsen: Hi. Thank you for having me.

0:20:12.6 KI: So your paper as I just mentioned, talks kind of a lot about organic agriculture and I think a lot of us have an idea of what that is. But just in case, can you give us sort of a quick explanation about this method and why some might consider it better for the planet, quote unquote?

0:20:24.3 AL: Sure. So organic agriculture is a production system that generally relies on more natural production methods. So in the US organic agriculture is governed by the National Organic Program. And particularly when we think about pesticides, it often means they're relying on more natural pest control methods. So not necessarily no pesticides, but generally no synthetic pesticides except those that have particular exceptions.

0:20:52.1 KI: You talk a little bit in the paper about your environmental footprint. How does it kind of affect that?

0:20:56.4 AL: A lot of people think that organic agriculture is basically one potential solution to reduce the environmental footprint of agriculture because of this reliance on more natural production methods, particularly again related to pests and pest control. The big picture, and particularly when we account for yield differences, the environmental impacts for organics are not fully understood. And most of that research has happened at the field scale. So comparing organic and conventional fields with respect to biodiversity or soil quality or economic outcomes, social outcomes, et cetera. But when we think about pests in particular and their natural enemies or predators, right? These are mobile organisms. And so what happens or the decision made at the fields might have impacts for their neighbors. And that's really what we're trying to get at here is we're interested in studying whether organic cropland has these spill-able impacts for nearby growers.

0:21:44.0 KI: So if this method is considered more environmentally friendly or more sustainable for the land, is there a reason why we don't see it super often? I think it only makes up about 2% of global agriculture.

0:21:54.5 AL: I think it is growing. But of course there are different challenges. Some of it might be economics, some of it might be just farmer behavior and knowledge. There are different structures that result in sort of the land use trajectories we see today.

0:22:11.5 KI: You talk a lot about spillover from these farms in your paper. But what is it that's spilling over? Is it pests, pesticide usage?

0:22:18.8 AL: So we're thinking particularly about fields. You know a farmer can have multiple fields, but we're thinking about those field interactions in space. And so as I mentioned before, pests and natural enemies of pests, which are a wide group of different organisms. We can think of insect natural enemies like beetles, for example, ladybird beetles. We can also think of parasitic wasps. We might also be thinking about spiders. We might be thinking about birds, we might be thinking about bats. There's a huge variety of different organisms that consume insect pests, they are mobile organisms. And we think that they respond to both local and landscape characteristics, field size or presence of hedgerows, where in this case the question was organic agriculture.

0:23:04.9 KI: How would you expect this spillover to influence surrounding growers?

0:23:10.1 AL: There's both an ecological and an economic aspect to this. And I'm an ecologist. So I think more about the ecological aspect, which is exactly the pests and predators and their movement in space and how they're impacted by these local and landscape characteristics, on the economic side, and my colleague Frederik Noack, who's a co-author on this paper is an economist. But we think in economics that farmers might also interact, right? It could be that this change in pests that are spilling over onto your field affect your pesticide use decisions. It might be that you spray more in response to pests, but it might be that there's just such an influx of pests that your benefits of spraying are actually reduced 'cause you treat, but pests come back. And so perhaps you actually spray less if your neighbor sprays less. And lastly it could be that you just learn, you look over the

fence and you see that your neighbor is doing something different and you learn from it. And so these different fields give us these different hypotheses about how organic agriculture and the landscape might affect a nearby growers. And that's basically what we're trying to get at with these spillovers 'cause your decision to produce organic affect something beyond the boundaries of your field.

0:24:17.2 KI: To do this, you analyzed a lot of data that was in Kern County, which is in Southern California. Was there a particular reason you chose this area?

0:24:25.7 AL: Yes, there are a couple of reasons, right? One is that Kern County is a really interesting agricultural system. It's often either the top or top couple agricultural producing counties in terms of value. And it also grows a wide diversity of crops like almonds, pistachios, and these high value, high pesticide use crops. And so it's a really interesting intensive, diverse agricultural system. And then on a more practical side, it's also a very data-rich system. And so it's a place where we have field level pesticide use data. We have field level crop and farmer information, and we have information on certified organic agriculture. So it sort of all comes together that we have good data and we have an interesting system. And so it seems the appropriate place to focus our attention.

0:25:12.3 KI: You were assessing a couple of questions. So you were looking at how organic farms influence other organic farms, how they influence non-organic farms, and then also what specific pesticides or things they were causing to change. So how did you go about measuring all of these questions and these impacts?

0:25:28.8 AL: Sure. So the first aspect was really identifying where organic agriculture was. And this is actually quite tricky even with all the data I mentioned 'cause we have information on where certified organic agriculture is, but often we don't know the exact field. And so we need to understand, well which of the potential fields are organic. And so we have to bring in some of that pesticide use data to identify which potential fields only use approved pesticides or no pesticides in order to identify which ones are actually organic. And then once we know which fields are organic, then we can measure how much organic agriculture is surrounding each of the roughly 14,000 fields that are permitted in Kern County each year. And that's basically how we build our dataset. And then we rely on a series of mostly panel data models trying to leverage this multi-year dataset and account for things like farmer specific behavior, crop specific heterogeneity and pesticide use year characteristics that might affect all fields within the system. And some regional aspects such as soil quality or something of the sort that might also interact with both organics and pesticide use. And so our main results rely on these panel data models and then we do some simulations based on those results.

0:26:41.1 KI: So what, if anything, surprised you the most about the results that you got?

0:26:46.6 AL: That's a great question. The honest truth is the whole project was pretty exciting and surprising. We haven't looked at the spillover effects for organics before. So the most exciting part was just getting our initial results and then trying to turn over as many different rocks, so to speak, to see whether they were robust as we could. And the truth is we were, I think, riding pretty high the whole time 'cause it was such a novel project for us.

0:27:16.3 KI: Yeah, and it kind of seemed like you got some two sort of related but different results were organic farms together. There were decreased insecticides when there were lots of them that could be together, but it seemed like the non-organic farms were increasing their pesticide use when surrounded by organic farms, which is a fascinating result.

0:27:33.5 AL: It's really interesting. As I mentioned a little bit earlier, there's some different ecological and economic underpinnings to this research and the economics literature, we might actually have anticipated that sure, farmers might increase their... As I said, use in response to increasing pests, but if there's all of this spillover, they might actually decrease it and sort of race to the bottom. Or they might just look over and look at their neighbor who's organic using less pesticides and try it, right? Just learn in their neighbor. In both cases, we'd expect decrease in pesticide use on unconventional fields, and we actually see an increase. We basically hypothesized that it's due to a different reliance on natural enemies or natural predators of pests that on organic fields there's perhaps a larger population of natural enemies that are available to sort of quickly control these incoming pests, whereas on conventional fields that natural enemy community is lacking. And so if there's a spillover of both natural enemies and pests, conventional fields perhaps either have lower spray thresholds or receive more of those costs because they don't have the natural enemy community.

0:28:38.6 KI: And so how do your results connect to that distribution of organic and non-organic farms?

0:28:44.1 AL: Basically our simulation suggests that low levels of organic cropland that effect on conventional dominates, right? So we actually have an increase in insecticide use relative to if there was zero organic. But as organic becomes more prevalent in the landscape, we see a decrease as we might expect because we start having more of those organic on organic impacts as well as the direct effect organic on insecticides. And so basically if you cluster, then you sort of harness all the benefits of organic... On organic and you minimize those costs of organic unconventional. So by spatially separating organic and conventional fields, you basically get less pesticide use on both conventional and organic fields.

0:29:25.2 KI: What testing did you do to sort of come upon this result? Did you use models? What sort of techniques did you use?

0:29:33.8 AL: Basically, we did this by building off our Kern County analysis, a slightly different analysis saying how does increasing the amount of organic from zero to 100% basically around each field and as a total amount of the landscape, right? How does that influence insecticide use? And that's basically the hazard model. The clustered model is basically doing something very similar, but now we're changing the number of organic and conventional fields and basically saying if you're conventional, you have all conventional around you. If you're organic, you have all organic and trying to understand the difference in simulated outcomes as a function of that dispersed versus clustered. And of course the real world is neither entirely dispersed or entirely clustered. But we wanted to understand sort of the balance of the difference in the insecticide use response.

0:30:22.8 KI: And so that organic on organic together, is it because there's more natural enemies sort of switching over all the organic fields or why did they together have like a net more positive impact?

0:30:32.6 AL: That's what we basically hypothesize, is that by having more of a landscape of reduced synthetic pesticides that we might imagine there are more natural enemies in general. So even if there's a spillover of both pests and natural enemies, there's natural enemies persisting in the landscape to adjust the spillover of pests. But it is important to note that we don't actually have pests or natural enemy data. So we're inferring this based on prior literature in agricology and in particular on of course additional work on the on the ground would be extremely valuable.

0:31:06.0 KI: And so how do you hope that these results that you're getting could be applied towards agriculture or land management? Like how can they inform that and going forward.

0:31:15.9 AL: How we're thinking about it is basically there are a lot, there's a lot of interest in organic agriculture. It's increasing quite rapidly as an industry, but also there are different policy pushes to increase organics in the coming years and decades. Like on the EU's Farm to fork program as well as the California Air Resource Board has some targets in their scoping plan, right? So these are the major initiatives to increase organic agriculture. And the question is... That we are trying to get at is are there some unintended aspects that we should understand as organics might be increasing in the landscape? And so from the policy perspective, it suggests that thinking about these potential unintended consequences and how we might mitigate them by spatially clustering or incentivizing some type of spatial clustering of organic agriculture as it continues to increase in proportion in many places, right? That would be one way to leverage these results. When we think about farmers, if their neighbors are rolling out additional acreage of organic cropland, maybe they should pest scout a little bit more. Maybe they should think about their planting decisions. I'm sure they already are. But these are aspects where it might be valuable to think about these spatial dimensions that connect fields in agricultural landscaping.

0:32:27.7 KI: Ashley Larsen is an ecologist at the University of California Santa Barbara. You can find a link to the paper we discussed at science.org/podcast. Thanks for coming on the show, Ashley.

0:32:35.6 AL: Thank you for having me.

0:32:42.5 SC: And that concludes this edition of a science podcast. If you have any comments or suggestions, write to us at science podcast @aaas.org to find us on podcasting apps, search for Science magazine, or you could listen on the site science.org/podcast. This show was edited by me, Sarah Crespi and Kevin McLean. Special thanks to Katherine Irving for her segment on organic agriculture, and we also had some production help from Megan Tuck at Prodigy. Jeffrey Cook composed the music on behalf of science and its publisher AAAS. Thanks for joining us.

0:00:04.7 Sarah Crespi: This is the science podcast for March 15th, 2024. I'm Sarah Crespi. We have two neuroscience stories this week. First up, freelancer Sarah Reardon asks, why do infant's memories fade? We discuss ongoing experiments that are looking to pin down the hows and whys of infantile amnesia. Next on the show, more brain stuff. Researcher Huiquan Li is here to talk about how the brain encodes generalized fear. This is a symptom of some anxiety disorders like social anxiety and PTSD. I think my earliest memory is from when I was just about two, two years old. I'm sitting or maybe walking on this like mustardy brown carpet. Turns out though, that this is probably not a real memory, but something that I picked up from photos or descriptions of the place I was living right when my younger sister was born. You know, and actually, if I really think about it, I just don't remember anything until I was in school at six. I think it's maybe like one or two back there. This week in science, freelance science journalist Sarah Reardon wrote about this puzzle of infantile amnesia. Why we don't remember our babyhoods. A time when we are learning so much about the world, but we still don't remember learning it. Hi, Sarah. Welcome back to the science podcast.

0:01:28.4 Sarah Reardon: Hi, thanks for having me.

0:01:30.0 SC: So are you going to tell us your earliest memory that you believe is actually a memory?

0:01:34.1 SR: Yeah, I think I remember our family dog who died when I was three, but it could just be from photos. I definitely remember the Gulf War.

0:01:45.2 SC: Oh, wow.

0:01:45.8 SR: So that was actually dateable, but I wasn't very old then. I guess I was five.

0:01:50.3 SC: Yeah. It's funny how little I remember. And I think some of it's kind of gone away as I've gotten older, but there's definitely a huge chunk that's always been missing. And so I guess the big question to the story, and it definitely makes me think, you know, when our brains are so busy devouring everything, we're learning to eat, to move, to see, to talk, all this stuff we need to remember to get on with our life. We don't remember learning these things. What are some of the explanations out there? What are some of the ideas about why we do forget this, this key point in our lives?

0:02:25.1 SR: One thing I learned from reporting that I thought was really fun was that the first person to really coin the term infantile amnesia and study it in any sort of depth was Sigmund Freud. And he, of course, thought that it was because we had this horrible psychosexual experience of being born, we needed to wipe that from our memories or else we would be traumatized forever. And as I talked about in the story, he wasn't entirely wrong. It's not to forget being born, but there is a growing amount of evidence that these memories are suppressed for some reason, rather than just not being formed in the first place. So now the question is how and why and why and why does it matter?

0:03:00.9 SC: So it could be possible that some of our earliest experiences are housed somewhere in the brain, just archived, but just not accessible.

0:03:08.3 SR: Yeah, that's the thinking.

0:03:09.6 SC: What are some of the reasons that people besides Freud think that we don't remember this part of our lives?

0:03:15.7 SR: For a long time, people have just kind of dismissed this as, well, it's an immature brain, baby's just been born. It's not important that we remember things. And so these neurons just aren't able to form these memories in the first place, or they form them for a little while and they just get deleted to make room for other things. And that could be true. And then the other hypothesis is that they are formed and they're there forever, but are somehow suppressed to make room for new memories.

0:03:42.7 SC: I was really surprised to learn from your story that other mammals have infantile amnesia. I guess I just never really thought about whether a kitten would remember or not remember its earliest days. So what does that suggest about what's happening with us if we're seeing these other mammals go through the same thing?

0:03:58.1 SR: Yeah, yeah. And that had been one of the things that people had thought for a long time was that it was linked to language development, that until we could describe our experiences in words, we weren't really remembering them. But the finding that mice and rats and other sorts of mammals have this as well kind of negated that theory. But it's really interesting. One researcher found that a few, what they call precocial mammals, which are mammals that are born with their eyes open, able to fend for themselves right away. Guinea pigs are like that. They're not dependent on their mothers, really. They can just fend for themselves. They don't seem to have infantile amnesia. So maybe everything they learn, they don't have parents around that they can just offload their care and the need to remember things.

0:04:39.9 SC: So it's much more important that they remember where they live or what is a scary thing. But this brings up an important point. We're talking about a specific type of memory. We remember how to talk, but we don't remember what we're calling episodic memory, which is what events or happenings or what defines that.

0:04:57.7 SR: Episodic memory is... Has been described to me as sort of the what, where, when. I went to Disney World when I was three years old and I met Mickey Mouse. That would be an episode that occurred in your life. And it's a little hard to study that in animals because they can't tell you what, where and when. So instead, researchers have been looking at what they're calling contextual memories, which are like, when I'm in this box with a patterned floor, I might get a shock if I step over here. And that's sort of a proxy for episodic memories that's being studied in mice.

0:05:29.0 SC: One of the researchers you talked with, I think they were based in Berlin. They were working with us on this question with a big group of toddlers. What are some of the questions they're trying to find out from working with, I think it's like 300 toddlers. What are the experiments like and what are they trying to learn from this group?

0:05:47.9 SR: They're trying to study this contextual memory again, rather than having them recall episodes, which there's been a lot of work on that, having people recall early episodes in their life. And like you were talking about earlier, you might be picking this stuff up from photos. So it's really hard to trust some of that data. So this is the first prospective study where they are giving toddlers these experiences and then seeing what they remember months later. And so they're having these kids learn when they're in a certain room that's got spaceships on the walls, for instance, one of the boxes has a toy. If they're in another room, it's a different box that has a toy. And so the kids can learn that, but they're not going to remember it very long. And so they're repeatedly doing these tasks over the course of months to see when did the kids start actually being able to remember those cues and that information.

0:06:33.8 SR: And the neat thing about this experiment is it can be replicated exactly in mice. So

they're having mice do the same thing with bits of food, and they're going to be trying to figure out whether some of the brain activity, some of the patterns and characteristics that they're observing in the kids are observable in mice. And then they can start doing more invasive things with the mice to try and understand what's happening at the brain level in a way that you can't with humans.

0:06:55.6 SC: Are we able to then pinpoint when these toddlers can suddenly start remembering when they go into the space room, the toy is going to be in a specific box?

0:07:06.1 SR: They're still early in the experiments, but they think right around 20 months is when this sort of switch occurs from being able to not remember anything to being able to remember things. So I should add that they call it infantile amnesia up to about age three, where you really can't remember much of anything at all. But between age three and 10, they have what is called childhood amnesia, where their memories are pretty spotty. And they're not very good at separating memories. A lot of things tend to run together. And that just gradually improves over the course of those years.

0:07:35.8 SC: Super interesting. Let's talk a little bit about the mouse experiments. You know, as you say, you can go a bit further. For example, you talked to some folks that use optogenetics, which is this ability to very finely control like certain neurons or certain regions of the brain. What are we learning from those types of experiments?

0:07:49.9 SR: Yeah, so with the optogenetic experiments, what they're able to do is figure out exactly which neurons in the hippocampus, which is part of the brain that processes memories, which neurons exactly are encoding that memory. It's sort of like a constellation of neurons. It's a set of them that will connect together and fire together. And that's what forms the memory. And they call that an engram. And so what they're able to do is to figure out when the baby mouse is first learning the task, let's say that the food is in the box over here, which cells are firing at that moment. And they can label those cells with a protein that then could be later activated. And so the baby mouse will go about his business. It'll forget how to do that as an adult. It doesn't remember that either. But if the researchers shine a light in the brain, these light sensitive engram cells will fire. And that causes the mouse to suddenly recall the memory and know where the food is again.

0:08:39.7 SC: So that suggests that there is a way to access it. A memory that was lost from Infantile amnesia or approximation of that.

0:08:47.9 SR: Exactly. And now it's a very artificial method. I don't know that everyone's entirely convinced this is evidence that this is what happens in nature and that we do all have these hidden engrams, but that's just going to take further research to sort out.

0:09:02.4 SC: So you talk a little bit about the role of neurogenesis, growing our brains, growing neurons in our brain that it might have in forgetting. So, you know, how would that work and how is that being tested?

0:09:12.7 SR: Yes, that's one of several hypotheses for what's happening. And the idea is that these engrams, they're being formed. So like we were talking about earlier, it's not that the brain can't form these memories. It can do it just fine. We just can't access them. And so the idea here is that forgetting, whether that's forgetting your childhood memories or forgetting where you left your car keys, could just be a function of an engram being written over with a new engram with neurons that the brain decides are more important. First one's still there. It's just not the one that's preferred at that point. Where that comes in with infantile amnesia is that, like you were saying earlier, the brain is growing really fast, learning all kinds of things, lots and lots of neuron growth that's happening as well. And so once that starts to slow down, maybe the brain is better at keeping things rather than

constantly writing over them.

0:10:02.5 SC: So what happens if you interfere with neurogenesis? Does that affect early memories?

0:10:07.4 SR: In this particular experiment, yeah, if they block neurogenesis, then they also seem to block infantile amnesia.

0:10:14.3 SC: Have they tried any other ways to block the loss of memories from baby mice?

0:10:18.3 SR: There's a few ways that that can be done. And one paper that was out in Science Advances last year found that if they infect the mother mouse when she's pregnant with a protein that sort of mimics like a viral infection, the baby mice, the males only for some reason, are less likely to have infantile amnesia. They seem to be able to form memories much earlier. It's not entirely clear why that is. It could be that some immune cells in the brain seem to be implicated. They might be affecting how the brain is developing overall or how certain connections are being formed between neurons. But a lot of that's very early days still.

0:10:54.4 SC: But that does suggest that maybe there are some people that had adverse effects when they were really little or when they were in utero that might actually have these super early memories.

0:11:02.1 SR: Yeah, yeah. There is some sort of parallel evidence to that as well, that in animals, if you separate them for their mothers, for instance, their brains seem to mature earlier. And whether or not that's a good thing for the rest of their lives, we don't really know. Those animals seem to have higher levels of anxiety. And we know in humans in so many ways, those first few years of life are so crucial for forming your personality, forming your mental abilities. So it kind of makes sense that if that maturation process is sped up or interfered with in some ways, there could be some really lasting effects that are difficult, if not impossible, to reverse.

0:11:37.7 SC: Looking across all these different experiments that you report on, do you feel like they're getting closer to the answer to the why question? You know, why might we not remember this stuff?

0:11:48.1 SR: Yeah, there's several varying ideas. I think a lot of them come down to what the brain finds important. It's more important at that stage in your life, unless you're a guinea pig, because you can depend on your parents. It's more important at that stage in your life to be learning about the world in general, to be learning what a cat is versus remembering, I live next door to this particular orange cat. So you can forget about the orange cat, but you remember the word for cat. You remember what things associated with it. And you could kind of focus more on finding patterns than having individual memories.

0:12:21.1 SC: I really like this idea that you talk about in your story where there is this kind of huge capacity in the infant brain that we just can't even conceive of as adults. There's just big differences in it. And that might be one of the reasons that we're not able to access those memories.

0:12:36.7 SR: Infant brains go through a number of what are called critical periods. The example I always think about is like learning a language, for instance. We know that kids can learn a language so much more easily than adults do. That's because their brain is just very plastic, can pick up all sorts of things. And that critical period, they say it closes at a certain age. And after that point, you really can't reopen it. And your brain will never be that plastic and malleable again. And memory formation seems to be a similar thing where your brain is going along, picking up all sorts of things,

forming these memories in a very different way than it will later on in life. And so there's a lot of research into that as well. Like what is happening during these critical periods that's changing how the brain matures. And you were talking about like the experiences too. There's some research finding that depending on the experiences you have during that critical period, the brain will mature faster or in different ways than if you had a different set of experiences. So it really all comes down to just how crucial those first few years are.

0:13:36.3 SC: Infantile amnesia is an interesting puzzle. Definitely something that I could just keep talking about for hours. But can we talk a little bit about how learning the why of it, the how of it? You know, what can we do with that information to either look at how adults forget or remember or, you know, other things that we also care about?

0:13:55.7 SR: There could be some implications for early childhood learning, like preschool, daycare, even was it worth teaching children at this age? Should we be teaching them music? Do we have to be fighting to get them into the best preschool? One researcher I talked to said that she'd written a column for the New York Times for grandparents. So grandparents were concerned that their grandchildren might not remember them if they died too young. So how could they, how could you get your kids to be able to remember their grandparents? But there's this broader question too, which is very controversial over whether infantile amnesia, this kind of forgetting is similar to the forgetting we do as adults. And we talked about the neurogenesis for instance, and that whole idea is very controversial. But if it is the same kind of forgetting, we might be able to understand that a little bit better by studying this sort of as a model. There's some evidence, for instance, that during Alzheimer's, of course, your brain gets all of these plaques that just completely tear up its integrity and make it impossible to remember anything. But even before those start forming, people start forgetting things.

0:14:56.7 SR: And we're not entirely sure what's happening at that point. If we do understand this better, we might be able to start getting some clues into whether those memories are still there and just not accessible before the brain starts accumulating all of this damage. I do want to say that there's a lot of different hypotheses floating around, and they're not necessarily mutually exclusive. There could be some neurogenesis going on at certain points. There could be these critical periods opening and closing in ways that we don't fully understand just yet. But the fact that we have these optogenetic techniques, we're getting better at human brain imaging as well, with younger and younger children. We might really start to be learning a lot more about this and answering some of these questions over the next few years.

0:15:37.8 SC: This really reminds me of sleep research. It's something that is omnipresent in our lives, and we just never think about how technical it is and what it's doing and how important it is. We just don't know. There's just so much to learn about such a basic piece of human biology. It's really interesting.

0:15:54.7 SR: One of the researchers I barely quoted in here is doing stuff on naps and whether kids who give up naps at certain ages might have more or less mature brains. It might be more useful to teach them French if they've stopped napping on their own, but only those kids who've already stopped napping.

0:16:09.6 SC: That's so interesting.

0:16:11.0 SR: Yeah, it's all very new, but I thought it was really interesting.

0:16:14.0 SC: Wow, that's really cool.

0:16:15.1 SR: I just remember being forced to take naps and just reading under my covers. That's my earliest memory.

0:16:23.1 SC: All right. Thank you so much, Sarah, for coming on the show.

0:16:24.3 SR: Yeah, thanks for having me.

0:16:25.3 SC: Sarah Reardon is a freelance science journalist. You can find a link to the story we discussed at science.org/podcast. Stay tuned for a chat with researcher Huiquan Li about how fear after acute stress lingers in the brain.

[music]

0:16:49.3 SC: Generalized fear is a symptom in some anxiety disorders, in panic disorder or social anxiety or PTSD. Generalized fear is basically reacting in a fearful way to events or environments that don't relate specifically to the original stressors from the past. There are plenty of cues around suggesting that there's no danger, but you still feel afraid. This generalized fear can cause stress and reduce quality of life, and we don't know much about how to turn it off, but we are learning about how it might get turned on. This week in science, Huiquan Li and colleagues wrote about changes in the brain linked with the onset of generalized fear. Hi, Huiquan. Welcome to the science podcast.

0:17:30.4 Huiquan Li: Hi, Sarah. Thanks for having me here.

0:17:33.0 SC: Sure. Let's talk a little bit about the work you did here. It was in mice and also in some post-mortem brains. So let's start with what's happening with the mice. Going into this work, you had an idea of where in the brain the switch might be happening, where generalized fear might be starting, but not the specifics of how this change occurs. In order to get at those details, you looked at mouse brains across a variety of conditions. What were the different setups for the mice? How were they set up to experience generalized fear?

0:18:06.7 HL: We used a mouse model and used a foot shock as the stressor to trigger fear in mice. And we observed conditioned fear and generalized fear were produced after this foot shock.

0:18:24.1 SC: In some cases, the mouse would go into a space and get shocked, and then it would never want to go back to that specific spot. It would freeze. It would be afraid of going back there. That's kind of the basic fear response, right? But then generalized fear is something a little bit different in a mouse?

0:18:36.7 HL: Exactly. In the same environment, this type of fear is called conditioned fear. But generalized fear is that the mice were put into a novel environment. They have never been experiencing any stress in those environment, but they still show fearful response. As you said, that is generalized fear.

0:19:00.3 SC: So in this setup, you have one condition that gives you fear specific to a specific environment. And then you have another setup where you get generalized fear. And that means that the mice are afraid in different environments, novel places. So when you looked at the neurons in this region that you knew was important to generalized fear, how was it different after generalized fear had been induced in these mice? Tell us about the brain region and the changes that you saw there.

0:19:29.0 HL: We observed neurotransmitter changes in a brain region called dorsal raphe, that is in the midbrain. And we observed that the serotonergic neurons in this region changed their co-

transmitter from glutamate into GABA.

0:19:51.1 SC: Let's break that down real quick. There are basically co-transmitters. So there's two kinds of neurotransmitters being released by these neurons?

0:19:57.6 HL: Exactly. So they have serotonin as their major transmitter and they co-release glutamate.

0:20:06.7 SC: And when they were in the generalized fear condition, you saw a switch for that co-transmitter from glutamate to GABA. Is that right?

0:20:12.1 HL: Yes. And when we block the switch from glutamate to GABA, we observed that the generalized fear was blocked.

0:20:20.7 SC: Yeah. So this was all in mice. You were able to show this relationship between the neurotransmitter expression and generalized fear. What did you see in the human postmortem tissue that you were able to look at?

0:20:35.9 HL: We observed a similar increase in the serotonergic neurons co-expressing GABA synthesis in the individuals of PTSD compared to the control subjects, similarly as what we have found in mice. The correlation and causality between the neurotransmitter switch and the generalized fear production was demonstrated in the mouse model. In humans, we have found this correlation. The causality is hard to be investigated.

0:21:12.0 SC: Yeah, because you have to go deep into the midbrain, find this very specific region of neurons and say, oh, did you change what neurotransmitter you're dealing with? That's not easy to do in people at all.

0:21:22.8 HL: Exactly.

0:21:25.9 SC: Yeah. One of the things that you administered to the mice to see if you could block this progression to the different neurotransmitters, this switch in this region of the brain, was Prozac. So that worked on the mice, but there was somewhat of a limitation on the timing.

0:21:38.0 HL: True. When we provide Prozac immediately after the foot shock, two weeks later, the generalized fear was gone, was not observed for these mice. But when we provided Prozac two weeks after the foot shock, when the fear response is already produced, there was no effect.

0:22:01.8 SC: So it's not reversing the switch, it might prevent it from happening. So you showed that there's a switch in the neurotransmitters in this region of the brain. What happens next? So what are the downstream effects of these neurotransmitters being different? You know, how do we know that that might translate into generalized fear? What are some suspected mechanisms there?

0:22:22.0 HL: We have identified two growing regions downstream of dorsal raphe. One of them is central amygdala. The other one is lateral hypothalamus.

0:22:35.1 SC: So these two regions that you found downstream, you did see changes in their neurotransmitter setup, if you will. What do we know about the central amygdala and the lateral hypothalamus? You know, are these regions associated with fear in other settings?

0:22:48.4 HL: Yes, they have been studied by other researchers, that they have a role in fear regulation or anxiety-related behavior.

0:23:01.2 SC: So let's go to the other end. Before we get to the switch in neurotransmitters in the dorsal raphe in the midbrain, what do we know about the causes from that? How do we go from fear, a foot shock to a change in neurotransmitters?

0:23:11.4 HL: We have identified that stress hormones play a role in producing generalized fear, particularly when we have blocked the synthesis of corticosterone, that is a stress hormone. When we blocked its production, we were able to block the transmitter switch as well as generalized fear.

0:23:37.9 SC: So how do you see this research going forward and be integrated into therapies or interventions for generalized fear?

0:23:46.7 HL: I think our study have pointed two directions. One is with existing therapies. Our study has suggested that earlier intervention is likely to produce better effect. And for chronic PTSD or similar fear-related disorders, it may be hard when the patients have already a long history of the disease. Then our study suggests new therapeutic target to treat this disease.

0:24:26.7 SC: Yeah. Were you surprised that neurons would switch which neurotransmitters they used? I don't know. When I took neurophysiology for some reason, we didn't really talk about neurons switching up which neurotransmitters it would use. We kind of were like, okay, this is the one that you use. This is your destiny. Were you surprised that these neurons were able to change which co-neurotransmitters they were releasing?

0:24:51.2 HL: Yes. So for a very long history, like in classic neurobiology, people believe neurons have only a single neurotransmitter throughout their life and their neurotransmitter is fixed. But recently, in the last few decades, more and more evidence supports that neurons do not express only one neurotransmitter. And surprisingly, they can switch their transmitter. The Spitzer Lab at UCSD, as well as other labs who work on neurotransmitter switching, have now accumulated vast evidence in different regions in response to different stimuli that neurons have the ability to switch their neurotransmitters. And what is more important is that this switch contributes to behavior changes.

0:25:46.1 SC: So this plasticity has an effect, you know, all the way at what we do or what we think or how we feel.

0:25:52.5 HL: Right.

0:25:53.6 SC: Very cool. Thank you so much, Huiquan.

0:25:55.1 HL: Thank you, Sarah.

0:25:55.9 SC: Huiquan Li works as a senior scientist at Neurocrin Biosciences in San Diego. When she was doing the work for this paper, she was an assistant project scientist in the School of Biological Sciences and Center for Neural Circuits and Behavior at the University of California, San Diego. And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at sciencepodcasts@aaaas.org. To find us on a podcasting app, search for Science Magazine, or you can listen on our website, science.org/podcast. This show was edited by me, Sarah Crespi and Kevin MacLean, with production help from Megan Tuck at Podigy. Jeffrey Cook composed the music on behalf of Science and its publisher, AAAS. Thanks for joining us.

0:00:05.6 Sarah Crespi: This is the Science podcast for March 8th, 2024. I'm Sarah Crespi. First up this week we hear from online news editor Mike Price, about a large genome sequencing project in India that reveals past migrations in the region and a unique intermixing with Neanderthals in ancient times. Next on the show producer, Kevin MacLean talks with researcher Matthew Tierney about how vitamin A and stem cells work together to heal wounds. This week, online news editor Mike Price, wrote about the largest genome project from India so far and what it reveals about ancient migrations in this region and Neanderthal mixing back in the day. Hi, Mike. Welcome back to the podcast.

0:00:50.8 Mike Price: Thanks, Sarah. Good to be here.

0:00:52.8 SC: Yeah. So, I had no idea that the intricacies of Neanderthal mixing around the different regions of the world, like I knew it happened in Europe, and I think that's because European genomes were sequenced really early, and there are sites that have Neanderthal evidence of their settlement there, but it's global, right? Everybody's got a little bit of Neanderthal DNA.

0:01:12.0 MP: Just about all non-African, have a little bit of Neanderthal DNA. Yes. And even some African populations too, from things like back migration. And there's a lot of puzzles involved in, in where the people of the world have gotten our Neanderthal genes from.

0:01:27.1 SC: So how is the population in modern day India? How is their Neanderthal industry different than what we've seen in Europe so far?

0:01:35.7 MP: So one of the things that they found in this most recent study is that while the Indian populations have about the same percentage of Neanderthal ancestry as as other non-African, so that's about one to 2% of an individual's genes were inherited from a Neanderthal ancestor. The population wide assortment of Neanderthal DNA is much more varied in India than it is in any other population that they've looked at so far.

0:02:07.3 SC: They just have a lot more of the Neanderthal genome spread throughout their population in little fragments.

0:02:12.8 MP: That's exactly right. You can reconstruct about 90% of the known Neanderthal genome from genomes within modern day Indians. That means that you could put together most of the Neanderthal genome from the bits and fragments that are scattered throughout Indian populations. And then also something kind of interesting is that there are far more population specific genomic sequences in India than anywhere else. So what that means is there are unique Neanderthal sequences found in populations in India that aren't found anywhere else, and there are more of those in India than any other population that they've looked at.

0:02:52.8 SC: Does that suggest there's some selective pressure going on? There's some, environmental factors that allow those sequences to remain in the genomes of those populations.

0:03:01.6 MP: I asked some experts that that question, and unfortunately the answer is they don't know yet.

0:03:06.5 SC: Too soon to tell.

0:03:07.6 MP: Yeah. Too soon to tell is is the stock answer, and then unfortunately in this case it it is true. Yeah. They haven't been able to determine whether or not these genes carry a selective advantage. And in a lot of cases they're not even necessarily sure what the functional significance of these genes is.

0:03:24.0 SC: But this has been shown in other populations that they have something that was inherited from Neanderthal ancestors and it has an adaptive advantage because of the unique circumstances that the people live in.

0:03:34.4 MP: Yeah, that's absolutely correct. And then some of the people that I talked to for this story did mention that there's a decent shot that some of these genes probably carry immune advantages that would've helped fight off diseases, and those advantages would've been inherited from Neanderthal ancestors. But this is all work to be carried out in the future to to see whether or not that adaptive signal actually is present, and strong and comes through clearly in these genes.

0:04:00.6 SC: Getting to the study itself, we just jumped right into the admixture path, but we should also, it also reveals something about migrations in this area, because you got to remember people all started Africa and they got to where they are now over some period of time, and it's very complicated and it's a very interesting question that there's all different ways of addressing. But one is to look at the genetic structure of the modern day population and ancient populations and see where everybody relates through time. So what did this new kind of much larger effort at sequencing genomes in India tell us about where people historically came from?

0:04:36.1 MP: A few years ago, a research team led by David Reich and Priya Mujani put out a a couple studies looking at ancient genomes from throughout Eurasia. And by reconstructing those ancient genomes and looking at how they related to modern day populations in South Asia, they had found that there were three main sources of ancestry that form the backbone of modern day Indians. There was a, and sort of an indigenous South Asian population of what would've been hunter gatherers that arrived in South Asia many tens of thousands of years ago. At some point, that population mixed with a group of Iranian farmers, they were able to find that Iranian related ancestry that entered into the Indian population around 5000 to 3000 BCE. And then towards the tail end of that, there was this other pulse of migration from Eurasian step herds. These would've been the Yamnaya herds that herded things like cattle and goats, and sheep, and brought in that other level of animal domestication into the population.

0:05:51.4 SC: That's the picture that came to the researchers who did this study. They knew from the ancient DNA evidence this kind of mix was there. But what is a new study of all these modern genomes give us?

0:06:02.7 MP: The primary thing that this new study did was it allowed us to gain a little bit more insight into the Iranian ancestry part of this puzzle, digging more deeply into modern populations. And they had about 2700 genomes represented from modern populations across the whole variety of, of geographic locations and linguistic groups and casts and religions. By looking for this Iranian ancestry and mapping it back onto ancient genomes that they've looked at in the past, they were able to get a finer, detailed look at where exactly this Iranian ancestry originated. The strongest signal that they found came from this remote outpost near what is today northwestern Tajikistan called Sarazm. And Sarazm, back in the day, 5000 BC ish was a trading outpost, that was not quite in the mountains, not quite in the planes, not quite in the steps, but it was sort of this place where all of those things would've come together.

0:07:05.8 MP: And so it would've made it a natural place for freighters and travelers from all these different regions, from Eurasia to meet up and exchange goods. And what they found was is that the ancient Iranian ancestry that had been found in Sarazm was the closest match for the Iranian related ancestry present in modern day Indians. So what it seems like is that Sarazm was the place that this pulse of Iranian ancestry originated and then came down into South Asia. But what's also kind of cool and and neat to see is that you can also see Indian ancestry in individuals that were present in

Sarazm as well. What that means is it wasn't just a one-way street. You had people from South Asia going up into Sarazm and trading their own goods more than likely. And so it wasn't just a one-way street of migration, it was, it just sort of reveals how interconnected the ancient world was.

0:08:01.6 SC: So there's another outstanding question that is addressed in your story, and this is about the effects of the Toba Super volcano eruption. This was a catastrophic event about 74,000 years ago in what is now Indonesia. And it was so big that some people think this caused a bottleneck for all of humanity, and we went down to a very small number of people and then had to repopulate the earth from there. But that's not a done deal, that's not a settled thing. And there is another question related, did India lose its population and have to grow it up again? So yeah, what does this study suggest about what happened?

0:08:39.2 MP: I'll preface this by saying this is a very controversial question, and this study doesn't put to rest any particular argument on one side or the other, but what this study does find is that for the modern day population that has been sampled and based on ancient genomes from the region that we have, it looks like everyone living in India today derives their ancestry from a group that entered into India around 50,000 years ago, which would've been after the Toba eruption. It doesn't say that there weren't modern humans in India before the eruption 74 to 80,000 years ago. But what this is suggesting is that as far as we can tell, those people did not contribute to the modern ancestry of Indians living today.

0:09:29.0 SC: So. They might have died out or their genes might have died out. We don't know.

0:09:32.6 MP: Exactly. We don't know. And I'll also say that I have talked to some other experts who say that that could be an artifact of low sampling of ancient genomes in the region. So it could be the case that as we find more ancient genomes, that you could detect the signal of more ancient ancestry. But we don't have clear evidence of that yet. And it's not supported by what you see in this most recent paper.

0:09:57.7 SC: Is there any archeological record of people in India earlier then?

0:10:01.6 MP: Is an archeological record? There are stone tools that have been found at this site called Daba in Central India that look an awful lot like what people would've been making modern humans. But there are other people who argue that they could have been Neanderthal made, that they could have been made by other archaic commons. There's no clear distinctive evidence that these were made by modern humans made by our own species. Though you will find people who will tell you that there is clear evidence and some of the most knocked down drag out fights in archeology are over whether or not you can tell who made what. So, I'm not going to step into that argument. I'll let them fight it out in the journals.

0:10:40.8 SC: You gotta keep your neutrality.

0:10:42.3 MP: I've gotta keep my neutrality here. I've gotta get, I've gotta keep my invitations to conferences.

0:10:48.4 SC: Well, Mike, is there anything else we could learn if more ancient genomes from this region were uncovered? Is there anything else that we would love to be able to solve about South Asia? If we could have access to that information?

0:11:02.0 MP: There, for questions to be answered about really pinning down exactly where the, let's say the Yamnaya step ancestry entered into. And we know approximately who these people were, but pinpointing the archeological sites and specific regions where they would've come from

would be interesting to learn. And then beyond that, I think if we want to know more about where and how and when these Neanderthal genes entered into the population, it's going to require more archeological work. And so until we have archeological evidence of Neanderthals in India, which we don't have for now, it will remain an open question of whether or not the Neanderthal genes in the Indian population were present to begin with.

0:11:51.0 MP: They might have been there with the settlers that came into India, they might have had earlier intermingling with Neanderthals and brought that with them, or it's possible that they encountered Neanderthals somewhere on the subcontinent and there was a new pulse of gene flow from relations there. But we don't know, and it's pretty speculative to say whether or not that was the case, but that is one possibility that this study raises is that one potential explanation for why you see this just sheer diversity of Neanderthal genes in this population is maybe they met a genetically diverse population of Neanderthals who was living there. But I will reiterate pure speculation, there's no archeological evidence of Neanderthals in India. And so until they find that, then it remains purely a guess.

0:12:44.1 SC: It just hard to find Neanderthal sites or is there a special set of conditions that preserve them and they're just not present where we wanna know more?

0:12:53.8 MP: The conditions in South Asia aren't as favorable to preserving fossils as they are throughout most of Europe, so that just makes it a lot harder to find them if they are there in the first place.

0:13:05.0 SC: Thank you so much, Mike. It's been really fun talking.

0:13:07.4 MP: It's been a pleasure. Sarah.

0:13:07.9 SC: Mike Price. Is an online news editor for science. You can find a link to the story we discussed at science.org/podcast. Stay tuned for a chat with producer Kevin MacLean and researcher Matthew Tierney about the role of vitamin A in stem cell plasticity.

0:13:32.6 Kevin MacLean: Stem cells help maintain healthy tissues, regenerating new cells that serve the same purpose as their predecessors, but when tissues get damaged, stem cells can adjust their function to produce cells that help with repair. This is particularly important for the skin, which has to deal with cuts and scrapes and sunburns all the time. Understanding the mechanisms that regulate and change the fates of stem cells has a lot of potentially important implications from wound care to cancer treatment. Matt Tierney and colleagues studied the effective vitamin A on stem cells and tissue regeneration in the skin. Hi Matt, welcome to the Science podcast.

0:14:12.7 Matt Tierney: Hi, Kevin, great to be here.

0:14:12.8 KM: So we're talking about stem cells today, specifically about this process where they can shift from one developmental pathway to another, something called lineage plasticity, which was definitely a new term for me. Can you talk a little bit more about what that is and what you are aiming to study with this work?

0:14:32.0 MT: Yeah. Absolutely. So lineage plasticity is a crucial feature of the stress response in tissues, particularly following disruption of their local environment or niche. Then our setting in the skin, we've defined it as when molecular features of their new and original lineages become co-expressed. And this helps grant stem cells the unusual flexibility to choose either fate during the tissue repair process. There's still a lot we don't know about the signals that control in these plasticity and help distinguish its involvement in pro regenerative versus degenerative states. And so

here we, I guess, set out to identify its critical regulators in the skin.

0:15:09.8 KM: So you wanted to figure out what was controlling these stem cells ability to, to shift from making one kind of cell to another when there's damage or something like that. So I definitely wanna get into how you go about doing that, but first, why is this such an important phase or phenomenon to study?

0:15:29.9 MT: Yeah, absolutely. The onset and the resolution of lineage plasticity acts sort of as a double-edged sword in the context of regeneration. So it's necessary to redirect stem cells to the different parts of the tissue that are most in need, but it also leaves those same tissues, vulnerable, perpetual states of repair and even some types of cancer if lineage plasticity isn't properly resolved.

0:15:47.9 KM: So switching into this state of lineage plasticity is good to repair damage, but if they stay in that repair mode, that can also cause problems.

0:16:00.1 MT: Exactly that this, a perpetual state of lineage plasticity has been associated with both non-healing wounds and types of cancers including in the skin.

0:16:08.5 KM: Okay. So that's why it's important to understand not only how to enter lineage plasticity, but also how they switch back or, or resolve.

0:16:19.5 MT: Yes, exactly. So without getting ahead of ourselves, we found that there's a particular signal that is anti-correlated with lineage plasticity, and so it's loss from those particular regions of the skin. In this case, the hair follicle as its niche is disrupted in the context of wound repair, ends up reducing the overall availability of this signal during the wound repair process. And it allows lineage plasticity to be upregulated, but then after the wound has begun to repair itself, that signal comes back on. Once that signal is restored, lineage plasticity is resolved.

0:16:53.6 KM: Why is the skin such a good place to be studying all of this?

0:16:57.7 MT: The skin is a, a really excellent model system for these types of questions, being a barrier tissue that's constantly exposed to environmental insults and also that contains several discrete stem cell populations, each normally insulated in their own compartments, including the epidermis, the hair follicle, dis sebaceous gland, etcetera, but then can be released from those constraints by a wound and enter the state of lineage plasticity.

0:17:20.3 KM: So stem cells that are in each of those different compartments could potentially be recruited to act in wound repair if needed?

0:17:27.3 MT: Yeah, absolutely. So, in the manuscript we use a relatively understudied shallow abrasion wound model that mimics everyday scrapes and scratches, which removes just this top layer of the skin. And so you can consider it almost to be sort of a brush burn or a rug burn or, or what have you. So it removes just that skin layer and if done properly leaves the stem cells of the hair follicle within the dermal layer intact and allows those stem cells to essentially have a choice At this point, they can either remain in the stem cell niche of the hair follicle, contribute to cyclic rounds of hair regrowth, or they can be mobilized upwards to the skin and repair that epidermal barrier.

0:18:09.5 KM: How do you start looking at what the controls and regulators are in this process? How do you utilize this model to understand that.

0:18:17.0 MT: Trying to assess this in vivo? In our situation, our work was done in mice is quite

laborious. And so we had an initial point of leverage that came from two prior studies in our lab together showing that the molecular signatures of lineage plasticity were recapitulated when skin stem cells were placed in traditional cultures. So this set up a much more accessible and tractable system for us to try to model and manipulate this signature. And so we adopted a high throughput screening approach and identified several important signals, including retinoic acid as a vitamin A metabolite that ended up being essential to resolving lineage plasticity and returning stem cells to their original physiological identity.

0:18:57.3 KM: Just looking back through, I think I saw there were more than like 70 compounds you were testing. Were you putting all these through sort of battery of tests or watching what that process was? How did that, that process go?

0:19:12.2 MT: We understand the molecular signature of lineage plasticity in the skin to be the co-expression of two. Normally lineage restricted transcription factors, SOX nine and KLF5 in the context of a hair follicle stem cell, which is normally marked by SOX nine. When placed in culture, we know that it will also turn on KLF5 and co-expressed these two transcription factors together. And so we simply read out using a fluorescent reporter system levels of KLF5 and attempted to lower those levels such that SOX nine remained the only transcription factor expressed.

0:19:49.3 KM: Sorry. Walk me back through that last bit again. Normally one or the other expressed, but, when are they both expressed?

0:19:56.2 MT: In healthy skin SOX nine and KLF5 act antagonistically toward each other, but in the context of a wound repair, they enter into an environmental circumstance that allows both to be co-expressed. And that is because ultimately that now we know that there are certain signals, that enable this.

0:20:14.2 KM: Okay, so which one goes with which again?

0:20:16.0 MT: So SOX nine is canonically a marker of hair follicle stem cells and KLF5 a marker of epidermal stem cells under normal conditions. When co-expressed this is a marker of lineage plasticity indicating that those cells can become either fate when one or the other eventually is repressed.

0:20:38.9 KM: All right, so you see both express, that's your signal to know that they're in a state of lineage plasticity and then when they're not, in this repair state anymore, they go back to just expressing one or the other.

0:20:52.8 MT: Yes. Once the wound repair process is completed, those transcript factors again label their unique compartments within the skin, Linus plasticity is resolved.

0:21:04.8 KM: Okay. So let's get back to the compounds you're testing. Retinoic acid came up as something that was important. Is retinoic acid, is that, is it the same as vitamin A or retinol?

0:21:17.2 MT: Absolutely. We use vitamin A and retinol interchangeably retinol or vitamin A being the dietarily received. But retinoic acid is produced locally in various tissues in the body through a series of enzymatic reactions.

0:21:30.7 KM: So how did you know retinoic acid was an important compound to focus on?

0:21:36.4 MT: We had identified retinoic acid as one of several key factors in our initial screen as being important for lowering KLF5 levels and resolving lineage plasticity in the manuscript. We

eventually identify retinoic acid as most potent in combination with an inhibitor of protein kinase C as being capable of resolving lineage plasticity when stem cells are placed in culture.

0:22:00.6 KM: And this was already like a compound that was sort of already in the realm of like tissue and skincare, right?

0:22:09.0 MT: Sure. So in particularly in the skin, we've long known that retinoic acid or retinol signaling in general is critical for a number of different skin phenotypes. We've probably seen it at at your local pharmacy as a possible skin remedy for a number of things.

0:22:21.7 KM: Yeah.

0:22:22.5 MT: And there were initial clues that vitamin A or retinoic acid signaling could be important for this concept of lineage plasticity. As we've known for some time that eliminating the signaling cascade in hair follicle stem cells progressively results in hair loss and the formation of epidermal cysts. But we had not known formally how the signaling cascade interacted with lineage plasticity, or I guess we just hadn't explored this particular line of thinking.

0:22:49.1 KM: So now we know that retinoic acid is something that you're wanting to pay attention to. What happens next, to sort of figure out what's going on mechanistically?

0:23:02.8 MT: We took two different approaches after the identification of retinoic acid to formally understand whether or not this truly regulated or resolved lineage plasticity. We first wanted to understand if retinoic acid was able to resolve lineage plasticity in culture, we would have expected that these stem cells would have regained their physiological identity as hair follicle cells and would be capable of differentiation. We also tested this as sort of a proof of concept in vivo and in the context of wound repair. So we found that manipulating vitamin A signaling during wound healing when lineage plasticity is high, was able to refine stem cell fate switching in the wound bed and rebalance their contribution to different aspects of tissue repair, including either the restoration of the skin barrier or the resumption of normal hair regrowth.

0:23:52.4 KM: I guess zooming out a little bit, I feel there's a difference between, what people might think stem cells are or do and what maybe they actually do. Do you come across that, is there anything, what do you feel most people misunderstand or don't get about stem cells in sort of a broader sense?

0:24:13.7 MT: Yeah, I guess said perhaps a different way it takes a village in order to accomplish the task that stem cells are often credited with. And so while stem cells are obviously critical as the direct cellular contributors to regenerative processes, it often ends up being that there are a series of signals or other cell types that are present during any of these different processes that are essential to direct that process. And it's critical that we understand what those are so that stem cells can function properly and act to pro regenerative end instead of engaging in the sort of dysfunction or degenerative circumstances or even potentially cancer that might exist otherwise.

0:24:55.2 KM: Oh, interesting. So it's sort of like raw materials and, and needing instructions for them.

0:25:00.3 MT: Yeah. I don't know if I love the, the sports analogy, but the coach player analogy I think tends to work at its surface level here.

0:25:08.1 KM: Wait, what do you mean?

0:25:09.6 MT: Once you start getting into the sort of actual pathologies that come with a stem cell that goes rogue, it sort of backs off quite a bit, but I tend to think of stem cells as being the actual, as the players in the circumstance endowed with an incredible ability to athletically act, but in need of direction from a coach in order to collectively engage all players involved in an act, get the most out of their collective potential. It's not the greatest analogy, but.

0:25:37.0 KM: No, no, I get what you mean. So what's next? Where do you wanna take this research?

0:25:44.2 MT: So I think with this work, one of the major accomplishments has been defining the minimum requirements needed to form mature health cell types from stem cells outside the body. And I think this work has the potential to transform the way that we approach the study of hair biology generally. Meaning that now we have, in this case, an ability to direct stem cells to their differentiated lineages in isolation. This enables us to much more accessibly and tractably pursue aspects of their biology that are much more difficult to study in vivo context. I also think therapeutically there are a number of potential applications to test treatments against these new targets and conditions like non-healing wounds and cancer when lineage plasticity becomes dysregulated and is often left chronically active in the skin, both retinoic acid, but also some of the downstream targets that I think we've identified in this manuscript represent potential therapeutic avenues towards affecting different degenerative circumstances.

0:26:44.5 KM: Great. Well thank you so much Matt. It was really nice talking to you.

0:26:48.5 MT: Appreciate it Kevin. Thanks for taking the time.

0:26:51.3 KM: Matt Tierney is a postdoctoral fellow at Rockefeller University. You can find a link to the paper we discussed at science dot org/podcasts.

0:27:00.2 SC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at science at podcast at AAAS.org to find us on podcasting apps, search for Science magazine, or you can listen on our website science dot org/podcast. The show was edited by me, Sarah Crespi and Kevin MacLean with production help from Megan Tuck at Prodigy. Jeffrey Cook composed the music on behalf of science and its publisher AAAs. Thanks for joining us.

[music]

0:00:05.6 Sarah Crespi: This is the Science Podcast for March 1st, 2024. I'm Sarah Crespi. First up this week, a new approach to slowing climate change, dehydrating the stratosphere. Staff writer Paul Vossen, joins me to discuss the pros and cons of this geoengineering technique. Next on the show, science robotics editor, Amos Matsiko is here to give us a rundown of papers and a special series on magnetic robots in medicine. We also chat about how close old science fiction books came to predicting modern medical robots.

0:00:43.0 SC: Solar geoengineering, this is getting the sun to stop heating up the earth quite so much at a planetary scale, has been talked about for decades. And often, the theorized interventions for solar geoengineering involve adding little particulates or different things to the atmosphere to reflect away some of the sunlight that's coming in. Staff writer Paul Vossen joins us to talk about a different approach to slow climate change through solar geoengineering, in this case by dehydrating the stratosphere. Hi Paul.

0:01:14.9 Paul Vossen: Hello.

0:01:15.4 SC: Hi. So our stratosphere is a little too well hydrated right now?

0:01:19.6 PV: I mean, it's not very well hydrated [laughter] ever. It's way up there and water tends to fall down and onto our heads as rain make clouds. Not a lot gets up there, but when water does get up there, it acts as this kind of powerful greenhouse gas.

0:01:37.4 SC: Yeah. So we're in the troposphere, that's where we live and all our weather is, and the stratosphere is this layer above that where water doesn't really have much of a job, and when it does get up there, it starts to contribute to warming?

0:01:49.0 PV: Yeah. So, you know, once you get up past this kind of, it's called the tropopause, the top of the troposphere where you cross over the, there's a few definitions for it, but it's really this point where as you're going up, you know, it gets colder and colder and colder and then suddenly it starts getting warmer and warmer and warmer again, and you've just crossed the tropopause when that happens. And when stuff gets up there, it kind of stays, especially if it gets up there in the tropics, it stays around up there for years. Sometimes if it's light enough, wind stuff gets up there like from the bush fires in Australia a few years ago or that eruption of the volcano in Hunga Tonga, can have these years long impact.

0:02:30.5 SC: So, perhaps affecting how much water is in there could have years long impact on how much heating or warming the stratosphere is contributing.

0:02:39.4 PV: Yeah.

0:02:39.8 SC: This is in the draft that I saw, you do say that there's some speculation about how much percent contribution to warming there is from this water up there. Do you wanna mention that?

0:02:48.0 PV: It's really uncertain what's going on [laughter] with water vapor in this stratosphere. There are not a lot of measurements. We just don't get up there that much. We have satellites, but they're not perfectly measuring this. The satellites tend to see that there hasn't been a change in the amount over the past few decades, but there's been some research basically from this one site in Colorado run by NOAA where they monitor it, that seems like water vapor increased and then may have boosted the warming in the late 1990s by a bit. That percentage is really uncertain. There's a

paper in science about that 14 years ago. But you know, I don't know if that's kind the end all be all on how much it caused, but the mechanism there is clear, like water vapor catches the infrared heat coming off the planet and then gets a little bit warmer and shoots the heat back down.

0:03:39.5 SC: We have a mechanism for how it could contribute to warming. So let's talk about the mechanism for how we would dehydrate the stratosphere.

0:03:46.1 PV: For decades, researchers have known that there's only a few spots in the planet where water vapor crosses over, barring big volcanic eruptions, like on a regular basis. And the primary one is this area in the western Pacific, roughly the size of Australia, where these huge towers of convection, just super hot. So you got lots of air rising and even though that's the highest point for where the stratosphere starts, because it's higher up at the tropics, there's just enough energy to kind of loft air up into the stratosphere. And there's lots of water vapor there. Most of that does fall out, but still you can reach this point until right before you cross over into the stratosphere, that water vapor can be well over 100% relative humidity.

0:04:32.3 SC: Wow.

0:04:32.8 PV: When you're over 100% relative humidity, usually you get clouds, but if you don't have any like little bits of junk in there to start like nucleate the clouds to like make the clouds happen, maybe it all rained out or there's just none of these seeds exist, then it doesn't fall out and it crosses over to the stratosphere.

0:04:50.8 SC: Are there people living underneath these giant towering convection areas?

0:04:55.8 PV: No, no. This is east of the Philippines over the ocean.

0:05:00.8 SC: The idea here then is to say, well, let's provide some seeds. Let's shake that rain out before it crosses into the stratosphere.

0:05:07.4 PV: Yeah. So, I mean, this is not going to be the biggest climate impact, let's say that first. This is not on the scale of these reflecting the light to drastically cool things. It's like a tangible one, but what's remarkable is kind of a bang for your buck type of proposition that they, you know, this is kind of a back of the envelope type laying out the idea. So no, this is totally firm, but...

0:05:28.5 SC: I will not go out and do it tomorrow.

[laughter]

0:05:31.3 PV: The thing is like, well you couldn't but the amount of material you might not need, so it's only 1% of these air parcels hold kind of 50% of the potential water rained out. So only 1% of this Australia sized region has most of the excess water. So potentially you could go with as little as like two kilograms of cloud seed per week, and cause a big tangible impact in the amount of water vapor going to the stratosphere. So the amount a drone could lift up or a balloon, you don't have to fly huge aircraft campaigns necessarily.

0:06:05.7 SC: And then wipe out your climate benefit. Right? [laughter] Yeah. So you could take a drone or balloon and fly this small amount of material up weekly to seed clouds, rain this out and then dehydrate the stratosphere. That's not taking water that's already up there out, it's just slowing down how much gets up there.

0:06:23.3 PV: Yeah, it all comes out eventually. If you're just stop it before it gets up in there,

you're dehydrating the natural cycle.

0:06:30.8 SC: So we keep saying, it's not a huge impact. It's not gonna be nuclear winter. [laughter] Is there any kind of comparison that we could make about how large of an impact this would have on climate change?

0:06:41.9 PV: Our editors were just pressing me on that revisions in the story. And it's hard to say, to fix an exact figure on this in an optimistic scenario. Shooka was the lead researcher that said it could be 0.1 watts per meter square radiated for instance, so you understand that, right?

0:07:00.0 SC: Means nothing to me. Yes, thank you.

0:07:00.9 PV: But you could say roughly that methane added by humanity, that's like maybe 10% of that, but cooling versus warming, right? So it's not totally insignificant.

0:07:13.4 SC: That sounds interesting, yeah.

0:07:14.5 PV: Another way of putting it, I think could be a few hundreds of a degree Celsius, which makes it sound smaller, but it's global. Yeah, it's a big...

0:07:22.4 SC: But it is global. We're doing something global with something that's not exactly a big lift. Okay, so we have the mechanism and the potential impact, but would there be any local effects or any concerns about what happens to these seeds once they are rained out of the sky?

0:07:40.5 PV: So the big concern here, and as the authors acknowledged, there's some of the kind of top people in this field, is that if these cloud seeds, say they fail to make clouds there or they get redistributed and form clouds that don't go into the stratosphere, instead make these cirrus, these thin wispy clouds higher in the troposphere, so clear sky, and then these seeds accidentally get there and create clouds. These cirrus clouds warm the planet. They are essentially water vapor. They don't reflect much light. So kind of the net, they cause warming. So you could, if you didn't do this right, accidentally warm the planet instead of cool it.

0:08:21.7 SC: So it's a negative, it might like zero out whatever effort you're doing here. You just can't tell.

0:08:26.6 PV: But their point is that you wouldn't create a lot of these because you're doing this in such a small area. So you're having a global impact with water vapor and the stratosphere, but it would be a very local impact likely. But it's as they say, this is just the start and they need to study this better.

0:08:42.7 SC: Yeah. You mentioned in your story that geoengineering is kind of getting a new hearing amongst scientists and policymakers. What are some of the drivers of that?

0:08:51.7 PV: I think the biggest driver is for a long time, there's been a slippery slope argument of we start doing this and then we'll lose all motivation to carbon emissions. I don't know if that's been the case. I mean, we haven't been curbing emissions anyway, to the degree we are, to some degree, of course. But things have just been warming so much and getting CO2 out of the atmosphere, the economics of that still need to get way better. So there have been calls for a decade by the National Academies of the places that we need to research this, not deploy it necessarily, but just to research it, get all the ideas and suss it out a bit more if this ever needs to be done. And I think more people are opening up to that idea of the research, if not, no one I think is chomping at the bit to actually deploy this.

0:09:39.0 SC: Yeah, there was a piece in Science, I think it was probably last year, this was in the commentary section, it was a policy for basically saying, we need to figure out what could work and what could do damage to make sure that when we run out of options, we have an option that is least harmful. So we can't just say, oh, well, this is how scientists destroy the planet. We shouldn't even look at it, right? We have to look and see.

0:10:02.1 PV: This paper was out of NOAA, the National Oceanic and Atmospheric Administration, and they've been tiptoeing into this realm a bit more. You have just lots more of credible scientists who are willing to explore this.

0:10:16.4 SC: Really interesting. And is a policy piece of it also moving forward? So looking at how humanity as a whole could come to an agreement or who gets a say in what gets done?

0:10:27.6 PV: Yeah, when I was talking with one of the outside researchers for this, they're saying how the EU is now sponsoring research into governance of solar and geoengineering. And we just had last week Switzerland calling the United Nations to think about this more. I don't know that we're out there on consensus that there's been a lot of talk about how do you do governance? That's the kind of easy thing to do in theory, right? But it's not to solve because one nation can just go do this, like take two kilograms and spew it up there. But that's been talked about a lot.

0:11:00.5 SC: All right, Paul, thanks so much for talking with me.

0:11:02.7 PV: Oh, my pleasure. Thank you.

0:11:04.0 SC: Paul Vossen is a staff writer for Science. You can find a link to the news article and a related Science Advances paper at science.org/podcast. Stay tuned for a chat with Science Robotics editor Amos Matsiko about merging robotics and medicine.

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0:11:27.8 SC: Last month, Science Robotics published a series of articles focused on medicine and robots. The journal's editor, Amos Matsiko, is here to talk about it. Hi, Amos. Welcome to the Science Podcast.

0:11:37.9 Amos Matsiko: Hey, Sarah. Thanks for having me.

0:11:39.5 SC: All right. So let's start with basics. I read at least the titles of everything that comes through robotics. I tend to keep an eye on it. There's interesting video in there. It's very cool topics we cover on the podcast. And I have to kind of ask as the basic principle, what is a robot? Is it a little piece of folding metal that can spring around in response to temperature change? Is it a tiny helix inside the human body that spins in response to magnets? Is it an arm that has a job? Or is it a blubbery, rubbery thing that moves around because of air pressure? I mean, all of these things I've seen written about in Science Robotics, what's the common theme and what makes them robots?

0:12:17.2 AM: It could really be all of the above that you mentioned. So there are various definitions of a robot. But broadly speaking, a robot is a system that is capable of carrying out a specific complex task or a series of tasks through either direct control from an operator or through pre-programmed actions, or even autonomously with the aid of intelligent control systems so that the robot can interact with its environment. Robots should really be able to sense the environment, make some sort of decision and take appropriate action.

0:12:47.0 SC: So a lot of what I've described is researchers pulling together pieces that could eventually make something like what you're describing.

0:12:54.5 AM: Exactly.

0:12:55.3 SC: How they move or how they respond or how they sense, all that stuff needs to be tried out in pieces and then put together into a formally recognizable robot.

0:13:04.3 AM: Yeah, exactly. I think many years ago, and still even today in science fiction, robots were only seen as being anthropomorphic, meaning that they need to have physical characteristics similar to a human. So we're talking arms, legs, a head and so on. But now there's a diverse range of robots in many aspects of life from the factory floor on assembly lines, to the hospital for all sorts of many complications. And even in our homes, I know quite a few people today that have a Roomba robotic vacuum cleaner, and it's one of the most widely used consumer robots. And they're really quite intelligent. You know, they can create a map of a room, they can plan their navigation as they vacuum the floor, and some can even change the vacuuming settings depending on whether they're moving on a wooden floor versus whether they're on a carpet.

0:13:49.9 SC: One of my favorite things that the journal does is this analysis of sci-fi and robotics along all these different themes. So for example, how does sci-fi do at predicting medicine robots or medical robots? And we're gonna, we're gonna get to that at the very end here, but I do think we should start with why is now a good time to focus on this intersection of human health and robots? What's going on in the field that made it ripe for this discussion?

0:14:15.2 AM: This is one of the key areas of Science Robotics due to the broad societal implications. Recently, there have been a number of advances that have led to the development of more capable robots, which have ultimately opened up new opportunities for robots in many applications in the clinic. In particular, advances in areas like computer science, specifically with regards to control and autonomy, and also advances in material science. There are now more possibilities of deploying robots in the medical arena than ever before. So this special issue that we're publishing in February, we're focused on studies that harness magnetism in medical robotics in new and unique ways as well.

0:14:54.8 SC: Should we take a little dive into history before we go into the paper? So when I think about robots in medicine, I think I think about robotic surgery. Is that kind of one of the main contributions or what are some of the other ways that robots have participated in medicine in the past?

0:15:10.2 AM: Robots have been used in the clinic for quite some time. So for diagnosis, for example, there are robots which are used now for triaging or pre-screening patients, similar to how a general practitioner can ask a series of yes/no questions in order to narrow down to a possible medical condition. There are now robots which can do these quite autonomously and cleverly. There are also robots which can carry out dermatological scans, say for diagnosis of skin cancers. There are also several robots which have been developed to aid surgeons to plan procedures. For example, there are research groups which are working on developing soft robotic models of the heart based on actual patient data. So there are several tools which can be used in the preoperative stage of care, but also as you said, robotic surgery, perioperative care. This is also quite important in the robotic space. You probably heard of the Da Vinci robot, it's one of the most widely used robotic devices in the clinic today.

0:16:04.1 AM: It's got a number of articulating arms, which are inserted into the patient's body, and the surgeon can control these robotic arms. The surgeon can also visualize the tissue with

stereoscopic cameras. There are also some other robots for rehabilitation. And most common one is an exoskeleton suit, and it can be used to provide assistance to patients with motor disorders. For instance, patients who are recovering from stroke. There've been studies which have showed that exoskeleton suits can actually enhance their recovery and improve their gait and balance, just after a couple weeks of training with exoskeleton suits. Robots have been used quite broadly.

0:16:41.2 SC: Really end to end.

0:16:43.7 AM: Exactly. Yeah.

0:16:44.3 SC: Yeah. So what we're gonna talk about today is a little bit more of a slice of it. So this is robots controlled with magnetics. One of them I looked at, and this is something that always gets me when I'm looking for videos to like put on our various channels, TikTok, Instagram, whatever it is, robots that swim around inside the body. They're tiny and they can get places that maybe you wouldn't normally be able to get. So what's going on in the space? What do, what do we have in the journal this month about that?

0:17:12.0 AM: Yeah, so you're probably talking of micro-robots, these as a name suggest, micron sized. One of the studies by Jin-Fang Zhang and colleagues at Guangzhou University of Science and Technology, they focused on treating cerebral aneurysms using soft magnetic microfiber bots. An aneurysm is essentially a bulge in a blood vessel due to weakness in the vessel walls. And if these aneurysms burst, they can cause some really serious problems. And currently in the clinic, they can be treated by inserting platinum coils to seal the aneurysm. But there are also other conditions which may require a blood vessel to be blocked entirely, such as in a procedure called tumor embolization.

0:17:51.3 SC: Whereas you cut off the blood supply to the tumor so that it's starved and that the cells start to die.

0:17:56.6 AM: Exactly. And so the authors in this study developed an approach which delivers these microfiber bots minimally invasively, using magnetic fields. So rather than using a catheter which is inserted into blood vessel...

0:18:08.8 SC: It's a very long thing, right? It just keeps going and going. It stays connected and it gets where it needs to go.

0:18:14.0 AM: Exactly. Yeah. So rather than doing that, why not use magnetic fields, which doesn't necessarily need direct control of the microfiber bot itself? That was one approach that used microrobots. There was also another study which was done by Sylvan Mattel and colleagues in Canada. They're essentially focused on improving the delivery efficiency of magnetic robots to target tissue.

0:18:37.0 SC: So this is more about not necessarily the job they're gonna do when they get there, but how to get them there in hard to reach places that maybe a catheter couldn't go or it's deeper in the body where it's harder to steer things?

0:18:49.5 AM: Exactly. Microbots are usually administered by basically injecting them into the blood vessels and the surgeon can use magnetic field to control their motility. But because they're very tiny, there are issues with regards to the effects of gravity and also blood flow, which can affect their efficiency in reaching these targets. And so the authors developed an algorithm which can determine the optimal patient position or orientation in an operating table that would essentially allow gravity to aid navigation of the microrobots.

0:19:19.4 SC: Do they keep moving the person as the robot moves through them?

0:19:23.6 AM: Not necessarily move the person in real time, but the algorithm can determine the optimal position that would take advantage of gravity so that these microrobots can reach their targets quite effectively. And they also did some studies in vivo to target the liver, and they showed that just by repositioning the animal...

0:19:42.6 SC: This was pigs.

0:19:43.5 AM: They could increase the efficiency from 47% to well over 86%. This is really quite impressive.

0:19:51.7 SC: And that's a hard to reach spot. It's very deep in there. It's very hard to get a field in there that you need that's not going to hurt you or the robot. So that's really amazing.

0:20:01.5 AM: Exactly. If we're talking of drug-loaded microrobots, this is really key that you get to the desired location because you don't want to have the drug suddenly being eluted in the wrong location. So this is quite an important study in something as simple as the position of the patient having a really huge impact.

0:20:19.6 SC: I could imagine a robot turning a person very smoothly as the microrobots are inside the person. Just like, oh my goodness, this is very sci-fi. All right. So I think there's a few more papers we should touch on before we go to sci-fi. So let's talk about one more paper in the special section and then we'll let people find the rest on their own. What else should we touch on?

0:20:39.7 AM: Another study in the issue by Bradley Nelson and colleagues at ETH in Zurich, they featured a very flexible and dexterous continuum magnetic robot. And the aim of this study was essentially to reach millimeter-sized vessels in the brain. So I talked earlier about stroke and brain aneurysms and these are really serious conditions, and each minute in delay in reaching specialist care can have really big consequences in terms of severe physical and neurological disability and ultimately even cause death. There's actually a phrase called time is brain, meaning that time is really critical in order to save brain tissue.

0:21:15.3 SC: Yeah, absolutely.

0:21:16.3 AM: In this study, the authors utilised a number of techniques to improve access to the target tissue with something called the continuum robot. This robot had a number of unique features. So first of all, on the outer surface of the robot, it had helical protrusions. Once it's deployed into the blood vessels, it uses rotation, kind of like a corkscrew, in order to enable forward motion. And secondly, the authors also used an articulating magnetic tip, meaning that it can generate greater bending angles.

0:21:46.5 SC: So it can go around corners.

0:21:48.2 AM: But not just any corners, but very sharp corners.

0:21:50.6 SC: Right. Like branching blood vessels, like it can go back through a very angled section. And that's super important for getting up into the tiny vessels in the brain where some of this danger is. Oh, wow. Okay. So there's more to read. Please do check it out. We're going to link from the episode page. Now, I do have a question in here about the future. What are some of the areas for growth that people are going to be looking at maybe five, 10 years from now in robotics

and medicine?

0:22:17.1 AM: Material science is going to be quite important. Making materials that have more capabilities, but also materials that are safer to be used in the human patient. Also, computer science and artificial intelligence are going to play a really big role in making medical robots more capable. For example, there are a couple of studies that were published recently. One was on an autonomous system for anastomosis of the intestines. It was a system that was capable of stitching intestinal tissue autonomously.

0:22:48.5 SC: So if you've got a hole in your intestine, the system can then repair it from inside?

0:22:53.3 AM: Exactly. But it can also be used to aid a surgeon because suturing is not quite as challenging as some other procedures within surgery. So if you can develop a system that ca autonomously suture at the end of a procedure, then that will certainly help with the entire operation.

0:23:10.1 SC: Okay. So I don't want to miss talking about sci-fi. This is always, I love it. Of course, I'm thinking as we're talking about Prometheus, that movie where there's a surgery robot. It's like one of the Aliens movie, which is ridiculous. I don't even think it deserves any judgment from us. It's just a fun movie. But do you feel like, has sci-fi been predictive of the direction of robotics and medicine?

0:23:33.5 AM: Not just medicine, but technology as a whole. I think sci-fi and technology have been intertwined for quite some time. And there are now so many cases where sci-fi inspires technology and vice versa. There was a novel, a short story called Microhands by an author called Boris Stepanovich Zhitkov. And this featured an inventor who creates a pair of micro-sized mechanical hands, which he uses for robotic surgery and tumors. And these microhands were controlled remotely by gloves which have haptic feedback. And the inventor uses microscopic glasses to visualize the microhands.

0:24:10.4 SC: That is so many things that people are trying to do right now.

0:24:14.0 AM: Exactly. So that's quite similar to what's happening today.

0:24:16.9 SC: And that book is like 100 years old, maybe a little bit less?

0:24:19.8 AM: It was published in 1930. So just slightly less than 100 years. And one of the key things with the book is that it highlights some really big challenges that still need to be addressed today in order to make these microrobots or medical robots applicable in the clinic. As you scale down in size, there are many issues in terms of how do you navigate through tissue? How do you visualize tissue?

0:24:43.4 SC: We're good at driving cars.

0:24:45.3 AM: Exactly.

0:24:46.0 SC: And so we kind of have all these analogues that we can build into computers for driving cars, but we're not really good at driving little tiny, you know, paper clips around. That's a totally different mindset for the forces involved and the considerations. It's super interesting. Yeah.

0:25:02.2 AM: Yeah. So science fiction has really played a part, as I said, inspiring researchers, but also researchers can inspire science fiction alternatively.

0:25:10.8 SC: Do you have a favorite robot out there in the real world, in sci-fi movies? Can you pick a favorite?

0:25:18.0 AM: I always gravitate towards medical robots in sci-fi. 'Cause That's sort of something I'm passionate about. In the movie Ender's Game, it actually featured a surgical robot that performed brain surgery to make a human with superpowers, essentially. But what was particularly interesting in that was that this was an actual surgical robot that was developed by researchers in the University of Washington. This was an actual robot that somehow appeared in a sci-fi movie. So that was quite cool.

0:25:45.5 SC: But obviously the robot's purpose is not enhancing humans.

0:25:48.4 AM: Sure. Sure. Exactly. Yeah. There was also another movie. You may have seen it called Robot & Frank. It's actually a comedy, but it features a companion robot, which was given as a gift from a son to his elderly father who is suddenly developing progressive dementia. And although the elderly individual was initially against the robot, he subsequently formed a strong friendship with the robot. I think in the future, we're going to have companion robots being deployed in all sorts of populations, not just the elderly, but also children in high schools as well. Yeah, I can see them being quite diverse and...

0:26:24.5 SC: Just like Megan, right?

0:26:25.5 AM: Exactly.

0:26:28.4 SC: All right, Amos. Thank you so much for coming on the show. This has been really interesting.

0:26:31.2 AM: Thanks for having me.

0:26:32.1 SC: Amos Matsiko is the editor for Science Robotics. You can find a link to the works we discussed at science.org/podcast.

0:26:40.4 SC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at science podcast@aaas.org. To find us on podcasting apps, search for Science Magazine, or you can listen on our website, science.org/podcast. This show was edited by me, Sarah Crespi, and Kevin McLean, with production help from Megan Tuck at Podigy. Jeffrey Cook composed the music on behalf of Science and its publisher, AAAS. Thanks for joining us.

[music]

0:00:05.6 Sarah Crespi: This is the Science Podcast for February 23rd, 2024. I'm Sarah Crespi. This week we have news hot off the presses from the AAAS annual meeting in Denver, newsletter editor Christie Wilcox attended and she brings us tales of tracing horses in the Americas and seeing the world through the eyes of AI using so-called image omics technology. News intern Sean Cummings also shares a conversation from the AAAS meeting with researcher Danielle Wood. They talk about using outer space to bring sustainability and equity to us down here on Earth.

0:00:43.0 SC: Next on the show, what makes snakes so special besides their amazing leglessness. Freelance producer, Ariana Remmel speaks with researcher Daniel Rabosky about the drivers of all the different ways that snakes have specialized from spitting venom to sensing heat.

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0:01:03.9 SC: All right, so now we have Christie Wilcox. She's the Daily newsletter editor, but she also attended the AAAS annual meeting in Denver last week. She attended lectures, ceremonies, panel discussions, and just the whole time sending me audio clips and audio clips and audio clips, which is great. No complaints. Christie, how was the annual meeting?

0:01:26.9 Christie Wilcox: It was so much fun. It was a whirlwind, although it was a little cold. Definitely it was cold for my coastal Pacific Northwest body, and I'm not used to that altitude, but it was so much fun. So, so much fun.

0:01:42.9 SC: What I definitely want to share is where you managed to talk to so many people on the same topic. I think it's really interesting, and this is a conversation with this, the winners of the Newcomb Cleveland Award.

0:01:52.3 CW: So it's the Newcomb Cleveland Prize. It's the oldest running award that AAAS has.

0:01:58.2 SC: Yeah. And this is for a science paper that talks about ancient DNA and tracing the arrival of horses in the Americas. Can you just give us a super quick summary of the actual paper and its results?

0:02:11.4 CW: Yeah, so what they were looking at is horses originated in the Americas, but then some 10,000-ish years ago, they crossed the bearing land bridge into Eurasia and didn't look back. And so they were gone from the Americas. And then it wasn't until about 1519 when we had Spanish arriving in Mexico, that horses came back to the Americas. And it was long thought by Western scientists anyway that those horses didn't really make their way up across the Great Plains and into the Rockies until more like the 18th century. It took a couple of hundred years is the way that western scientists thought.

0:02:53.8 SC: To go from Mexico to the American West.

0:02:56.9 CW: Yes, but the indigenous peoples that lived in that area have long had these stories and oral traditions and science saying that no, we've had horses forever, man. And so there was this conflict between what the Western scientists thought had happened and what the native tribes and the indigenous peoples thought had happened. And so what they did in this paper is it was the Lakota actually went to scientists and said, we have all of this information in science. We want you to look into this with us. We want you to work with us and do the science to show what really happened.

0:03:34.6 SC: Okay. Let's bring in some of the people that you talked to about this paper. There were a lot of authors on it, and I think you grabbed about four for this conversation.

0:03:43.0 William Taylor: So I'm William Taylor. I'm an assistant professor and curator of archeology at the University of Colorado in Boulder.

0:03:48.5 SC: William was originally working on the history of horses in Eurasia on the Steppe, and then he was able to collaborate with all these different groups from the American West, which is actually where he's from. And here he is going to talk a little bit about how this connection with the indigenous perspective of the Lakota and other groups really supported the research in unique ways.

0:04:08.3 WT: For example, one of our really important finds came from southwestern Wyoming. We're able to talk over the significance with folks who knew that oral tradition and the indigenous perspective on their history and their story. And so we started to realize that what could have been dismissed as an archeological result that didn't fit the narrative coming from historical records, instead got to be embraced by folks who were bringing that expertise. And so not just our Lakota leadership here, but also our partners with the Comanche, Pawnee, Pueblo folks that really able to, in part because of this sense of sort of friendship and trust, share the ways in which that oral tradition was being reinforced by the emerging archeological discoveries.

0:05:00.8 SC: So what they found is that the native tribes were right. Those horses moved across the Americas much earlier than Western scientists thought. They found this because of ancient DNA, but also they found horse bones and they found the actual bones that dated back to the 1500 and 1600s when supposedly horses weren't in the American West.

0:05:23.1 SC: All right. We're going to switch voices here. This is another Sarah. This is Sarah Trabert. She's an associate professor in the Department of Anthropology at the University of Oklahoma. And back in 2017, she was talking about these horse bones that she found in an ancestral Wichita site. She was talking about this at a meeting and met with William Taylor.

0:05:45.8 Sarah Trebert: I think my poster abstract had horse as one of the key words because we're really excited because horse bones are relatively rare to find in context archeological sites. And Will Taylor was searching through the program for horses. He saw me, stopped on my poster. We went and had drinks, and he was just really interested in learning more about horses on the Great Plains, and I'm a Great Plains archeologist. And so that's how I ended up connecting with Will. And then it just snowballed from there.

0:06:13.9 SC: It's interesting because for the paper for the method, they did end up using an older technology radiocarbon dating to update our ideas about what was happening with horses at the time.

0:06:25.2 ST: What's key here is that we're applying technology to horse specimens and bones that had long been thought to be much older in times like Pleistocene era horses, because there hadn't been a lot of research attention on the idea that you could actually find horse bones that are later in time from the 1500s onward after the Spanish reintroduce horses to North America. And so radiocarbon dating was the first step is to identify which horses are pleistocene era and which would've been kind of before Spanish colonialism, and which horses were much more recent that we tend to associate with tribal nations today.

0:07:00.3 SC: So on top of radiocarbon dating, the researchers looked at isotopes and teeth and marks on bone to show that these weren't just wild horses that wandered and managed to survive. Here's William Taylor again talking about this human-horse relationship as evidenced in the bones.

0:07:16.7 WT: I think some of the really important things are just these snapshots that show us the complexity and the depth of that horse relationship. So we have a snapshot from Kansas, which shows us a horse that was ridden, a horse that was fed corn in the winter with a snapshot from southwestern Wyoming that shows us a horse that was integrated into ceremonial practices, but also given veterinary care and raised locally, right? Each one of these contributing little different pieces, but as we sort of see them stitch together, this incredibly rich kind of tapestry of that antiquity of that horse relationship began to emerge. And I think because of the investment of so many partners, especially on the native end, we were able to really understand the connections that folks like myself could have missed with a different team.

0:08:12.2 SC: One of the things that's so important about this is this collaboration between different tribes and scientists that work in ancient DNA or scientists that work in the history of horses. It was a big collaboration with kind of a lot of give and take.

0:08:26.2 ST: Not only was it difficult to get all these different perspectives and people together and they had to work really hard to bring everyone onto the same page, it took a lot to literally bring them onto the same page. I mean, just even from the very beginning, just submitting the paper.

0:08:42.3 WT: Every stage of this process tested the limits of the scientific system. That begins literally with entering people's names, the actual letters involved in inputting the full Lakota names. The system wasn't equipped, so we had to have editorial assistance from the beginning helping us with very unconventional requests. Our editor, Dr. Vinyere, but also this whole team of folks, Valda, Corinne, even Taholden, had to think through things like, how do we incorporate Lakota translations of a concept into our supplementary material? Or can we put an actual quote, the words of our elders, Loretta, chief American horse, directly into the text?

0:09:31.6 ST: The sentiment that William and a couple of the other researchers shared that this is sort of a proof that we can do this. We can bring together these many different perspectives. We can include all sorts of scientific systems in our research, and it's not one way or the highway.

0:09:48.4 WT: These are things that are totally new and different and sort of shocking to the system that we have in place. But there's a tremendous amount of bravery, compassion, and kind of persistence from folks at every step of the way. And I think the legacy of that, we'll probably outstrip the individual findings of this paper or this award or anything.

0:10:14.6 SC: We're gonna switch to Yvette Running Horse Collin. She's a researcher at the Center for Anthropo Biology and Genomics at the University of Toulouse. She has some thoughts on the future of this collaboration.

0:10:25.5 Yvette Running Horse Collin: Around the world, you can see that organizations, governmental systems, people are asking for indigenous peoples to step forward with their traditional knowledge and their sciences. We have our own scientific systems that developed completely separately of the Western scientific system. At least for us as Lakota, our entire scientific system is based on the sustainability between all life forms. So it's a critical time for us to be able to come forward and begin this conversation in this way. And for us, receiving this amazing recognition is such a beautiful platform and it sends a message to the world that this is a good time for this now, and we can create a safe, respectful place to have true scientific exchange and dialogue.

0:11:19.2 YRHC: In our way collaboration is very deep, it's very intricate, and it's completely connected. And in western science, that's not often the case, right? People maybe put their piece of

knowledge forward and then they put something together that's different for us. And so it was wonderful that our collaborators were open and willing to understand the level of collaboration that we do, and it allowed us to get to this point. Now, for us, this is very much a beginning. We're very excited about where this is gonna go, and it took us years to learn how to work fluidly together like this. Now, we're ready to roll.

0:12:00.2 SC: Alright, Christie, this is super cool. Thanks so much for talking about the horse paper, which is basically what we've been calling it for an entire two-year period. But let's also talk a little bit about what else you did at the meeting. Who else did you get a chance to talk with? What else did you see while you were there?

0:12:15.7 CW: Yeah. Oh gosh. It was such a good meeting. There were so many amazing sessions that I attended. I think one of my favorites was a session on imageomics, if I'm saying that right. They tried to make us practice it, so I'm hoping I'm saying it right. So they basically have started this new discipline of science, which looks at imagery or visualizations, both from things like pictures, literal visuals like that, but also LIDAR data and these other sorts of visualized data streams and taking that and using AI and our amazing computing power that we have now to analyze all of this data and create computer vision, not just human vision.

0:13:06.4 SC: Can you say the word again?

0:13:08.7 CW: Imageomics. I think.

0:13:10.8 SC: Can you spell the word Christie? I have not got it.

0:13:13.7 CW: It's image omics.

0:13:15.1 SC: Okay. Omics. Image Omics.

0:13:16.9 CW: Okay. Image omics.

0:13:18.3 SC: Image omics. So we're adding omics to things when we are just fire hose of data. You got to figure out patterns. And then this is patterns in the visual. Oh, it's so interesting.

0:13:30.4 CW: Yeah. And it was really fascinating because, I mean, they showed a whole bunch of different projects, but one of the ones they talked about was this project turning an AI into a taxonomist essentially. And so they taught this model, this algorithm, to look for traits in a very piecemeal way. So if I'm trying to identify a bird, I don't sit there and just look at the whole picture and say, oh, that's a bunting or whatever. I'm looking at what color is the eyes or what color is that band on the wings? What color are the feet? These very different discrete traits. And so this AI that they built does that. It looks at and from its own set of data, figures out what those traits are and where to look, and then looks at them all and then can classify really closely related species, but tell them apart, this AI can look and see what are these really tiny differences between the mimics and the regular species. And it can tell the species apart. It blew my mind.

0:14:34.6 SC: Are they using the UV?

0:14:36.4 CW: No, no, this is just from regular pictures.

0:14:40.0 SC: Oh, it's so interesting.

0:14:41.1 CW: I mean and that's fascinating. But then they also were able to do what they call

butterfly vision or bird vision. So they were able to take things like the known visual acuity of butterflies versus humans versus birds, and then "look at these images" with these different acuities and see how the butterfly, because the butterflies need to be able to tell each other apart. They need to mate with the right butterflies.

0:15:07.8 SC: And that's how you learn about the evolution, right? You can't just say, well to people, these are the sexier butterflies. We need to know what the butterfly thinks of its friend over there.

0:15:18.3 CW: Right and how does it know that the four spotted one over there is the other species?

0:15:23.8 SC: So interesting.

0:15:24.9 CW: It was absolutely mindblowing and the kinds of information that they were pulling from this. And then I just really love the sentiment that also it can go beyond our vision because science has always been visual and the computer can see things that we can't, computer vision isn't constrained by our vision, and they showed that with the bird versus human vision. Then they're like, do you see a difference between these? And everyone of course is like, no, no we don't. It's like because the birds have better vision that they have a better visual acuity, so we can't see the acuity that they see because we don't have it. And so the two pictures look the same to us, but they did not look the same to the computer.

0:16:05.1 SC: Super interesting. Alright, Christie, thank you so much for coming on, for being our roving podcast reporter at this year's AAAS Meeting. If you want to find a link to the coverage of the meeting or a way to subscribe to the Daily Newsletter Science Advisor, just visit science.org/podcast. It will be linked from the episode and yeah, thank you so much, Christie.

0:16:28.4 CW: Thank you for having me.

0:16:30.2 SC: In addition to the conversations that Christie was able to capture during her time at the annual meeting news intern Sean Cummings also grabbed us some fascinating tape. He spoke with Danielle Wood, director of the Space enabled research group at MIT about the sustainable use of orbital space and how space exploration and research can benefit everyone.

[music]

0:16:56.3 Sean Cummings: Sometimes to create positive change on earth, you've got to look to the stars. That's certainly true for Danielle Wood, an aerospace engineer at MIT interested in how space technology and research can promote justice, accessibility and sustainability on earth and in space alike. I sat down with Dr. Wood before her presentation at the 2024 AAAS annual meeting to learn more. What's your scientist origin story going as far back as you can remember? How do you remember first becoming interested in space generally and then in the more specific approaches towards space science that you've become interested in?

0:17:28.3 Danielle Wood: I grew up in Orlando, Florida, and we had opportunities to basically see what NASA was doing from the point of view of launching from Kennedy Space Center and when I was young, I was also in my mom's classroom for a couple of years. She had a policy when there were announcements about space mission launches that we would go outside from class and try to see it. She invited somebody who had experience working in the space program to come to our class and do a rocket launch day. I picked one of the roles to let me help push the button, actually launch the rocket that day. I thought I really won. So I think things like that were just ingrained in our

culture. This idea that space is exciting. It didn't mean that I planned to have a career in it, but very fortunately in my high school, we did have some great teachers and guidance counselors and one of them advised me to apply to NASA's Summer Highschool Apprenticeship Research Program called SHARP.

0:18:12.8 DW: And I was there for the launch of the Chandra X-ray Observatory. It was in July, 1999, and it was special because Eileen Collins was announced as the first female commander of space shuttle mission. Also on the flight was Dr. Catherine Coleman. A night launch is a special kind of thing. The light from the launch fills the night sky for a few seconds as if it's daytime. A little bit later after the light, you feel the power of space shuttle in the mission hits you as a sound wave and you just think this is something almost impossible. And yet, they're somehow launching this telescope to take X-rays into space on this crazy rocket. And there's two ladies over there apparently that are awesome, that have PhDs. What a great place to work. So I decided to study aerospace engineering because of that. But even though I was really excited about it, I had another question which was that let's look at the broader community of black women.

0:19:02.0 DW: And many of them don't get to go to my team in the US but also across the world. And I thought, well, that is not fair and I think if I'm so lucky to be here, how can my life somehow address these kind of unfairness aspects of life? A friend said that she was going to go volunteer at a school in Kenya over the summer, basically after my first year in college. And that seemed like an interesting opportunity to link back to my issues that I saw. So I spent the summer of 2001 visiting and working at this school and doing lessons in English and math. I went back to that school two more times and I kept asking, can I get involved with projects related to African development opportunities for girls to have better education and also still work at NASA or some space program? And eventually, I met some NASA people who had similar questions. They wanted to use NASA technology to help people in different countries and to kind of think about who had sort less access to basic services, education, food, protection for the environment. And I thought, oh, these are people that have the same value I have and actually work for NASA. Amazing. And that totally switched my plan. Then I said, I'm going to dig into being in the space community here, but I'm going to try to ask how it can be involved in space and keep my interest instead of African development or equal access to education and rights of women. All central in what I do.

0:20:09.7 SC: What does it look like for space exploration and technology to be used or designed for everyone? This line I saw in your bio, it's all over the place, space for everyone. So what does it look like for space engineering technology to be designed for everyone with justice and accessibility in mind versus not doing? So, are there any examples that come to mind?

0:20:31.3 DW: It's great to think about what it means for space to benefit everyone. I think there's two dimensions to ask. I often say, I first would ask how can I redesign space systems that were not designed for everyone, but it could be fixed, I'd say to make them more effective. And the second would be, what about the new things we haven't built yet? Lemme start with the case of things that already exist. A great example is the global positioning system. When the US was first building this technology, it was directly for the purpose of guiding missiles. And you could say, well, there's some benefit if you guide a missile more effectively, you can avoid hitting civilian targets and try to hit military targets. So hopefully fewer civilian casualties. But nonetheless, it is an instrument of war. It turns out that many groups besides the military would like to know where things are, like to know where they are and where vehicles are and where items that have the little sensors on them are.

0:21:14.5 DW: And now so many of us depend on our daily life satellite based positioning. Throughout my day, I'm like, I need to go from here to my hotel. I need to check in. I'll be using satellite positioning throughout. But even from very particular humanitarian things like during a

disaster, there may be a need to have positioning information and you're doing animal tracking to try to investigate invasive or endangered species. So there are examples where that has gone from being particularly military technology all the way into a true social benefit that so many of us would depend on. Another example of this, just close with this in Chile and South Africa, they have a natural advantage based on their location and the weather and the weather patterns, atmospheric patterns. There are places in those countries where it's ideal for doing ground-based astronomy. There's been indigenous astronomy in those areas.

0:21:54.7 DW: So the people who live there, they know that astronomy is what you do in those places for many generations. So Chile is a great story where they've been a popular place for international telescopes for a long time. And certain researchers who've highlighted, there are some periods where many international players where come to Chile and invest in telescopes and international people would have observation happening in Chile. But Chileans were not so much involved. The Chilean government said, oh, we want to consciously ask how do we involve the Chilean universities and the Chilean school children and make sure there's a pipeline of next generation astronomers or people in related fields who are benefiting and making laws for example, that international telescope must include Chilean researchers as well. So these days there's much more of a connection between an international benefit of having many people playing in Chilean space, but also the Chilean community. So I had a chance to go to Chile and meet the Chilean astronomers. Many would say our PhD program was enabled because our government put this in place. I met school children who are part of communities that go around to their neighbors explaining the benefits of having a natural environment where you can have excellent astronomy and they have little t-shirts that say we are the protectors of the night sky.

0:23:00.7 SC: The other thing was designing new technologies. So what are some new systems or tools or technologies for promoting justice, accessibility, sustainability through space that you and your team are excited about?

0:23:11.7 DW: The one that I'd like to talk about partly as a proof of concept. I'm trying to prove that I can use beeswax as an ingredient for fuel on small satellites in space. If I feel like if I do that, then it throws up many questions and one of them is like, why can't we use national materials that don't cause climate change in their production? And beeswax is interesting. The reason I'm inspired that way, it comes from collaborating with others who have been studying candle wax. There's also a very beautiful idea. Candles are certainly a peaceful image, and there's a team at Stanford that identified in the '90s that the candle wax, common paraffin, it can be combusted. It's actually just made from carbon hydrogen. So you can mix with oxygen under pressure, it burns and it's low cost. It's just that most candle wax in our current market comes from the production of fossil fuels. And it's sort of a natural byproduct. So it's very plentiful and affordable because it's, we do a lot of fossil fuel production.

0:24:02.2 DW: So that's fine as a starting point, I guess a good place to research. But I thought, well, there's other waxes. You can make waxes from plants and from of course animals. Bees make them naturally. Just to think could there be this material? But also the actual production process is actually a carbon sink rather instead of a carbon source. And so part of what I'm doing now is a series of experiments, first on planes and then on rockets and then on the space station just to find out how the manufacturing would work in space. And then later, I want to try actually combusting the wax. I'd love to have this question of could I learn, is there potentially interesting question of having compared the different bees in different waxes, do they behave differently also when I want to manufacture, in this case a grain of fuel in gravity. Maybe, maybe, I don't know that the melting and the density and sort of the reaction to low gravity could be slightly different for different kinds of beeswax.

0:24:49.2 DW: So if so, I'd love to know that. And then they'd be able to say, this country has a particularly wonderful beeswax to be used for space and that country will become a space exporter.

0:24:58.0 SC: What are some of the most common or most significant roadblocks that you encounter when trying to either design these new systems or technologies or redesigning old ones for justice and sustainability?

0:25:11.6 DW: So a great example, I think one that I really, I spent a lot of my time on is asking, why is it so hard for people to use NASA's food data about the environment? You can take measurements from space using optical light or using radar and using lasers, and you can get all those types of measurements about the atmosphere, about the polar ice gaps, oceans, inland water, trees, many of the other things. So the data gets put online, these interesting websites, many different websites. So first you have to know where it is and it's free as scientists can go download them. And they were designed for people who do Earth science and have PhDs in Earth science. So the assumption is that the person who might download it had mentorship from somebody else with a PhD who taught them some specialized software tools and they have expensive computers and they have time to sit down and work through all the data sets and really understand it and then use it.

0:25:56.9 DW: All of that's super helpful if you're a scientist. So what's not true is if you're a policymaker addressing mangrove management in Brazil or addressing cultural resilience in Indonesia or addressing drought in Angola present in all these areas. You didn't have time. You did other things with your life. You didn't get the PhD here in remote sensing and microwave sensing, it's not your specialty, right? You're a specialist in drought response. So it's true, you can have free data and that's great, but it hasn't yet been customized local solutions or designed such that people who don't have PhDs in our science can use them. And it's possible to overcome those, but it takes time and money. So we often are asking, what's the balance between technical quality of information and convenience of using it.

0:26:35.9 SC: If using space technology to promote sustainability on Earth means putting these satellites up in space to sense things like soil moisture or whatever else you wanted to sense back on Earth. It seems like that might be counter to sustainability in space because putting more and more of these objects up there.

0:26:50.2 DW: We're at a critical point, and I would actually say a dangerous point or a point of great concern where we are able to send things in around the Earth on a regular basis and we've almost sent too much. We don't exactly know how much too much is, but we probably are getting close to it, which is so many things in space that we can't track them all at the global scale. It's not a central place to have document where all things in space are being operated. Plus there's many objects that are not. They're derelict, they're old, they're trash, and no one who is actually operating officially anymore. You can't talk to 'em anymore. That kind of behavior of creating hazards and leaving trash and having unsustainable behavior is the wide is spread, right? If you go to the moon, if we go beyond the moon, if we have stations living, they're orbiting around the Earth. So that what I want to say is our responsibility toward behaving well is going to get critically pretty important.

0:27:33.9 DW: And we haven't finished planning that or thinking clearly about it. I used to be focused entirely on the part of like, let's have satellites in space so that we can monitor the Earth. And then I became more sensitive to the idea. Two ideas. One is that my country, the US where I'm proudly born and raised, we have put a lot of things in space such that when I work with colleagues like in African countries, I start to realize, oh, the US is taking so much of the capacity of being able to operate in space. The other countries might want to also have their own access. One challenge is that the US does already take a lot of the popular places to operate in space and the other countries

would have more danger to go there.

0:28:04.8 SC: If there were just going to be one or two commonly held notions or stereotypes or misconceptions about space exploration, space technology, how it's done, how it's created, who does it, who it's for that you would like to dispel, what would those be?

0:28:26.3 DW: I have a long list of misconceptions about space. I'd love to dispel. I wish I could have 10 or so. Let me try to do two or three. One is that as a person who's grounded in African, African diaspora studies, I'd love to share that there are so many countries that see space as their heritage. And then I say, wow, people in my country in the US don't know that you're out here in Angola and Rwanda and Ghana doing this great work and how fun is it to share that? So point number one is there's space leaders all over the world. Point number two is that space is not the wild west because there are indeed treaties that were negotiated with a lot of clever diplomacy in the '60s and '70s. And by the way, one of the most importantly, those treaties, it says that, we wouldn't put weapons of mass destruction in space. So early on, there was some fear and some possibility as the nuclear age is opening that the US and Soviet Union could have put warheads that kind of sit on orbit all the time, pointed each other from space.

0:29:22.1 DW: So that could have happened. And I would say that the reason it didn't happen is either this treaty and those who looked around and said, we don't necessarily want to constantly at ready nuclear war, but our treaties do leave some flexibility. Since they did not know, the treaties could not have guessed all the technologies that were coming about, which means, well, you have to further clarify how to follow them over time. So it's really important. Good question. Just means that today's youth, they're in such a great position. Part of my fun job as a professor is to say, how do I get middle school students, high school students, college students in charge of answering these questions because it's their future that's coming up right away. I lead a program to train middle school students to program robots on the International Space station so that they can say they're already working on space robotics and they themselves could say, yes, I'm a space person and when I grew up, I'm going to be involved with voting on issues that might affect how we peacefully operate on Moon. And it started when I was 11, so that's my future.

0:30:09.0 SC: That was news intern Sean Cummings talking with researcher Danielle Wood about how space can benefit us all. You can find links to these talks and to the newsletters that Christie mentioned at science.org/podcast. Stay tuned for a chat with producer Ariana Remmel and researcher Danielle Rabosky about the multitudinous possibilities of snakes.

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0:30:39.5 Ariana Remmel: Snakes. These slithering sinuous serpents elicit a lot of strong feelings in people across both human history and cultures. Snakes are technically a subgroup of lizards, which together make up the order of scaly reptiles called squamata. But looking at the roughly 4,000 species of snakes found on Earth today, you'll see that these fascinating creatures have noodled their way into myriad lifestyles and habitats. So how did snakes as a group evolve to be so diverse? This week in science, Daniel Roboski and colleagues wrote about how snakes likely owe their extreme biodiversity to a burst of innovation early in their evolutionary history. Hi Dan. Welcome to the Science podcast.

0:31:22.6 Daniel Rabosky: Hi Ari. Thanks for having me.

0:31:25.1 AR: So why snakes? How did you become interested in this group of reptiles?

0:31:30.9 DR: That is a question that the answer to which goes back a long time, and I've always

been interested in snakes as a biologist from when I was a child with snake enthusiast. But more generally thinking about the kinds of questions I've been working on in my career. One of the things that we are really interested in is the diversity of life. One aspect of that, that often isn't appreciated. Everyone's familiar in some ways with the fact that there are these spectacularly diverse groups of organisms on the planet.

0:31:58.9 DR: But paired with that, there are often many, many other groups that aren't particularly diverse. And there are many groups that have been downright species poor throughout much of their existence or groups where we can look back in deep time in the fossil record and see that they have barely changed in terms of their anatomy, their structure, their way of life. It's a real pattern. It's played out over and over again.

0:32:21.7 DR: So one of the ways we try to get at that question is by taking a very large view of groups of organisms like the squamate, reptiles, lizards, and snakes with about 10,000 or so species. And so that gives us lots of instances of potentially of groups that have managed to diversify and lots of groups that haven't. So we wanted to say if we take this large view of lizards and snakes, can we find some of the keys that explain why some groups have become really successful and why other groups haven't? I would also say that when we define success, I'm using this sort of informally in the sense of has a lot of species or has become very ecologically diverse.

0:33:00.5 AR: Can you tell me a little bit more about how snakes are related to other reptiles? For example, what makes snakes different from lizards?

0:33:07.6 DR: That's a really good question with an answer that is surprisingly difficult to pin down precisely, From a perspective of a family tree, snakes are within lizards, so they're a group within this broader whole, and most of the traits that people would think of as snake-like end up not necessarily on their own being diagnostic of snakes. So there are in fact a number of highly specific anatomical traits that really make snakes unambiguously snakes. But from the perspective of all the informal kinds of traits that we might talk about like leglessness. So leglessness has evolved repeatedly across squamate reptiles. So many, many groups have lost their legs independently. It's one of the most remarkable things to me that there are so many groups of lizards that have these snake-like traits, and yet there's still this sense that snakes have done something from an evolutionary perspective that these other groups of lizards have not.

0:33:57.4 AR: So it seems like the evolutionary family tree of snakes and lizards and how they fit in with reptiles is incredibly complicated, which is what your team was seeking to investigate. So I wonder if you can tell me a little bit more about how you went about collecting evidence to see more about what these drivers might be.

0:34:18.8 DR: Early on, we decided that to address a question like this, we were going to have to work across several different types of data, and we wanted to bring them together. So on one hand we needed a really good evolutionary tree and understanding of the relationships between species, the timing of the unfolding of those relationships. That's this process known as well the structure is known as phylogeny or evolutionary history, and the best way of doing that now is frankly with genomic data, which we can use in conjunction with the fossil record to make inferences about time. And we had essentially DNA samples from, usually from museum specimens that had been archived in accessible natural history collections. These are specimens from around the world that spanned a large fraction of higher level reptile diversity. So we had about a thousand tissue samples like that, and we sequenced partial genomes from each of those.

0:35:12.3 DR: And we used all that information with a bunch of sophisticated computing methods for taking that genomic data and turning it into an evolutionary tree. On the other hand, we knew we

needed a bunch of ecological data, and some of these data are not very easy to get. So this is data on the diets of snakes and lizards in particular. So most previous studies have worked at that much coarser scale of essentially coding species as eating vertebrates or eating insects. We said that is really a fundamental limit to how much we can know about how evolution has happened. We're going to take a completely different approach. We're going to go right to the raw specimens, get as many direct observations of what species we're eating, and we're going to synthesize all that together. And so the best way of getting that kind of information is from preserved museum specimens because you can access their stomach contents.

0:36:00.6 DR: And those stomach contents are this tremendous window into what an organism has been eating. We can go in and see, hey, here is a snake. It has this species of bird in its stomach, or here is this particular species of lizard, and it has this mix of termites and ants and beetles in its stomach. It's really difficult to collect that kind of dietary information without preserved specimens because a lot of these animals are very, very difficult to observe in nature. There are many, many animals in our dataset here where no one has ever seen them eating a thing in the wild.

0:36:32.4 AR: I would not have expected that museum specimens would also preserve stomach contents. But I guess now that's kind of obvious. Were you able to see a difference in the diets that snakes versus non-snake lizards have evolved to prey on?

0:36:48.9 DR: So honestly, that is one of the most striking aspects of our study. There has been speculation for a long time about ecological differences between snakes and lizards like herpetologists who specialize on these things, have this intuition for the idea that these things are different. That said, there has never been any broad scale quantitative synthesis that really gets at this particular question. And so with these 60-some thousand dietary records, and we looked at this and plotted these things out, we could immediately see that there was this massive fundamental shift between snakes and lizards in terms of what they're doing dietarily. And I mean, it is so different that to a first approximation, almost every lizard is essentially a specialist on arthropods, so your insects and arachnids and so on, and to a first approximation every snake isn't. So it is a really, really big split. And some of the really interesting things are that when you get these crossovers, what are those groups like?

0:37:50.2 DR: Turns out there's a whole bunch of interesting things that happen. When snakes go back essentially and eat the things that seem to be lizard like namely arthropod like insects or other invertebrates, it turns out that snakes usually eat different invertebrates then are being eaten by lizards. So for example, what you rarely see snakes specialize on are things like insects and spiders. But you will get some oddball lineage of snakes that have evolved specializations to feed on things like snails and slugs and earthworms. In some cases, what I like to think of as dangerous or armored or defended arthropods like centipedes or scorpions or spiders, but they don't eat, for the most part the things that are sort of the easy picking resources that most lizards tend to eat. Things like ants and termites and beetles and spiders and grasshoppers and crickets. Those things are largely off the menu for most snakes.

0:38:47.2 DR: And snakes really tend to specialize on vertebrates in particular. And the other thing I would add to that is there is a big difference, and this is another new to our study that I would say has been speculated about but never really tested, which is that snakes really are more specialized than lizards in terms of the diversity of prey items that they will feed on. So if you think about the dietary niche of the average snake species, it is much narrower in terms of the taxonomic things that it will eat than the average dietary niche of a particular lizard species.

0:39:21.5 AR: So in my understanding then that snakes as a group eat a larger diversity of prey items, even though snakes as an individual species might be very specialized in what kinds of foods

they're going after.

0:39:36.9 DR: That is absolutely correct. Snakes on the whole span a much broader range of total prey items, and yet if you look at any individual snake species, you find that they tend to be more specialized overall.

0:39:50.3 AR: So with all of these different data sources, what stood out to you in terms of the characteristics that contributed most to snake biodiversity?

0:40:00.4 DR: If I was to summarize this to the simplest possible explanation it is, I think the fact that snakes evolve faster than other groups, and we find that across the board in most axes or dimensions of snakes, whether it's their ecology, their diet, their anatomy, the way they sense the environment through their chemo reception, most of these aspects have not only shifted between snakes and lizards, but they are changing even to this day, faster than they are in lizards. It's like they just run hot. The whole snake evolutionary engine is running faster than it is in lizards. I think it's a huge question to figure out precisely why that is. One we can't answer with our data, but we can definitively say on some level that they have this property and it does separate them from lizards, and there's a really good reason why we think that that would be connected to their success.

0:40:47.8 AR: Did your results say anything about when this started?

0:40:52.0 DR: The answer that I think we have come up with in this sense is that it's complicated and perhaps even something that we will be unable to answer in terms of finding the precise trigger. But I can tell you that loosely we are confident that this sort of stuff happened from the late Cretaceous to let's say the Paleogene. So it is roughly around the time when non avian dinosaurs went extinct. So the way I would think about this is that there are all these things that have changed in the ancestor of snakes, perhaps in concert, where we have these synergistic changes happening in the way their skulls evolved, in the way they have evolved to use the landscape through their sort of locomotion in the way that they can sense the environment and acquire prey. And collectively, it seems that the outcome of those things is what gives us snakes today, this tremendous diversity of snakes.

0:41:43.0 DR: Now, if you are trying to establish the precise cause of a particular thing that has happened and it's really only happened once, then you are going to have a hard time with any degree of statistical confidence unambiguously saying that change X caused this particular type of outcome. That's one of the reasons that in the paper we use the word singularity. This is a word that has been used in cosmology, for example. It's sort of a one-off kind of event where your information that you had available to you before it happened wasn't sufficient to tell you that you were going to get this big sort of event. So in that sense, there's still this big mystery that's simultaneously why we think this and use the word singularity, but it's still also that we don't have confidence in the precise cause, and it may be something that we will never be able to establish causality for, especially if it's a one-off type of event that involved this synergy between multiple types of things.

0:42:38.6 AR: Does this tell us anything about conservation strategies or how we might better understand the natural history of these animals as our world continues to change?

0:42:50.0 DR: There are huge chunks of Earth's surface, often with very high species diversity, where most of the species are simply very poorly characterized. While it's not necessarily an immediate application of our work, it certainly showcases the importance of this type of basic natural history data for answering these fundamental questions about life on Earth. And I mean, I can't stress enough how few species on Earth we have these type of information for in general. And it is this enormous challenge for our field to recognize that we are living here in a world where

species are going extinct for a variety of reasons, or their populations are changing in real time because of human impacts, and we haven't even collected the most basic aspects of their biology, including things like what they eat, how abundant they are, how they use the landscape, what eats them, all of these things we need to really understand how life has come to be the way it is, along with what we need to do to conserve a lot of these organisms.

0:43:47.4 DR: And even worse than not having the data that we need, we are essentially burning that data in real time. So if I had one priority in that sense, I would say we should be collecting as much data about the world, and especially the places that are data deficient as quickly as we possibly can because there is not enough time and there are not enough resources to do this well, and it is the one thing that in 20 years or 50 years, we are going to most regret not having done.

0:44:15.0 AR: Wow. Thank you so much for joining me, Dan.

0:44:18.0 DR: Yeah, thank you so much for having me Ari. It was a pleasure to speak with you.

0:44:21.9 SC: Daniel Rabosky is a professor of ecology and evolutionary biology and a curator at the Museum of Zoology at the University of Michigan. You can find a link to the research paper we discussed at science.org/podcast.

0:44:37.9 SC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at science podcast at aaas.org. To find us on the podcasting apps, search for Science Magazine, or you can listen on our website science.org/podcast. This show was edited and produced by me, Sarah Crespi and Kevin McLean with production help from Megan Tuck at Podigy. Special thanks to all the folks at the AAAS annual meeting, particularly the heroic efforts of Sean Cummings turning around his space segment at Lightspeed. Jeffrey Cook composed the music on behalf of Science and his publisher AAAS. Thanks for joining us.