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0:00:05.5 Sarah Crespi: This is the Science Podcast for November 4th, 2022. I'm Sarah Crespi. Each week we talk about news and research from science and the sister journals. First up this week we examine urban ecology's roots in Berlin, contributing correspondent Gabriel Popkin joins me to discuss turning wastelands and decommissioned airports into forest and grasslands within the confines of the city. After that, we hear about a gene therapy strategy for epilepsy. Researcher Yichen Qiu talks about introducing a small set of genes into neurons in mice. These genes can detect hyperactivity and respond by quieting the cell, ultimately suppressing seizures.

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Now, we have Gabriel Popkin. He's a contributing correspondent for Science. We're gonna talk about his feature this week on a very long running Urban Ecology project in Berlin. Hi Gabe?

0:01:06.0 Gabriel Popkin: Hi, Sarah. Good to be with you this morning.

0:01:07.8 SC: Oh yeah. So you were in Berlin for fellowship, or what were you doing in the city?

0:01:12.7 GP: In 2021, I did a two month Arthur F. Burns fellowship, which took me to Berlin, which is a city I had visited a number of times before, but never had a chance to spend a long time in. And while I was there, one thing I discovered is that the city of Berlin has been studied for decades by ecologists, and they've found some pretty interesting things.

0:01:33.6 SC: When you say a really long time, we're talking like 60 years, a 60 year long project.

0:01:38.1 GP: It was pretty soon after World War II, and World War II absolutely devastated the city of Berlin. Berlin lost a lot of population, and not surprisingly, during the war, and a large fraction of the buildings and infrastructure were also just reduced to rubble. After the war, Berlin became sort of this island, or I should say West Berlin in particular, Soviet Union controlled East Germany. Berlin, if you look on a map, is kind of in the middle of the former East Germany. And West Berlin was sort of this outpost that was allied with the West. So it was controlled by the US, the UK and France. People living in West Berlin could get out, they could fly to West Germany, for example, but it wasn't easy. So these ecologists who were starting their careers at that time, some of them had the idea, let's actually do ecology research right here in Berlin where we are, in particular, they were interested in some of these sites that had formally been industrial sites or major kind of rail hubs and had been demolished during the war and weren't immediately rebuilt. In a way these sites, you can think of them as what you get after a volcanic eruption, just complete annihilation of everything, just a blank slate for ecosystems to start rebuilding themselves. And so in particular, this one ecologist, Herbert Sukopp was just starting his career at that time at the Technical University of Berlin, and he started doing research on some of these sites.

0:03:07.8 SC: This is 60 years ago. What do those places look like now?

0:03:12.1 GP: It's really striking. I've seen photos, for example, of this old rail yard in the south of

Berlin which was just a kind of a bustling dusty place before the war. And now some of the tracks are still there, but it's completely grown up into a pretty mature forest. So it's been converted into a park and the city of Berlin or whatever organization manages the park, has actually has to do work to try to prevent it from being completely overtaken by trees. They bring in these herds of sheep and have them graze on certain areas to maintain open grasslands. Because if you don't do something like that, you just get nothing but forest. You know, a lot of Northern Europe is kind of native forest. There are a lot of species that actually don't live in forest. They need open grasslands. That's just one example. But you know, you go to a number of these sort of what they call wastelands and you just see kind of an amazing amount of life growing on them.

0:04:10.4 SC: Yeah. You also talk about an airport that was decommissioned.

0:04:14.0 GP: Tempelhof. I mean, it's gotta be one of the most interesting places on earth, to be honest. It was a Nazi era airport after the war, because it was in West Berlin, it became a really important hub for West Berliners to get in and out of the city and also to get supplies in and out of the city. And it, in particular, believe it was 1948, the Soviets blockaded Berlin and prevented anything from reaching the city from the west. And this was like a really critical moment in the early days of the Cold War. And the US and the other allied countries arranged an airlift, I think it was mainly the US that led this. And they brought in supplies and landed them in Tempelhof Airport. Thousands of West Berliners came out to cheer this, Tempelhof just became a really kind of important place in West Berlin after that. But by the early 2000s, it was very obsolete as an actual airport. The runways were way too short for modern passenger jets. It was closed. And one possible future could have been that it just would be developed because Berlin is a growing city and needs more housing. But actually what happened was, it was turned into one of the biggest, most interesting urban parks in the world.

0:05:24.5 GP: And it's similarly being kept, mostly open. Farmers actually cut the grass for hay. They also do bring in sheep and grazing animals. And this is largely being done for biodiversity reasons, for ecology reasons. These big open grasslands are becoming really scarce in not just Germany, but a lot of Europe as agriculture has kind of expanded to take over much of the rural landscape. And so animals, birds such as the Eurasian Skylark, for example, but also many species of grasshopper and kestrels is another kind of bird that you see at Tempelhof. These animals really need these large open grasslands. And Tempelhof has become sort of this oasis in the city, not just for people, but for a lot of different species.

0:06:09.0 SC: There are actually a lot of surprises in your story in terms of what's living in cities, what's living in these wastelands where you're seeing the rare animals, for example, there's wild boar in Berlin, which I had no idea. And they're a problem, but they also disturb land and actually help grasshoppers, rare beetles. And then you find very unique things living next to roads where diesel fumes are constantly spraying all over them. Does it seem like what's happening in Berlin with these wastelands, with these rare animals showing up in all these weird places, does it seem like it's breaking a lot of the rules that ecologists have kind of laid out for what happens in urban spaces?

0:06:46.3 GP: That's an interesting question. Rules in ecology are not necessarily like the laws of physics. But I think certainly in the, let's say mid 20th century, the general view was that cities were

not great places for nature, for wildlife, for species other than humans. And most ecologists were not that interested in studying cities, but were more interested in going out to seemingly pristine rainforest or a coral reef or the Arctic, or just some place where it seemed like humans hadn't had much impact. And you could sort of see the rules of nature playing out as they were intended, that might have been the thinking. And I did hear from a number of people that Herbert Sukopp and his colleagues were kind of the first people to say, Hey, let's just do ecology the same way it's ecologists have been doing it in forests and grasslands and so on. Let's do it in a city. They did really find that cities harbor a lot more species, a lot more biodiversity, a lot more important and interesting interactions than anybody would've thought. Today, I think we're all kind of aware that there is wildlife in cities, I mean, they have wild boars in Berlin, here in the US we have deer.

0:08:01.2 SC: Coyotes?

0:08:02.5 GP: Yeah, the idea of like wildlife in cities is not so strange, but the idea of really studying it intensely, trying to figure out which particular types of species live in which particular types of environments in a city, that really came outta Berlin and Berlin is still a leader to this day in doing that kind of research.

0:08:21.3 SC: Well, what kind of more modern research is being done there today?

0:08:24.3 GP: A lot of these early studies, they focused on particular sites, certainly some of the kind of most interesting and important obvious sites to study. But more recently, they call themselves the Berlin School of Ecology. They've been trying to sort of put this all in a more systematic framework, one could say, and look at the entire city and try to determine what factors related to urbanization really impact the species living in a city. So one obvious one is, how much of the surface around a place is paved over? Because if you have pavement everywhere or buildings everywhere, that's gonna cause problems for some species that do need a certain amount of area of habitat. And they've also been looking at a lot at the effect of building heights, which I think is kind of a novel idea coming out of the Berlin school. They've been studying these grasslands that exist all over Berlin. Some are fairly large like Tempelhof and some are quite tiny. And they're just looking at, does it matter if the grassland is small or big? What species can tolerate living even in areas where there is a lot of pavements and buildings and what kinds of species need maybe larger areas to really make a living?

0:09:33.6 SC: So we talk about biodiversity in these spaces in a city, but what kind of biodiversity? I don't know if we need to talk about the quality of biodiversity, but we are talking about mixing species that live there already or that have come from other parts of the world. Is that the same kind of biodiversity that people think of when we say, Oh, well, it's on the decline and we're really worried about saving species?

0:09:58.1 GP: I think it's important to note and to be clear that cities can't save every species and there are definitely winners and losers within cities, but I think there are some, perhaps surprising examples of species that do really well in cities. One of the examples that's come out of the Berlin research as well as research in other cities around the world is that wild bees can do quite well in cities. And if you think about it, I mean, what does a bee need? It needs a place to get nectar, a place to get pollen and a place to nest and lay its eggs. And it turns out a lot of these bees don't need like a

huge area to do this. As long as they have the flowers they need throughout the growing season and a safe spot to nest, they can do quite well in small areas. A lot of us are aware that bees are not doing well in general, and this is largely being driven by land use trends in rural areas where farms have expanded, they sort of become more intense. They used to be like you might have a farm field, but there would be lots of wild flowers growing on the margins of the field, maybe between fields, even within fields.

0:11:02.7 GP: And now between the fact that people just farm thousands of acres at a time and use chemicals really intensely, a lot of those habitats in farmland have disappeared. This is certainly a trend in Germany. Cities do seem to be becoming oasis for species like bees. Another type of pollinator called hover flies, it turns out, don't do so well in the small grasslands in the highly urban areas. So it can, even between different types of insects, it can really vary alot.

0:11:30.8 SC: Oh yeah. You mentioned that, some cities have seem to become havens for bees, but do you feel like this is a broader trend, that there are going to be commonalities in cities like what lives there or specific like subsets of species tend to live in cities or that there's biodiversity in cities is going to be a thing, you know, how do we know how generalizable this is? Since Berlin has been doing this for a really long time, but maybe other cities haven't had as much intense research?

0:12:00.0 GP: We can certainly say, in general, cities are going to become more and more important for biodiversity because cities are growing, more and more people are moving to cities and we're just sort of taking over the land, earth land. I think this kind of research is gonna be really important. Not surprisingly, much of the urban ecology research that's been done has been done in the sort of wealthier parts of the world, Europe, the US, Australia. I think increasingly China, Singapore is another hotspot and a lot of the results that are coming out of these cities do seem to converge. Bees, for example, seem to do well in a variety of different cities, but I don't think we can generalize from that to, let's say, the sort of mega cities that are emerging in tropical countries. One ecologist I spoke with really called that out and said we need a lot more urban ecology research in tropical places because it could be totally different set of species that live in those areas. We could see really very different trends there.

0:12:58.2 SC: Really interesting. What do you think after spending time in Berlin and talking to all these ecologists, What's your big takeaway from all this?

0:13:06.9 GP: One of the most important things is that wildlife is only gonna be able to survive in cities if we allow it to. A lot of these species that are living in cities like Berlin are doing so I think not because humans like invited them in or really went out of their way to make a habitable, hospitable home, but just because the species were already there, it turns out they can make a living in the urban environment. Maybe in some cases they find their way in, but they happen to create a nice environment for it. It seems as cities become denser and as we become wealthier, which is going to continue to happen, we are gonna need to be more and more intentional about making sure that we are creating spaces for wildlife in cities. Because one could easily imagine if you just mow every lawn in a city weekly because now you can afford to pay someone to do that, you've suddenly wiped out a whole bunch of habitat that you probably weren't even thinking of as habitat necessarily. There's certainly some species that kind of culturally we tend to not wanna be around like snakes, for example. Even though the vast majority of snakes are harmless, and I think we are

gonna need to do some work, kind of cultural work to maybe retrain ourselves a bit and to not just feel like, okay, we need to get rid of every living thing in our environment other than ourselves and our pets.

0:14:26.6 GP: But to become more tolerant of species like spiders. Spiders actually do a lot of good, they eat insects that we don't like. Snakes can also do good. So I think, you know, as cities evolve, we humans are also gonna have to evolve with them.

0:14:40.8 SC: Thanks so much, Gabe.

0:14:41.8 GP: Thanks Sarah. It was really fun talking to you.

0:14:43.5 SC: Gabriel Popkin is a contributing correspondent for Science. You can find a link to the feature we discussed at science.org/podcast.

Stay tuned for my chat with researcher, Yichen Qiu, about a gene therapy approach to suppressing seizures in epilepsy.

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For epilepsy patients. Only about one third get results with drug treatments in the long term. In a paper this week in Science, Yichen Qiu and colleagues write about a gene therapy strategy that specifically turns off only the hyperactive neurons. The introduced genes are only active when a neuron is firing above a certain threshold. Once the cell has calmed down, the genes turn themselves off. Yichen is here to talk about this approach to targeted calming of neurons. Hi, Yichen?

0:15:42.4 Yichen Qiu: Hello.

0:15:43.0 SC: The idea here is to turn off only neurons involved in seizures, the ones that are hyperactive. Is this not something that other epilepsy treatments are able to do?

0:15:53.5 YQ: I think maybe a good way to think about the differences is to imagine a luxury hotel with hundreds of hotel rooms and the rooms are brain cells. In this case, we are trying to put out a fire that happens in some of the hotel rooms. The conventional anti-seizure medications puts out the fire by simply pouring the water all over and hoping that the water will put out the fire that happens in some of the hotel rooms. So in this case, that even though the fire is put out, it is affecting the rest of the hotel. However, our approach is operating more like an automatic sprinkler system. It senses the rising high temperature, abnormal rising high temperature in some of the rooms, and it puts out the fire only in those rooms and stopped it from spreading to the rest of the hotel. So once the fire has been put out, the sprinkler will automatically stop itself and the rest of the hotel remains as normal.

0:17:00.6 SC: One thing you call this system is closed loop. So why is this considered closed loop?

0:17:06.0 YQ: The way that this approach works is that it will automatically activate itself when there is a increase in activity level, while at the same time take an effect to try and bring down the activity level back to the physiological status. And once the cells have gone back to normal, this approach will automatically stop.

0:17:33.8 SC: Right. So that means that you don't need to turn it on with electricity or with light or with a drug. This construct just acts up when it needs to act up.

0:17:43.0 YQ: Yes.

0:17:43.8 SC: How does your detector work? How does it know that a neuron is overreacting or doing too much?

0:17:51.3 YQ: Our gene therapy is composed of a few core elements. So the first element is a potassium channel. So this potassium channel calms the cells down when it is expressed. The second component is a promoter sequence, which is a DNA sequence that drives the expression of that potassium channel, this special promoter sequence that we are using in this approach, actually detects the changes in your neuron's activities and it will activate or inactivate itself accordingly. Therefore, we are controlling when and where the potassium channel gets expressed based on the changes in activity levels.

0:18:41.0 SC: So what is the promoter listening for? What happens to activate it? Why? How does it get activated?

0:18:48.8 YQ: So this promoter has several components which are responding to a important cell signaling molecule, which is the calcium signal. This signal is only present when there is an increase in the activity level inside the neurons. So in this way, when there is increase in the activity level of the neurons, it sends down the calcium signal onto the promoter and then activates this promoter sequence. Then this promoter will then activate the expression of the potassium channel.

0:19:27.0 SC: And the expression of those potassium channels can then change the ion content of the neuron and chill it out. So basically it's returning to normal, this basic physiological state that we want when these additional channels are around. How are you able to get this promoter and this effector gene into neurons in, I think you did it in mice and then in organoid? How did you get this gene into mice?

0:19:51.4 YQ: We package everything all together into a single viral vector. So this viral vector is so far considered to be the safest viral vector for delivering gene therapies into mammalian cells. It is non-replicating and so far that we have seen a really good efficiency to bring the gene therapy into the brain cells.

0:20:17.3 SC: Were you trying to infect every neuron in the mouse brain with this vector? Or were you looking for specific populations of neurons?

0:20:25.0 YQ: So in this study we have delivered this gene therapy specifically into the

hippocampi of the mouse brain. And the data have shown a fairly promising anti-seizure effect.

0:20:38.2 SC: Does that mean that the mice stopped having seizures entirely or they were suppressed, or what kind of results did you see in mice?

0:20:46.0 YQ: And so in this case, when we deliver the gene therapy into the animal epilepsy model, we have seen a strong reduction in the seizure frequencies.

0:20:56.9 SC: Let's talk about this organoid you used. Can you tell us about what it is and how it can help with this kind of study?

0:21:03.8 YQ: So organoids are quite a new technology with the aim to build a 3D structure from human derived cells. It is sometimes known by the media as brain in the dish, although it is quite far away from there. But it has given us a more advanced model to test how things are like in a more human-based environment. So in this case, when we deliver the gene therapy into the organoid, we're also seeing reductions in the level of hyperactivity in those organoids that are being treated.

0:21:48.3 SC: What time scale does this happen on?

0:21:51.2 YQ: As far as we know, the promoter is activated within the first hour of detecting any increase in activity. It could be as fast as within minutes. We're looking at more from a population effect that collectively, dynamically calming the neuronal network or the neuronal circuit is sufficient to deliver a anti-seizure effect.

0:22:20.1 SC: This isn't altering the genome, this isn't something germline. It's not gonna be passed down to offspring, but it is, you know, if it's in a brain, in a human brain, for example, this gene therapy would be present for life. Is that right?

0:22:34.8 YQ: So the idea would be that the viral vector should remain fairly stable once it enters the brain cells. And because the majority of the brain cells do stay with us for the entirety of our life. In theory, this therapy should remain fairly stable once it is delivered.

0:22:56.2 SC: The promoter that you use, cFOS is something that's already present in the cells in the brain. It's already kind of a natural component of the brain function. Is there any concern that it'll be activated by other things besides hyper excitability?

0:23:12.6 YQ: So far, based on the data that we've collected, we have not yet seen adverse effects by this gene therapy being turned on in the physiological conditions.

0:23:24.6 SC: What do you see as the next steps for this gene therapy strategy for epilepsy? Are you gonna test it in other models? Are you gonna put it in a a human, you know, are clinical trials on the horizon?

0:23:36.6 YQ: Well, we're very excited by the result of this study, and so far in this paper we have looked at how this therapy behave in both the animal epilepsy model as well as organoids. So we're

collecting some data with the idea in mind that it would be incredibly great if one day we could arrive at the point of the clinical trial. At the same time, we also acknowledge that there is enormous amount of work that needs to be done before we're arriving at that point.

0:24:12.1 SC: What about other neurological diseases that involve hyperactivity and neurons? Are there some other ways that this gene therapy strategy could be used?

0:24:21.8 YQ: In principle, other diseases which has a component of hyperactivity, including some type of neuropsychological disorders or Parkinson's, could potentially also benefit from this approach. However, I believe that for many of neurological disorders, they often have really complicated disease mechanisms that we have not yet fully understand.

0:24:51.9 SC: Thank you so much, Yichen.

0:24:53.3 YQ: Thank you for having me.

0:24:54.7 SC: Yichen Qiu is a recently graduated PhD student and researcher at University College London. You can find a link to the paper we discussed at science.org/podcast.

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And that concludes this edition of the Science Podcast. If you have any comments or suggestions, write to us at science podcast@aaas.org. You can listen to the show on the science website at science.org/podcast or search for science magazine on any podcasting app. This show was edited and produced by Sarah Crespi with production help from Podigy, Kevin McClain and Megan Cantwell. Jeffrey Cook composed the music on behalf of science and its publisher, AAAS. Thanks for joining us.