After the Fact | Scientists at Work: The Big Idea Between a Small Fish and Heart Disease

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TRANSCRIPT

Dan LeDuc, host: Welcome to "After the Fact." For the Pew Charitable Trusts, I'm Dan LeDuc. While the coronavirus continues to be a major public health challenge, we're turning to another health concern facing Americans, and we're visiting a lab working to solve it. Our tour happened earlier this year, before the quarantine took effect. And before we go there, our data point for this episode: 48%. That's the percentage of adults in the United States that the American Heart Association says suffer from heart disease. In this episode of our "Scientists at Work" series, we traveled to the Carnegie Institution for Science in Baltimore to visit with Steven Farber. He's a Pew biomedical scholar, and his lab investigates how dietary nutrients such as fats contribute to important functions that support good cardiovascular health. Steve's research is revealing new ways to combat health conditions like diabetes and obesity. But to figure out what's going on in the human body, he is looking at something much, much smaller: zebrafish.

[Music transition]

Steve Farber, Pew biomedical scholar (2002); adjunct associate professor, Carnegie Institution for Science: This is our beautiful building. We always call it a new building. We moved in in 2005, but it still feels new.

Dan LeDuc: Oh, God, yes. Feels very new.

Steve Farber: So we're going to go down to the zebrafish facility. This is a state-of-the-art facility that can handle upwards of 80,000 fish.

Dan LeDuc: I can smell the aquarium all around me, and I see row after row of lots and lots of tanks.

Dan LeDuc: So, wait. … What do zebrafish have to do with human health? Before answering my question, Steve wanted me to have a close look at these tiny fish under a microscope.

Steve Farber: If you look in there, it's sitting on its side, but you'll see the heart beating. It's moving.

Dan LeDuc: Wow.

Steve Farber: Since the fish are optically clear, we can see right into their bodies and ask a whole range of questions not possible in other systems.

Dan LeDuc: These tiny see-through zebrafish actually have a very similar genome to humans, and Steve and his team believe that watching how zebrafish respond to fats, known as lipids, could save lives by aiding in the development of new treatments for heart disease.

Dan LeDuc: Set the stage for us on the research you do today and how people have changed over time.

Steve Farber: I'll start out and say that I'm not directly an evolutionary biologist, but in thinking about human disease today, we often use the term environmental mismatch. And what that means is, humans have evolved on this planet for a really long time. And through much of that evolution, they had nutrients and food sources that were different than the modern industrial food system. So when we refer to the problems we face now as an environmental mismatch—what I mean is, not that long ago in Africa, we were wandering around hunter-gatherers, and it might be many days before we could successfully kill some big game. And you evolve ways to manage these periods of feasting and the periods of famine. Now, in just a very short window of time, we have constant food. And so genes that evolve to actually make you very thrifty with your calories, that made you very efficient to deliver those calories to your body and store all those, actually become liabilities. People with some of those genes broken are actually better off and more healthy than the people who have the gene today. There's huge genetic variance. There's huge things we cannot explain, like why some folks are just seemingly resistant to these effects and others are not, nor do we fully understand the kind of diets we should have. There's been a lot of contradictory advice given to people over the years so that most folks don't know who to believe. So I think there's just a huge knowledge gap in this space that has a profound impact on human health. So our hope is to use the zebrafish model to fill in some of those knowledge gaps.

Dan LeDuc: I just want to go back to the beginning more for you as a scientist, to back in the day in graduate school, what made you say, I want to do this?

Steve Farber: I think there are scientist journeys that are very linear. Mine was very nonlinear. So I have this crazy background, engineer, policy, technology policy, which I think, I don't think my outreach activities would have been as successful if I didn't have formal training in that space. But my interests got me into lipids, lipids in the brain. The brain has a lot of lipids.

Dan LeDuc: Tell people what a lipid is.

Steve Farber: Well, it's the fatty molecules that we eat. Oils. The things that make up our cell membranes are called phospholipids, but in baking, they're like lecithin. These lipids are key to making up all our cells. And it just goes to show you, I happened to be reading *Science* magazine, trying to figure out what I was going to do as a postdoc, and I saw an article that said, "Zebrafish hits the big time." And one of my advisers said, you know, you should think a little about the zebrafish. It's an up-and-coming system. And this was in 1995. And it seemed to intrigue me, because I thought I could study biochemistry and biochemical processes in vivo. That I appreciated right at the beginning. I could study them in vivo, because I could look through their bodies.

Dan LeDuc: Well, you're very much a scientist that goes beyond just knowledge for the sake of knowledge. You are a scientist that has always sought to apply knowledge that you learn immediately.

Steve Farber: When you're an engineer, there aren't that many scientist-engineers, but you tend to like tools. I'm like one of the people like you'll come to my lab and a piece of equipment breaks. A lot of biologists are not the types that'll take it apart and fix it. Like, I fix equipment in my lab. That's my favorite avoidance behavior. To not write a grant, I'd fix a centrifuge, and I teach people in my lab we fix stuff, because I can't stand throwing all this good technology in to a landfill.

Dan LeDuc: So tell us why the zebrafish is such an important—the zebrafish is one of your tools.

Steve Farber: Just to set it up, I mean, people have questioned me. Even my former president of this institution said to me, Steve, there's like 200,000 papers on lipoproteins, you know, bad cholesterol. Every medical school has somebody working on this. What can a lab of 12 people do in this space? I love a question like that, because I know why. It is because there are many, many knowledge gaps into why cardiovascular disease happens, how it starts. Why do you get insulin resistance? Why do people get adult onset diabetes? There are so many questions. We still don't understand what genes do. But it's amazing in science you start out trying to learn as much as you can and then that spark

happens. And for me, it was with my graduate student five years ago. We were at a meeting together. And the spark—we got this idea, and we were texting each other during the meeting, just like as if we were in high school. We kind of birthed this idea, and it was just so much fun with that graduate student, James Thierer. He's fearless. And he just thought, this is a wacky idea. We should do it. And he executed it so amazingly. And it started this entire new direction for me.

[Music transition]

Steve Farber: So the pump room is over here.

Dan LeDuc: OK, the smelliest place is definitely the room filled with small aquariums—which are filled with more than 80,000 zebrafish.

Steve Farber: You can kind of hear the pumps are pushing out water on each side so 260 gallons a minute are flowing out to all these tanks.

Dan LeDuc: You can smell the aquarium all around me, and I see row after row with lots and lots of tanks.

Steve Farber: We have 16 racks, and they hold different sized tanks, and they're different developmental stages, but they're all zebrafish. And you're probably wondering, why do you need so many tanks if they're all the same fish? But we've engineered some of these fish. We put a protein like the kind in fireflies that makes fireflies light up. We attach that protein to the bad cholesterol protein that makes LDL cholesterol. So we are entering an age of cutting and pasting DNA with crisper technology and others where we can kind of engineer these fish to have different properties. And since the fish are optically clear, we can see right into their bodies and see these cells and ask a whole range of questions not possible in other systems. But the idea of using the fish to study lipid biology is one of my contributions.

Steve Farber: Here I'll show you the room where we look at them. Now, these are not expensive microscopes. Here we go. Perfecto. If you look in there, you'll see the heart beating. It's moving.

Dan LeDuc: Oh, wow.

Steve Farber: Can you find the heart? They kind of have their swim bladder right now.

Dan LeDuc: What are these? Are those actual fins?

Steve Farber: Those are pectoral fins. Those are where arms evolve from.

Dan LeDuc: Oh, no. I do see something, you know, vibrating like a heart.

Steve Farber: In the middle.

Dan LeDuc: Yeah, right in the middle. That's big.

Steve Farber: Now if we move this to another microscope, we could be looking at the valves inside the heart as it's beating. We can look at every single cell. That's why the fish is premier for cell biology and the work that we do on lipid metabolism.

[Music transition]

Dan LeDuc: In many ways, zebrafish are providing an ideal subject to better understand certain health conditions and how different medicines can make a difference.

Dan LeDuc: So it's a combination of creativity, but also new technology.

Steve Farber: The biology community and even the general public have heard that biologists use these green fluorescent protein or red fluorescent protein—there was a Nobel Prize for those. With modern genome engineering, we used a fresh approach. We were able to kind of cut the DNA at the right spot and insert the light-emitting protein right into the gene very precisely. So now we made the first-ever fish or vertebrate that's got all of their particles glowing.

Dan LeDuc: So you actually started marking these bad cholesterol particles, and because it's the zebrafish are so clear and easy to see, you could watch what was happening.

Steve Farber: We see these lipoproteins in places we did not expect. And they explain some weird things that happened to people that have diseases that mess with their lipoproteins like, for example, we see a lot of lipoproteins around the areas where tendons form. So we're asking, why are these tendon areas places where these lipoproteins go?

Dan LeDuc: Now, what's the key lesson that you learned from this, and how do you apply it to human health?

Steve Farber: Once we created these fish and once we realized with our collaborator, Jeff Mumm at Hopkins, who has a big robotic platform, we could take something the size of a coffee mug filled with 12,000 zebrafish embryos. We can pour it into the robot, into a vessel, and it will put a single embryo in a 96-well plate. And we'll fill up these plates with single embryos, and then we use a robot to distribute every drug that's ever been used in people. So we started with something called the Johns Hopkins Discovery Library that our collaborators created, and it has 3,200 compounds. And then we just put the camera over the plate and we measure what lowers the bad cholesterol, and we could quickly rule out things that kill the animal and things like that. So out of 3,200, we only got 26 hits, and they're really interesting.

Dan LeDuc: Stuff that actually works.

Steve Farber: Yeah. And these are drugs that are already deemed to be safe. So now we can put these compounds into mice and we can even put them into people, because they're already FDA approved. Like our dream compound would be like some fungus drug used for toenail fungus that could actually be amazing to lower cholesterol. So we're looking really carefully at these 26 hits, and it's not we're not even done. We did the known compounds. Now we're about to take a deep breath and do 20,000 compounds that have never been tried.

Dan LeDuc: These would not be on the FDA-approved list and see how they do.

Steve Farber: These would be completely new. So this is just a small lab tackling a really big problem, but from a novel way.

Dan LeDuc: You've launched something called Project BioEYES. Is that part of your effort to try to make a difference?

Steve Farber: Well, it's a program that's a hands-on activity for K-through-12 children. There's programming as young as pre-K to fifth grade to middle school, into high school. And this program uses a fish, where kids have to figure out which is a male and a female and set up a mating. And then they have to collect the embryos and watch development, and ultimately they'll see the beating heart. And I want to preface it by saying, you know, yes, this program has reached 130,000 kids, and largely kids that don't get this kind of enriched activity. But the key to its success was its conception with a teacher, with Jamie Shuda, who knew how the classroom works. And you team up the scientists with the crazy ideas with the teacher that understands the demands of a classroom setting and a school setting. And BioEYES came from that. And I think that you don't wake up in the morning and say, 'Oh, I'm going to make a program that impacts education all around the

world.' It's a bunch of little steps. And it's just immensely gratifying that I've been fortunate enough to have this experience. Just last week, well, a month ago, let's say time flies here, but I was giving a seminar at NYU, and one of the postdocs was talking to me and said something to the effect of, 'Oh, yeah, I had the fish come to my classroom in Philadelphia, and it was a reason I kind of got into science.' And this isn't the first time that that's happened to me. I mean, this is really a gift. And I try to tell my colleagues, like, it can be immensely rewarding to be inspiring the next generation. And for goodness' sake, folks, we really need it. We're doing a woefully poor job in STEM education in this country. And it's going to be at the heart of addressing a lot of problems, health problems, environmental problems, problems with inequity. The technology is here to stay. So you either have a populace that's trained to think about big data that think critically or you don't. And I think it's going to be at the heart of how well we're going to do as a country and as a world.

[Music transition]

Dan LeDuc: Thanks so much to Steve Farber and Carnegie Science for hosting us on this tour earlier this spring. We wish the best of luck to him and all the researchers who continue their important work to discover new medicines, vaccines, and other insights that protect all of us. To learn more about Steve's work and see images from his lab, visit us at pewtrusts.org/afterthefact.

Until next time, for The Pew Charitable Trusts, I'm Dan LeDuc.

Female voice: "After the Fact" is produced by The Pew Charitable Trusts.