Of Unknown Etiology

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SPEAKERS

Chris Vulpe, Ricky Telg, Phillip Stokes

R **Ricky Telg** 00:04

This is Science by the Slice, a podcast from the University of Florida's Institute of Food and Agricultural Sciences Center for Public Issues Education. In this podcast, experts discuss the science of issues affecting our daily lives, reveal the motivations behind the decisions people make, and ultimately provide insight to solutions for our lives.

P **Phillip Stokes** 00:30

Welcome to Science by the Slice, I'm Phillip Stokes. And this episode's topic is pretty heavy. It involves human health and disease, but also the prospect of new knowledge and impending hope to improve health outcomes. Here's the backstory. Since about the 1990s, there has been a recognized epidemic that has been the cause of death for tens of thousands of people in different locations all over the world, including communities in Central America, Sri Lanka, and India to name a few. This disease cannot be cured. And furthermore, scientists have struggled to determine the exact causes. It's called chronic kidney disease of unknown etiology, or CKDu. It's a version of kidney disease without known etiologies, or causes. What we know is that agricultural communities are most at risk. But it's not like all agricultural workers are impacted by this. The most notable explanations for CKDu are heat stress and dehydration, and toxic agents such as pesticides, or heavy metals, or a synergistic effect of both of those together. This lingering scientific uncertainty is somewhat of a roadblock with respect to prevention, as well as policy implications. Without a clear scientific consensus, governments and other organizations are unsure of how to best coordinate a response to the problem. So in this episode, I speak with a researcher who's working toward uncovering the mechanisms and molecular pathways that lead to kidney damage. And CKDu. Dr. Chris Vulpe is a professor and molecular toxicologist in the Center for Environmental and Human Toxicology at the University of Florida. And this research project, led by Dr. Vulpe is through the Southeastern Coastal Center for Agricultural Health and Safety. So now, let's go to my conversation with Chris, as I asked him to explain chronic kidney disease of unknown etiology.

P **Phillip Stokes** 02:38

Well, Dr. Chris Vulpe, thank you so much for being a guest on Science by the Slice, to talk about your research and the research project you do in the Southeastern Coastal Center for Agricultural Health and Safety. And it has to do with toxicology and chronic kidney disease of unknown etiology. Everything I've ever read about that that unknown etiology part, there's always this a very puzzling component. So what does that mean? What is chronic kidney disease of unknown etiology?

C **Chris Vulpe** 03:08

Well, chronic kidney disease of unknown etiology, or are called CKDu. It's a disease that's common in agricultural workers in semi tropical and tropical environments, which, as the name sort of implies, we don't know the cause of and it's unusual in that it affects young men and women quite early in in life, and it does not appear to be associated with some of the causes of kidney disease that we're familiar with such as diabetes.

P **Phillip Stokes** 03:50

Just a backup, maybe a moment, the kidneys serve a pretty essential function in our body, right. So it is to sort of filter out the waste and the things that we bring into it, right?

C **Chris Vulpe** 04:02

Absolutely. Yeah. It plays an absolutely essential role, and also getting rid of the toxins that accumulate in your body, both toxins that you're exposed to, but we also generate our own toxins the kidney needs to eliminate.

P **Phillip Stokes** 04:20

Okay, let's pause and talk a little more about the kidneys. First off, the kidneys are two bean-shaped organs about the size of a fist, located inside the abdomen, just below the ribcage on each side of the spine. They are a part of the urinary tract, which is the body's drainage system for removing wastes and extra fluid through urine. Put very simply, blood flows into your kidneys through an artery. Your kidneys act as a filter and remove the waste and toxic substances. Those wastes are then excreted through urine, while the majority of the fluid flows out of the kidneys through a vein back into the bloodstream containing The minerals and nutrients your body needs. Healthy kidneys filter about a half a cup of blood every minute, maintaining a healthy balance of water, salts and minerals in your blood. They also secrete a number of essential hormones that help control blood pressure, make red blood cells, and keep your bones healthy. Yeah, they're extremely important. And with kidney disease, this filtration process is impaired and there can be a buildup of fluid or body waste. Typical risk factors for kidney disease include diabetes, high blood pressure, or heart disease but that's not what we're referring to with CKDu. So let's join back in on my conversation with Dr. Vulpe as I asked him just why, in fact, we don't know more about CKDu given the kidneys essential role in our bodies.

P Phillip Stokes 05:55

And being such a vital, important organ, you would think I think there's this feeling that we would know almost everything there is about this process. And so having this new emerging issue, what is some of the data suggesting at this time? What do we know?

C Chris Vulpe 06:12

Well, I think that's one of the issues with renal disease is that it can go on for quite a while undetected, and you can have decreasing renal function. But until you go into acute renal failure, it won't be noticed. I think that could be one factor that plays a role with why it was under appreciated for quite a long time. One of the things that you asked was, why don't you see it? CKDu has been noted for quite some time in in Central America and India and Bangladesh. Unfortunately, we still don't have a good handle on what is what is causing it. And that is the kind of the basis of our work is to try to understand what are potential causes as well as to try to assess to a certain degree how to develop ways to detect it.

P Phillip Stokes 07:15

So what would you say are some of the risk factors within the agricultural industry and within laborers? What are some of those common denominators and risk factors associated with CKDu?

C Chris Vulpe 07:26

Well, for sure, it's being in a hot and humid climate and those appears to be important. You know, however, there are places where there doesn't appear to be a high prevalence of CKDu, such as Cuba, and other places which have very similar climates. So it's been a little bit mysterious, why it would appear in some places and, and not others with very serious climate. And the thought is, there must be something else in combination with the heat, the humidity, and then the associated dehydration that can sometimes occur in people in such an environment. And together, you know, these factors or risk factors increase the likelihood of developing CKDu.

P Phillip Stokes 08:19

So as a researcher, as a toxicologist, what are the key questions you and your colleagues are asking to learn more about this disease?

C Chris Vulpe 08:28

Well, one of the key factors that has been considered not just by us, but by many people is the potential role that chemicals and agricultural chemicals in particular, could play a role in the development of CKDu. And several chemicals have been identified as potentially contributing.

but there's no real, I guess, smoking gun, to absolutely demonstrate that they're involved.

P **Phillip Stokes** 09:00

So what is your research aiming to do? Could you just set the stage for what you're doing here at the University of Florida?

C **Chris Vulpe** 09:07

So there are a lot of possible factors which could be contributing to chronic kidney disease in agricultural workers. In addition to the chemical exposures. There's also been speculation about other factors such as airborne pollution and other things, but it's very difficult in a study of people to make a causal connection between exposure and the development of disease. So what we're doing is trying to test the hypothesis that it's the combination of heat and exposure to agricultural chemicals. And we're looking specifically at three chemicals right now. Glyphosate, which is the active ingredient in Roundup, Permethrin and Paraquat. And in animal studies, which are more controlled than human studies in which you can control the exposure, we're trying to determine whether the combination of heat and pesticide exposure leads to the development of kidney disease.

P **Phillip Stokes** 10:22

So if you could just share with us how are you doing this? What is your methodical approach here, because I know that your study is a bit novel and a bit unique and different than some of the previous studies. I know you're using laboratory animals. So if you could just kind of paint a picture and tell us a little more about that.

C **Chris Vulpe** 10:38

Most of the previous studies of CKDu have been epidemiologic studies focused on human populations, but in those sorts of studies, it can be difficult to determine what are the cause of disease. So we're doing a controlled study using an animal model, specifically rats to determine whether the combination of heat exposure and chemical exposure together can lead to kidney disease. And if these studies find a relationship between the two, then that provides some support for the idea that in people it's similar exposures that could be contributing to the disease. However, of course, it could turn out that we're wrong and then in fact, these chemicals play no role. So we're trying to test that hypothesis that these chemicals are playing a role. The other thing I'd say it's it's different in epidemiologic studies in people, people are exposed to a whole bunch of things at the same time. So as a result, it's very difficult to tease out which is the key exposure, is it the heat alone? Is it the heat plus this chemical, the heat plus that chemical? Or it's possible, of course, that it could be, you know, the combination of heat and one or more other risk factors or chemical exposures. And so the animal model allows us to sort of systematically test what are the possible causes of the disease. And of course, once you identify a possible cause, and that allows you to focus your studies and people to try

to, you know, better understand it. If we have good evidence that, you know, let's say one chemical plays an important role, then we can do more focused studies on that in in human studies, and really try to see if there is a relationship.

P Phillip Stokes 12:44

Right. I mean, that's such an interesting point, there are so many factors, humans are exposed to so many different, you know, things in our environment, and the things we eat are our lifestyle, our genetics, and you're able to pinpoint, isolate, like you said, in a controlled experiment using a live animal species that has a working system, right? And so you can't replicate that anywhere else, right?

C Chris Vulpe 13:10

Well, yeah, I mean, animal models are, in some ways, a model of last resort. I mean, if you can do the study in anything else, you want to do that, because you know, that's the the most appropriate and the most moral way to do the work. Unfortunately, at present, we don't have very good cell based models for understanding the effects of chemicals on the kidney. Now, I'm not saying that there aren't approaches that are being developed and there's been tremendous work with the development of things such as IPSC-based kidney cells, but unfortunately, at the current time, there really isn't an adequate physiologic model to be able to study this in cell culture based method, which is the why that we unfortunately have to use animal models. Of course, you know, always the goal with animal models is that it's being used to inform the human studies, and you do them in such a way as to minimize the number of animals to the absolute minimum of the number number that you need to use in order to get the results that you you need.

P Phillip Stokes 14:28

Well, I really appreciate you saying that. And I think that's really important for, you know, our listeners to hear who may be unfamiliar with laboratory animal studies. And so that's some good background knowledge behind that. What are some of the baseline findings or the baseline data that you have right now? And then yeah, maybe we can talk about some of the further implications with human studies.

C Chris Vulpe 14:52

Yeah, well, I mean, in order to understand what the combined effects are of heat and pesticide exposure, you really have to understand In the individual exposures. So a lot of the work that we've been focused on for the last period of time, has been understanding the individual effects of pesticide exposure alone and heat exposure alone and the first acute effects on the kidney, as well as the chronic effects. Because, you know, as you can surmise, you know, farmworkers are not just exposed once to heat and pesticide exposure, it is occurring on a regular basis, and they have repeated exposures. So we've been focusing on trying to understand what the individual effects of repeated exposures is on the kidney in the animal model. And our initial findings have indicated that these are both heat and different chemical

exposures are significant stressors on the kidney. So we've been trying to understand what the stress is, and what parts of the kidney are affected. And today, we have seen some evidence of effect on the filtration part of the kidney, which is called the glomerulus.

P Phillip Stokes 16:21

Are you finding these stresses are more adverse in in conjunction with one another with the heat and the chemical exposure? Is one more noteworthy than the other? Or is it? Is it this combination?

C Chris Vulpe 16:36

Yeah, I mean, actually, to date, that's where we're going right now is to study that combination. So we've been focused on the individual. And then the focus of this study, is really now to ask that question, what is the combination going to do? And what happens with a combination repeated over time, for a long period of time? And what does this repeated stress on the kidney do? And does that result in a kidney disease that looks similar to what's seen in people? And one of the ways that you determine that is by looking at the kidney by doing what's called pathology, as well as looking at what are the molecular events that are occurring in the kidney? You know, what changes are happening? And seeing are they similar to what we see in people?

P Phillip Stokes 17:31

That's fascinating that you're able to, like you said, isolate certain cells within the kidney, and you're able to look at it on such a smaller scale than you would add an epidemiological study, like you mentioned previously. So you have that baseline data. And of course, I know that you have more research to carry out. But what are some of the implications and some of the next steps within the research process?

C Chris Vulpe 17:58

What we're involved in is, is trying to ask, How similar are the changes that we're seeing in the rat to changes that are observed in people? Now you're right, we can't measure what's going on in the kidney in people. But what you can do is you can use what are called biomarkers. So biomarkers is really just a fancy term for basically a lab test. And we use biomarkers all the time in, you know, for instance, when you get a heart attack, right, they measure the heart proteins, or you look at liver disease, you look at some of the liver proteins, and you can do the exact same thing for kidney. And these biomarkers can tell you, you know, are the is the kidney being injured. But not only that, they can tell you where in the kidney, what what's being injured. One of the things that we're working on now is to look at populations where they have chronic kidney disease of unknown etiology, and look at the biomarkers in their urine. And first of all, see, well, what are the biomarkers? Is there evidence of kidney disease? And then secondly, are the changes that we see in people look like the changes that we see in our animal model? And again, this is another way to ask the question is the disease that we're seeing in an animal model, similar to what we're seeing in people, or more importantly, is what is being seen in people reflected in the work that we're doing in an animal model? And so they

kind of build on each other, right? You can't do these sorts of studies in people where you do exposures and heat, but we can ask, what's the effect on the biomarkers that we can take the biomarkers from people and say, hey, well, does this look like what we're seeing in the animal model? And if they are, then we can sort of infer that maybe the mechanisms are similar. They kind of add value to each other. And you can get the mechanistic information from the animal model, which can help inform the human studies. Because I think the other sort of goal of this, of developing these biomarkers is the idea of trying to develop early indicators, right, so that you can detect a disease before they get fulminant kidney failure, you know, so that's the other kind of goal with biomarkers is to be early disease indicators. And if you can measure it in urine, then you know, it's very simple, easy, fast, and can help predict the people who are going to be at risk, because they've already got some evidence of kidney disease. And that could be really helpful in preventing them from going on to develop renal failure, because there is no treatment for renal failure except dialysis or transplant. And so if we can prevent farmworkers from developing renal failure, then that will be a great, you know, outcome.

P Phillip Stokes 21:08

No, I think that's great. Dr. Vulpe, is there anything else we didn't touch on that you'd like to say, before we close out the podcast?

C Chris Vulpe 21:14

You know, we know very little about CKDu, even in places where it's pretty well studied. But here in the U.S. I would say it's even worse, because the healthcare system is such that we don't have a whole lot of information about how prevalent it is here in Florida, and many farmworkers, if they develop kidney disease, then they're going to not be able to continue their work. And those individuals may not even be identified as having the disease. So I guess what I'm saying is, I think there's an unseen potential burden of this disease. And because of the nature of transitory agricultural work with often migrant populations, that this disease can be hidden or not be noticed, perhaps if it was occurring in a, you know, a population with better health care and a more stable medical care system.

P Phillip Stokes 22:12

Yeah, I mean, it sounds like in a way, we don't have a certain amount of data, because some of those data points come in through our healthcare system, right, through doctors offices, and ERs and hospitals in different places. But yeah, when you have a group of individuals that maybe don't have as much access, or who are more marginalized, potentially, it may be harder to identify a cause and effect. Is that basically kind of what you're getting at?

C Chris Vulpe 22:39

Yeah, I think that's part of it. I also think if they have the disease, they may not continue to work in agriculture. And so those people will just sort of disappear. And so you'll you'll look at your population, and you'll say, Oh, they're healthy. But that's because the people who weren't healthy are no longer there. And so when you have a turnover of the population, I think that

can hide the disease. So I think that's potentially also getting at to one of the things that you were mentioning earlier, why haven't we noticed this? And the question is who's asking, right? And I think probably if you ask the Farmworker populations in many of these places, they'd say, Yeah, this has been with us. But you know, maybe it's not something that people have noticed.

P Phillip Stokes 23:23

And potentially, it has been explained as the cause from being one of those more traditional causes, like diabetes or something like that.

C Chris Vulpe 23:32

For sure. For sure, because a medical practitioner, also, they're not going to be looking for this necessarily.

P Phillip Stokes 23:37

Right.

C Chris Vulpe 23:38

At Least not in places where it's not familiar, you know, they're gonna think, oh, it's diabetes, or it's something else?

P Phillip Stokes 23:44

Well, I think that does certainly add to kind of, like we talked about at the beginning, the mysterious nature of this, just the puzzling nature of this disease, which I think makes your research project and all of those that are involved, so needed and so powerful. So I just want to thank you for talking with me today Dr. Vulpe on Science by the Slice. I really appreciate your time.

R Ricky Telg 24:11

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