Sarah Alger: Welcome to Proto, a podcast that explores the frontiers of medicine. I'm Sarah Alger.

Dr. Warren Zapo...: And I'm Warren Zapol.

Winter is indeed on its way. So today we're looking at animals that thrive in extreme cold environments.

Sarah Alger: We'll introduce you to a champion of hibernation, the Arctic ground squirrel. This rodent spends up to nine months, cozied up under the ice.

Kelly Drew: They have such a reduction in blood flow to the brain and other organs that it is really equivalent to the blood flow you would see in a person having a stroke.

Dr. Warren Zapo...: And we'll hear about the remarkable Weddell seals. This animal has evolved a unique way of storing oxygen to help it thrive in the frigid Antarctic seas.

Sarah Alger: The medical secrets of cold weather mammals, coming up on this episode of the Proto podcast, brought to you by Massachusetts General Hospital.

Each episode, we bring you a topic from the frontiers of medicine. I'm joined by an expert in that topic from MGH. My co-host today is Dr. Warren Zapol, Director of the Anesthesia Center for Critical Care Research at MGH and Ameritas Anesthetist and Chief at the hospital.

The Zapol lab is currently looking at what they describe as illnesses that can be therapeutically treated with novel inhaled gases. That includes new uses for the gas nitric oxide, which my co-host started working with several decades ago. In the 1980s, he hypothesized that nitric oxide could be used to treat blue babies, newborns who can't get enough oxygen. Nitric oxide has become a standard treatment for these patients. His interest in how oxygen is stored and used in the body has also sent him far beyond the pediatric ward. He began studying the Weddell seal, a mammal that lives in the oceans around Antarctica, which can process gases in its body in an extraordinary way.

Welcome to the protocol podcast, Doctor Zapol.

Dr. Warren Zapo...: Thank you very much, Sarah, for inviting me.

Sarah Alger: It's our pleasure. So what's out of the ordinary about this Weddell seal?

Dr. Warren Zapo...: The Weddell seal is a deep diving, extraordinary, huge seal. It's about 1000 pounds, maybe 2000 pounds in that range. And amazingly pregnant Weddell seals went as long as 90 minutes underwater.

Sarah Alger: Wow.

Dr. Warren Zapo...: So it's an enormous diving machine that is really, really capable.

Sarah Alger: So in the mid 1970s, you started going to McMurdo station in Antarctica to study them. But why, what did you hope to find?

Dr. Warren Zapo...: I wanted to know their strategy. At that time, we lost people from hypoxia, low oxygen levels in their blood.

Sarah Alger: So when you're talking about people with hypoxia, do you mean newborns? Do you mean older people with emphysema or other kinds of people?

Dr. Warren Zapo...: Sadly, it's all of them. Almost anyone who doesn't breathe for a while, human, we can lose him in the operating room. And we did. We could lose them in the intensive care unit. And we did. So if you disconnect, you don't last very long. So learning how to deal with low oxygen levels is a lot of the drive that got me studying Weddell seals in 1976. And I was interested to learn how animals could cope with low oxygen levels, where they would send blood flow, how they would deal with it. I really didn't know. And I was interested in and amazed at the specialization of the Weddell seal.

So you and I, 7% of our body weight is blood.

Sarah Alger: Huh.

Dr. Warren Zapo...: The Weddell seal, enormous big animal, 14% of their body weight is blood. So more blood and more cells per drop, a droplet of blood of a Weddell seal has about 60% hematocrit, which is a lot of red cells to carry oxygen around. So they are extraordinary oxygen collectors, much more than we are.

Sarah Alger: And how many trips have you ultimately taken to Antarctica?

Dr. Warren Zapo...: I think a dozen, maybe 13, something like that. Of which about 11 were grant funded by the National Science Foundation. So we were very lucky. We did something that Coyman, who was at San Diego, had worked out called isolated hole diving. So we would catch a seal, pregnant seal, non-pregnant small males, whatever we were studying and had been approved to study. And we would put the seal in a sledge, a big sledge. And sledge the seal out to a place where we could convince the Navy to drill a hole, usually took a bottle of scotch or two, but we could get them that drill an isolated hole for us 25 kilometers offshore. And then when we would anesthetize the seal. We had Bob Schneider, an excellent seal anesthetist. And we would anesthetize the seal, glue the microcomputer to its fur, which would molt and drop off every summer. And we had a great time. I mean, it was just exciting, and we had no idea what we would measure and find until we measured and found.

Sarah Alger: So we are joined by Dr. Allyson Hindle also from the Anesthesiology Department at MGH. Dr. Hindle continues to study the Weddell seals and conducts research with the anesthesia center for critical care at MGH. Welcome Dr. Hindle.

Dr. Allyson Hin...: Hello. Thanks very much for including me.

Sarah Alger: So Dr. Hindle, when were you most recently in Antarctica?

Dr. Allyson Hin...: I was most recently in Antarctica two years ago. In fact, almost exactly two years ago. This is the time of year when we would be packing up our things and getting ready to go to the ice. We work with the seals, in particular, in the south, the Southern hemisphere spring and summer when it starts to become daylight 24 hours a day. But the sea ice is still very strong and safe to travel on. By about Christmas time, it's getting a little bit warm and the sea ice is starting to break out, which makes it difficult for us to travel to reach the seals.

Sarah Alger: So can you give us a little background on what you've discovered about the seals so far, and what you're going to be looking at next?

Dr. Allyson Hin...: Sure. I think what Dr. Zapol talked about is so important to how we understand what these animals are capable of. Being able to take measurements of physiology in unrestrained freely diving animals truly opened our eyes to what kind of a model system these animals could be and what we could truly learn from them. So I continue to do some of that work as computers get a little smaller and their memories get a lot larger. We can start to send out computers on seals for much longer periods of time to start to get an idea of what the variation is for individuals, what their exposure is to low oxygen and what the range of their cardiovascular capability is.

At the same time, this is a really exciting time because I think we're now able to start to apply modern molecular techniques that are so well-developed for humans and for other well-known lab animals to crazy animals like seals. We have now the genome of the Weddell seals. So we're able to start asking questions about what proteins and what molecules might be important in how they manage their metabolic rate and survive low oxygen.

Sarah Alger: And have you found anything really surprising or exciting so far?

Dr. Allyson Hin...: I have to say the most interesting findings that we've had so far have largely conformed to Dr. Zapol's hypothesis that he made quite a long time ago. So, I mean, that's really rewarding that we're able to come back in with a modern look and we're able to apply some of these cool molecular techniques and really see what's happening at the level of the vasculature.

Trying to understand how nitric oxide, which operates in the bloodstream, causes arteries to relax so that more blood can flow through them. And if you're a seal, maybe they're using that or not using that to control where oxygenated blood is traveling within their bodies. So we've been able to show that in really important organs, like the brain, that needs to be paying attention the whole time that they're underwater, that a lot of these molecular mechanisms look like they could support a way for more blood to flow to the brain.

Sarah Alger: Do I have the right impression that you form some kind of relationship with the seals? Like if they're coming back to the same hole, you kind of get to know them?

Dr. Warren Zapo...: Yes. I think you do get to know that seal. And sometimes they're happy to see you and sometimes they won't dive, they sit there looking at you with a smile on, and especially if they've recently, you could see by looking in their plasma that they've had a big meal of cod fish. They love the Antarctic cod, which is about four foot long, weighs about a hundred pounds. And sometimes they bring one back for you if they like you. So, you know, I don't know.

Sarah Alger: Dr. Hindle, did they bring fish back to you?

Dr. Allyson Hin...: I haven't experienced that. But I can say that's not a fishtail. I have heard this story from many different researchers that I can confirm that that can happen.

Sarah Alger: All right. Well, thank you Dr. Zapol and Dr. Hindle.

Coming up, we'll hear about another animal that can survive in icy temperatures and the promise it holds for stroke victims and astronauts.

Dr. Warren Zapo...: You're listening to the Proto podcast, a production of the Massachusetts General Hospital.

Sarah Alger: The most recent issue of Proto magazine looks at a fascinating frontier for stroke research. Animals as varied as groundhogs, grizzly bears, and skunks can get by for months with low levels of oxygen to the brain. That's because this group of animals hibernates in cold weather. Proto editor, Jason Anthony, spoke with Kelly Drew. She has studied hibernation for more than 20 years as a biochemist at the Institute for Arctic Biology at the University of Alaska, Fairbanks, where the average temperature in January is a frosty eight below. Jason began by asking her for a definition of hibernation.

Kelly Drew: So hibernation is really energy conservation. So everything you can imagine about energy conservation on a global scale is something that these animals do on an individual physiological scale.

Jason Anthony: How might it be helpful to humans to understand this process of hibernation better?

Kelly Drew: Well, for humans, we hope to be able to apply some of the mechanisms we learned from hibernating animals to treat aspects of disease. Everything from severe critical care for cardiac arrest, or stroke, traumatic brain injury, or spinal cord injury, all the way up to metabolic syndrome, obesity, diabetes, that kind of thing.

Jason Anthony: So you mentioned stroke. What would the benefit be for stroke victims in studying, say an animal in hibernation?

Kelly Drew: Hibernating animals, they have such a reduction in blood flow to the brain and other organs that it is really equivalent to the blood flow you would see in a person having a stroke. But the ground squirrels have no injury from that. So understanding how they tolerate that low blood flow can give us clues to designing new therapies for people who have suffered a stroke.

Jason Anthony: You've mentioned these Arctic ground squirrels. I wonder if you could tell us a little bit about their lives, especially in the winter?

Kelly Drew: Well, it's kind of the perfect scenario for people who live in the cold climates. They are up and about in the spring time, they come up above ground. They immediately get to reproduce, have sex. They have babies. They eat as much as they want. They get really fat and then they go underground. So they don't have to be bothered by the poor climate conditions. And meanwhile, they lose their fat. They pretty much maintain their muscle mass and they wake up in the spring and get to do it all over again.

Jason Anthony: Do we know what it is that's protecting them during this long winter? Is it a chemical, or is it the temperature, or something else?

Kelly Drew: So we have found out that temperature really plays the biggest role. We've not found anything different that can account for this protection except for temperature. And temperature is dramatically protective. And we found that out at about the same time that we discovered in another parallel focus area, that we could induce this cooling with a chemical in the brain that regulates the onset of hibernation. So not only do we understand something about how the brain regulates hibernation now, but we also can apply that to non-hibernating species to promote cooling.

Jason Anthony: That includes humans?

Kelly Drew: Well, we haven't tested it in humans yet, but that's our focus. That's our direction, to move it into humans. So right now we're just working in rodents. We've tried it in pigs, and it completely eliminates shivering in pigs. But of course, it doesn't promote cooling, it just turns off, it turns down the thermostat. And so depending on the ambient temperature or the surface temperature that the animal is exposed to, they'll drop temperature after the thermostat is turned down.

Jason Anthony: So if we can cool an animal down without it feeling discomfort, what are the benefits then? How does low temperature benefit organs of the body or the body in different ways?

Kelly Drew: So low temperature does many, many things. I think the easiest to probably appreciate is seeing what happens if you put ice on a sprained ankle, or if you put ice on a burn. And so it eliminates inflammation, it attenuates some of the other pro-oxidant effects of injury. So it lowers the production of free radicals. In response to injury in the brain, it completely eliminates the release of what are called excitatory neurotransmitters that cause injury. And so just about every aspect of the injury process that has been investigated, cold tissue temperatures will attenuate.

Jason Anthony: So how cold do these squirrels get? How cold do they allow their bodies to get?

Kelly Drew: So the Arctic ground squirrel is most famous, because it can super cool. Its core body temperature can go down to below, down to about minus three degrees centigrade. So below freezing. But you don't have to get that cold to see a benefit. And so right now we are focused on the range of temperature that is tolerated by humans.

Jason Anthony: Have we been able to cool people in medical situations in a way that prevents further injury?

Kelly Drew: Yes, we have. It's the standard of care for cardiac arrest. So what most people don't recognize is that with cardiac arrest, even after blood flow is returned, people subsequently die, usually within a week, due to brain injury. And so clinical trials have shown that if you cool somebody to 32 to 34 degrees after a resuscitation, it can almost double the number of people who walk away from the hospital neurologically intact.

Jason Anthony: Are there other benefits of hibernation that we haven't touched on? Are there other ways that it might help in other medical conditions?

Kelly Drew: There are two important applications related to bone and muscle loss, following prolonged disuse and or just caloric restriction. So with dieting, particularly in the elderly, it's difficult to lose weight without losing muscle mass. The ground squirrels, they don't eat for up to nine months and they wake up without loss of muscle. They primarily lose fat tissue and preserve muscle strength and mass. And similarly, with bone, they don't move for up to nine months while they're hibernating, they're curled up in a ball and yet they don't lose the bone strength or density over prolonged disuse. So that is important for people that are recovering from broken bones and are bedridden. They often lose both muscle and bone mass. And understanding the ground squirrels do that as well as hibernating bears could lead to therapies for those conditions.

Jason Anthony: And I understand it might also have some applications in space travel?

Kelly Drew: For astronauts loss of bone strength and density is really an important problem after they returned to earth, as well as loss of muscle. So if we can understand how the ground squirrels protect against this loss of bone and muscle, we could develop therapies for astronauts, for long-term space travel.

Jason Anthony: So the Arctic ground squirrel is going to help us get to Mars.

Kelly Drew: I think so.

Jason Anthony: Kelly, thank you.

Kelly Drew: Well, thank you. Jason.

Sarah Alger: Kelly Drew is a biochemist at the University of Alaska Fairbanks. She spoke with our own Jason Anthony.

I'm joined again by Dr. Warren Zapol, Director of the Anesthesia Center for Critical Care Research at Massachusetts General Hospital, and Dr. Allyson Hindle, a key researcher at the Center.

Dr. Hindle, I understand that you also conduct hibernation research. What do you find promising about this field?

Dr. Allyson Hin...: I think that Kelly did a really great job of elucidating so many of the things that we can learn from hibernating animals. I think nature has a lot to teach us. What I hope that we will take from hibernation research in the coming decade is really to apply what we have learned from these animals into human clinical settings.

Sarah Alger: Typically, medical research has done on a limited number of kinds of animals like rats, mice, zebrafish, but what happens when you start to go beyond these species? Are there challenges to investigating with more exotic animals, like the seals or the Arctic ground squirrels?

Dr. Allyson Hin...: I think there're two main challenges for the seals, and this is true for animals that hibernate in Alaska. The logistics of doing work with them is obviously much more difficult. And many animals are protected and require specific permits in order to be able to access the places that they live or to work with them directly. So there's certainly more planning and more of a lag time that goes into the work.

But on the other side, when we talk about rats and mice and zebrafish, we have a whole toolbox of things that we can throw at problems to understand and unravel the molecular biology and the genetics of how their physiology works. And we are only now really starting to have those same tools for what we call non-model species.

So I hope that we will be able to use those tools to really advance our understanding of how animals can do what they do.

Sarah Alger: So how do you take findings like this in animals and try to apply them to people in some way? What are the next steps for something like that?

Dr. Allyson Hin...: Well, I think something that's important to remember is that when we're talking about mammals, even very diverse mammals, we share a lot of the same genetic and genomic information. So if we can get to the point where we're identifying the mechanisms and the genes that are making proteins that are protecting species out there in the world from extreme environments, or are controlling some sort of process that we think is key to their ability to thrive under extreme conditions, then we can ask the question about how that is related to what's going on in the human genome. We can look at the evolution of how those proteins are expressed in other animals. And we can see, maybe we have the code for it in our own genomes. We're just not using it right now.

Sarah Alger: Dr. Zapol, do you have anything to add to that?

Dr. Warren Zapo...: Interestingly enough, I spent a lot of time studying the spleen of a Weddell seal, which contracts as the seal goes into diving mode and squeezes out a lot of red cells. So maybe a third of your red cells are sitting in your spleen sleeping and your blood is not so viscous. And then when you go diving as a Weddell seal, we found their hemoglobin went up and the hematocrit went up to about 60%.

Sarah Alger: So the seal is able to use its spleen to increase its capacity to carry oxygen in the blood. Is that right?

Dr. Warren Zapo...: Correct. Absolutely right. And it does. So there's a lot of smarts here. But we found that human divers, when we used ultrasound, also when they started diving, their spleens contracted and their hemoglobin went up, not nearly as much as a seal. But I think as human physicians, we realize that for example, this idea of spleens contracting and raising red cell concentration is very important. And I think we learned not to let the red cell concentration get too low in humans. And we learn to transfuse humans at a higher level than we used to transfuse. So instead of letting people get down to 25% cells or 20% cells, which we frequently did, we now realize it's better to be at a higher level, like a seal.

Sarah Alger: Hmm.

Dr. Warren Zapo...: Like other creatures. So I think medicine learns sometimes from other mammals and their strategies.

Sarah Alger: Dr. Zapol and Dr. Hindle, thank you for joining us today.

And listeners, thank you for tuning in to the Proto podcast.

Dr. Warren Zapo...: Today's podcast was produced by Emily Silver, Bradley Klein and Jason Anthony.

Sarah Alger: Thanks also to our technical directors, Adam Keller and Chelsea Andes.

This episode, we also had help from Rob Prince, who is a Professor of Journalism at the University of Alaska Fairbanks. Rob is the host of Dark Winter Nights, a live storytelling event and monthly podcast about Alaskan life. You can find that at darkwinternights.com.

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