Ask A Biologist Vol 084 (Guest Andrea Graham)

One Wormy World

Around 4,000 years ago, on the wind-swept island of St. Kilda, Scotland, people started creating a food storage of sorts. They moved a population of sheep to the island, likely as a back-up food resource for when times were tough. Little did they know that their actions would affect 21st century science. Today, rather than ending up as a meal, sheep from this isolated population are the subjects of research on immune function. Evolutionary ecologist Andrea Graham takes Dr. Biology on a trip of exploration through the dangerous cliffs, windy conditions, and wormy world that the Soay sheep deal with on St. Kilda.

Transcript

[wind blowing – sheep sounds in the background]

Dr. Biology: This is "Ask A Biologist," a program about the living world, and I'm Dr. Biology. For our show today, we're going to be taking a virtual trip to the wind-swept island of St. Kilda to learn about the Soay sheep. If you're not familiar with this island, it's off the coast of Scotland.

And, yes. I did say sheep. You can hear them in the background. To be precise, we're going to be talking about some nasty worms that live inside some of the sheep.

How they either resist or tolerate the worms is very important to their overall health and survival. My guest today is Andrea Graham, an associate professor of Ecology and Evolutionary Biology at Princeton University. She's at Arizona State University giving a talk at the Center for Evolution and Medicine about Antibodies, Health and Disease.

For our show today, we'll be talking about resistance and tolerance in the body, along with immuno-parasitology.

I know, another word that just rolls off the tip of your tongue. But this one is simply a part of biology that deals with animal parasites in their hosts. In this instance, the worms are the parasites and the hosts are the sheep. Welcome to the show, Andrea Graham, and thank you for taking time to talk about your work with the Soay sheep.

Andrea Graham: Thank You. It's a pleasure to be here.

Dr. Biology: I guess the first question would be, why work on sheep, and why the sheep on St. Kilda?

Andrea: Why work on sheep? It's true that we think of sheep as being domesticated animals. They give us wool. They give us milk. They are very widely cultivated in agriculture. But it turns out they might be really useful for developing our understanding of how hosts deal with infections, as well.

One major reason is that -- unlike the mice that are very frequently studied in immunology research, in understanding how we fight off infections -- sheep actually live quite a long time, in terms of how their life histories are designed. They start to approximate the lifespan of a human host certainly much more closely than a mouse does. Because a mouse, at best, lives only two years.

These sheep, some of them live up to 15 years and beyond. We think that sheep may actually provide a better view of the mechanisms of defense against infection, in a species in which preservation of life, extension of lifespan, is more central to the biology than it is for mice. Mice are really rigged for breeding.

They're really good at making more mice and they don't tend to live quite so long. So we think sheep are good in that way. We think that these sheep on the island of St. Kilda are especially interesting, because they have lived without human intervention for a really long time. They're unmanaged. They don't get vaccines. They don't get drugs to clear them of their infections.

They're doing it on their own. They also have a heavy burden. They're exposed to a lot of infectious agents and this is super important too. Not only are the sheep interesting enough themselves and doing it without the aid of medical intervention but people are observing them very closely.

I joined this study really quite recently, but others have been studying these sheep since 1985 making the most detailed observations you can imagine. We know everybody's birthday. We know everybody's date of death. It's a really quite extraordinarily detailed data set about the lives of these individuals and the worms they carry in their guts.

Dr. Biology: Oh. We're going to get to the worms in just a bit. This is where the true gory parts come in but also the really good learning parts. St. Kilda, as I mentioned at the beginning of this show is an island, and I suppose that's good because these sheep are captive.

Andrea: That's right.

Dr. Biology: One of the questions I have is, how did they get on the island in the first place?

Andrea: Yes. This is quite an amazing part of the story. About 4,000 years ago, during Neolithic times, people brought sheep out to this island as a backup food supply in case the fishing and such failed.

It is strange to think of sheep living out in the middle of the North Atlantic on this very tiny island, but there they have been for 4,000 years largely unperturbed by humans, although the early inhabitants did hunt them when the seabird egg crops failed, as it were.

But yes, it's a strange environment for sheep, but since they're captive on that island, we can actually reliably capture individuals repeatedly, and that is super important for watching how host parasite interactions change over the course of a lifetime.

Dr. Biology: Right. Host parasites. These are those worms.

Andrea: The parasites are the worms. They're the ones I think about the most.

Dr. Biology: Right. So, these are the round worms?

Andrea: Yes.

Dr. Biology: All right. You also talk about infections. In Ask A Biologist, both the website and this podcast, we often talk about infections. You can get an infection from a cut. You can get an infection from catching of a flu virus or a cold virus.

There's also bacteria. In this case we're talking about something different. We're talking about a parasite. What are the relationships out of that, and how does the body defend against the parasite versus when I get a virus?

Andrea: The key distinction I'd like to draw here is the sheer size of these parasites. Viruses are just vanishingly small. You can't see them without the aid of very fancy microscopes.

Worms on the other hand, can range in size to being meters long. Some of the tape worms that live in the gut are the most extraordinary in terms of their sheer size. You do not need a microscope to see that.

The worms that the sheep have are somewhere in between, but you definitely can see them with the naked eye. The key thing here is that they're living in the gut. They're living in the stomach, one of the many stomachs of sheep, and the challenge for the immune system is to push them out, basically push them toward the exit as it were.

Whereas if your sheep are fighting a virus infection, it's much more a case of either getting a cell to gobble up that virus, getting an antibody, or other molecule to bind to a virus and stopping it in its tracks. But those are too small.

The molecules and cells that are really good in clearing a virus infection, they can't get any traction on these big parasites. And instead, basically on the immune system, co-opts the gut physiology, the one way traffic through the gut and pushes the worms out the other end. Mucus is a really big player in this.

The mucus that is used as part of normal digestion anyway, gets ramped up to a high level and shoves the worms out the door.

Dr. Biology: Can you get rid of these roundworms on your own if you don't have any kind of treatment?

Andrea: Yes, some hosts do. They have the right genes to help them get that purging done. But most, domesticated sheep need a lot of help with it. Certainly drugs that help paralyze the worms and make them easier to shift out of the gut, are incredibly important to agriculture.

Dr. Biology: There are a couple words I used earlier on, and there's a difference between the two of them. But, they're still both very important to our health and basically any animal health like in the case of our sheep. That's the difference between tolerance and resistance. Can we talk about those two words?

Andrea: Yes, of course. Resistance is a word that biologists use to talk about the ability of a host to kill the virus, kill the bacteria, kill the worm, or get it out of there. This whole purging mechanism that I was talking about is a resistance mechanism, because it reduces the number of parasites in your body.

Tolerance on the other hand, is a way of letting them be, letting them stay in the body, but maintaining your health despite their continued presence. We're just starting to understand what some of those mechanisms might be. But we are starting to think they're at least as important as resistance mechanisms in promoting health.

Dr. Biology: Right, because there's a certain amount of energy required to push them out or to get rid of them, verses if you can just cope with them in your body?

Andrea: And get on with growing, and living, and breeding, all these priorities animals have. We think that maybe just as important as clearing parasites.

Dr. Biology: Do all the sheep have the worms?

Andrea: Very high fraction of them do. The prevalence is often as high as 80 or 90 percent. 80 or 90 percent of the sheep, especially when they're lambs the young are very full of worms. The percentages drop off in adulthood and that's because the sheep's immune systems learn how to resist the parasites.

Dr. Biology: How do the sheep get the worms in the first place?

Andrea: That's important. It's transmitted by feeding on the wrong bit of grass basically. If the sheep are foraging for their dinners in the greenery on the ground, and if there are nematode larvae, young worms attached to that grass, they will ingest the parasites along with their food.

Then the parasites, from their point of view, they undergo some development in the gut. They partner up with another worm, they make some babies and that gets passed out in the feces. So that everything's happening in the intestinal tract and it gets passed out with the poop of the sheep.

Once the poops on the pasture, those little larvae can come out again and get ready to infect the next host. It's what we call a fecal-oral transmission, because it depends upon ingestion of another host's excreta.

Dr. Biology: OK, we will not be eating grass.

Andrea: No, don't eat grass.

Dr. Biology: All right, you had these sheep on the island and you have a bunch of scientist there studying them. How do you catch the sheep?

Andrea: That is tricky I must say, because we can't use sheepdogs even if the National Trust for Scotland would allow it. We couldn't do it because these sheep do not act like the sheep that sheepdogs are used to. When someone approaches these sheep, instead of flocking together and being herdable, they bolt in every direction, and they're bolting on a bunch of sea cliffs, and over Neolithic Ruins. It's really rough terrain, and they're of course nimbly running around.

All these scientists who spend most of the year in the lab, behind the computer, whatever they're doing, are trying to run around. There have been broken ankles, I myself lost all the skin on my left knee, falling, tumbling about. But, what we end up doing, with a lot of clumsiness along the way, is herding them into traps.

Basically, we herd them into gaps in the walls of the old settlement there. There are gaps in the walls into which we install hemp fencing, and we herd them in there and then quickly close the gate. Then we're able to herd them with tarps and things into a corner of that. But, only once we get them in a confined space by just chasing them through gaps is pretty low tech and pretty hard on one's joints.

Dr. Biology: We need a video of that. I bet that could be put to some comical music.

Andrea: Yes, absolutely. In fact, sometimes people make these videos inevitably. There's some great tumbling fall that one of the scientists takes right in front of the camera. Yes, there actually is good footage of this.

Dr. Biology: I visited your website, and I found a page that I really like. It highlights what scientists do. What I'm saying is, scientists ask questions. They seek answers. These are the how and why type of questions we all have, and I say we all have at least when we're young. When we're young, we're full of wonder, and everything's fun to explore.

You listed five clear questions on your website. I don't always see this in every lab website. The number one question is, why are hosts, here we'll talk about our sheep, prone to producing overzealous, and really like to do a lot of responses that cost proteins, and then we're going to have to talk a little bit about proteins, and may actually even cause disease? That's a really big question.

Andrea: It is a big question.

Dr. Biology: Let's unpack that and let's talk about it.

Andrea: I'd be delighted. That is my favorite question. That's why I put it at the top of my list. You're right. It's multi-layered. It's really getting at trying to understand why immune systems harm their bearers and trying to understand the genetic and environmental causes of that.

In particular, it defies our expectations about organisms in a natural environment, because we think that every bit of food that you eat that you could convert into growing stronger, so that you win the next wrestling match. If you are mounting an immune response, you often have to direct that calorie or the proteins that you eat into the immune response. Instead, you have to invest in it.

It's to the detriment of other stuff you want to do, like grow. There are many other priorities in life, but immune responses can detract from all those other priorities. What on earth are hosts in natural populations, who are very often food-limited? They're hungry. The sheep, for example. They almost never have enough to eat, especially at times of high density of sheep on the island.

What are they doing investing so strongly in immune responses, when it comes at this cost to the rest of what they might like to do? That's one part. Then, there's the other part. Like, the vertebrate immune system is supposed to be the pinnacle of adaptive evolution, this wonderful machine that can achieve things like remembering a flu virus for decades.

All these great examples of the wonderful things is the immune system can do, but it also can blast holes in the host's own tissue. I just find that a great puzzle. I want to understand that.

Dr. Biology: In other words, it can turn on itself.

Andrea: Correct. That's what I mean.

Dr. Biology: That'll get us into some of the things you've been doing with the autoimmune diseases. Some people know about some of the arthritises that are autoimmune, but you are spending time with a particular one called lupus.

Andrea: That's one of the ones I think about a lot.

Dr. Biology: Let's talk a little bit about what lupus is, and then how these sheep are going to relate to lupus. Because a lot of people when we think about research, it's not always really clear what we're doing out in the middle of an island in a really cold windy spot researching these sheep that are wild. What's the link?

Andrea: The easiest way to explain the link is that, lupus is an antibody-caused disease. What happens is these molecules that are so powerful in defense against infection, if you have too many of them or they start clumping together or binding self too avidly, they can cause harm especially to kidneys. Host kidneys end up being smashed up by antibody.

What we've done in the sheep is to ask whether the propensity to make that kind of disaster unfold is a natural thing at all, or if it's something about the relatively artificial environments in which modern people live where we don't have very many worms. We are not food-limited.

Have we alleviated the nutritional cost of immunity, such that we can invest in these very crazy, strong immune responses that might do more harm than good? We looked for the evidence that any of this kind of this autoimmune condition existed at all in the sheep. When we found it, we went on. That was finding a) it is out there in a population that's full of parasites and often food-limited.

It does seem to be some sort of natural phenomenon. What became more interesting is when we went on to study how it might be associated with survival of the sheep. We found that the sheep who were potentially prone to that kind of disease manifestation, they actually had a survival advantage. We've been busily trying to unravel that.

Because if stopping short of when the actual kidney damage starts happening, if hosts experience benefits of having that kind of strong immune response or even self-reactive immune responses, we need to know that, if we want to understand why lupus and lupus-like conditions might persist in human populations. It gives us a test bed for the occurrence and causes of this kind of predisposition.

Dr. Biology: In the case of lupus, if left unchecked, it starts to attack tissues in the body and organs. In this case, you're talking about the kidneys. What's interesting is if I read this correctly or if I understand you correctly is that, the body, when it has nothing better to do, because it doesn't have to worry about these other things.

Now, it's got extra time on its hand, extra energy on its hand, does it start to turn on itself? Is that the way I'm reading it?

Andrea: Yes. I would say we need to ask and answer those questions. There's a little more to it. That is that, parasites often immunosuppress the host. If you think about it, that would be to the worm's advantage, if we return to the worm example. A worm who can turn down the immune system of the host is a worm who's going to live longer itself, and who is going to be able to lay more eggs.

We expect that to be very much in the best interest of the worm. If that also dampens the chances that the host will overreact to its own tissues, that it will have collateral damage to its own tissues, then having worms can also bring us benefits. That's why we would expect that in parasite-poor environments, we would expect more of these kinds of excessive immune reactions.

Dr. Biology: I read something when I was looking into your work. You said this area of science that you're spending time in, it enables you to, jointly pursue interest in symbiosis. Also, the parasite ecology in medicine.

Let's talk a little bit about that, because we have been talking about parasites. That's a one-way street. That's where the parasite benefits and the host doesn't. Often, the host either gets weak or dies.

Andrea: Yup.

Dr. Biology: In a symbiotic relationship, there you have two organisms that are benefiting from each other.

Andrea: We would call that even a mutualism, where there's mutual benefit.

Dr. Biology: In your work, where is the symbiotic part?

Andrea: Symbiosis means living together. Ecologists would say that even the host-parasite interactions are on the symbiotic spectrum, because it's organisms living together. You're very right to draw the distinction between a parasitic relationship and a mutualistic relationship.

Everything you can point at in, say what we think about human health and interactions with the microbes in our guts through to the most horrible, nasty pathogens like Ebola that sweep through human populations will fit somewhere on the spectrum between their benefiting to our clear detriment in the case of parasites or where our normal physiology depends upon their presence, as in the case of a mutualism.

I think modern medicine is starting to realize that a perfectly clean gut - let's keep talking about the gut because the data are best there. A perfectly clean gut is a terrible thing for a host to have.

Dr. Biology: This comes up, because we think of bacteria as something very bad and it's clear that we have very beneficial and critical bacteria in our gut. We have more bacteria in our body than we have cells?

Andrea: Correct.

Dr. Biology: Without these particular bacteria, we wouldn't be living, quite frankly?

Andrea: Correct. That's right.

Dr. Biology: What's next on your list of things to do and things to find out about the Soay sheep?

Andrea: I would say my number one, what's next, is figuring out the tolerance variation among them. What did we pick up on, when we saw that some of them were able to maintain their body weight in the face of a very heavy worm burden and others lose body weight in the face of that same parasite burden? What are we picking up on there? We don't know.

We don't know how they might be achieving that, the ones that don't lose much body weight. They might be the lucky ones. They were exposed to some subset of the parasites that are out there that just happened to be kinder. We don't know if it's on the parasite side or the host side or both and I'd love to know.

Dr. Biology: One of the fun things about having guests on Ask-a-Biologist is that I get to go out and explore what you've been doing and how you got to where you are. You earned your undergraduate degree in biology and sculpture?

Andrea: Correct.

Dr. Biology: After that you taught both of those subjects at New York City in the public high schools. Can you talk a bit about your journey in biology and the arts?

Andrea: Sure. One thing I like to say is that, producing both of my final projects for that dual degree enabled me to do the other. Each one enabled me to do the other, because I feel that the scientific thinking and the scientific writing, exercises one part of my brain really well. But it lets other parts wither.

So, I was delighted that when I had writers block or reached some sort of dead-end in the science project, I would go into the welding studio and make progress on my final project, for my sculpture degree, which was a throne. I made a throne out of found parts of Model-Ts and tractors and that sort of thing.

Dr. Biology: Do you still sculpt?

Andrea: Not as much as I wish I did. Being an oxyacetylene welder is not exactly a portable hobby. It's a difficult thing to take with you and I've traveled to many places. I'm very lucky to have been based in lots of places for my work and I haven't managed to bring the welding kit with me, but I ought to.

I do keep up my artistic side in other ways, but not my sculpture and that is my favorite. I really do miss it. But then I was even luckier I think, to take it into the high school setting, where it was really experiential learning high school.

What I did was I took students out into the city in small groups to either investigate scientific questions and many of them had to do with human behavior. These were teenagers and human behavior is one of their favorite things to think about, hypothesize about. We would study human behavior, for example on the subway system or I would take them into the city to do found objects sculpture.

We would rummage in the city and come up with objects that would be the basis for our next sculpture project. So experiential learning and really engaging the students in the city that way, was absolutely wonderful. I feel lucky about that.

Dr. Biology: You mentioned that the benefit, for you with the art and science, is you got to exercise both sides of your brain. Does your art background enhance your science career or possibly the reverse, where your science career enhances your art?

Andrea: I would say it enhances my science. I think that after college I got better at thinking across both sides of my brain, even about scientific questions. I don't always think about problems in the same way other people have thought about problems. I think that's a real strength. I think that has helped me as a scientist.

I also think that it's part of why I think it's important to have a handsome website or maybe I also bring aesthetics to my science communication and I'm glad about that. But I think I'm maximizing the potential crosstalk between these two parts of my interests.

Dr. Biology: This leads me into my three questions, I ask my scientists. So we'll jump in. When did you first know you wanted to be a biologist and in your case maybe first knew you wanted to be an artist?

Andrea: I would say that I just completely love being out of doors, poking around creeks and puddles. I grew up in Colorado. I spent a lot of time in the mountains and the life form that I remember getting most excited about really early on was lichen. I just thought lichen was amazing and maybe that's even partly why I was drawn to studying symbioses.

I couldn't believe it was this amazing collaboration that led to these beautiful lichens all over the rocks. As for when I first wanted to be an artist, I was a tinkerer with found objects from the start as well. Maybe both of them arise from being very curious about the world around me and trying to think about it in new ways and maybe assemble new things out of what I collected.

Dr. Biology: Now, I'm going to take it all away. You can't be a scientist. I'm going to take away your art.

Andrea: OK.

Dr. Biology: And I know you like to teach. So I have to do the trifecta for you.

Andrea: Oh dear. OK.

Dr. Biology: The reason I'm doing this is I want you to stretch. If you couldn't do any of those, what would you do or what would you be, if you could do any of those. I mean, if you could do anything?

Andrea: Anything but those three. I think that's a pretty straightforward answer, because I love languages. I think that if I couldn't do any of those things I would want to be, I don't know if linguist is quite the right word, but I'm fascinated by shared word roots across languages and then the extent to which some languages have really weird, out of left field roots to their words.

I guess maybe I'm cheating because in a way it's another evolutionary problem. I'm basically saying if you're not allowing me to study evolutionary biology, I might study evolution of languages. So maybe I'm cheating but nonetheless I think I'd want to study languages. Learn more of them, get better at them. I have a few second languages that are extremely poor and rusty and I would love to be able to have them flow more.

Dr. Biology: What are the languages that you have?

Andrea: French is my best second language but I've also studied Hindi and Japanese. Hindi, I have used to good effect and so I know it could be resuscitated in my brain if I only used it more. Japanese, I have never visited Japan. I've helped a couple of tourists who knew even less English than I knew Japanese. I was able to use it, but basically not very much.

The thing I like about those languages is they're ostensibly rather different from each other, except that Hindi does come from the Indo-European language group. So it's not surprising that there are commonalities there.

Dr. Biology: For our final question. What advice would you have for a young biologist or perhaps someone who wants to move into the world of biology from their current job?

Andrea: I think I would give the three word advice. Go for it. I think biology is a really, fascinating, fundamental science, but I think people are really appreciating, it is the wave of the future. It has not been as amenable to our analytical methods as physics and chemistry so far. It brings layer upon layer of complexity. We need all sorts of brains working on it to really figure it out.

It's also incredibly important to not only our health in the context of my own work but in terms of food security and climate. Just about every major challenge we face today, there's a biological element. We need all our best brains on the task.

Dr. Biology: Well, I'm biased of course. I would have to agree with you. Well, Andrea Graham, thank you for visiting with me today.

Andrea: Been my great pleasure. Thank you.

Dr. Biology: You've been listening to Ask-A-Biologist and my guest has been Andrea Graham, an Associate Professor of Ecology and Evolutionary Biology at Princeton University. If you'd like to explore more about the Soay sheep and Andrea's research, we have a story in our PLOSable section.

It's called, "Coping with Parasites in a Wild World." It's written by one of Andrea's colleagues, Adam Hayward. There is also an added bonus to the story. Like all our PLOSable stories it's linked to a primary research paper published in one of the PLOS journals. You can think of it is a fun way to get started reading articles written by scientists.

The address is, askabiologist.asu.edu/plosable/parasites-wild-world. Don't worry if you couldn't write that down. We're going to have the link from the podcast page. You can also learn about the Soay sheep project at soaysheep.biology.ed.ac.uk. That's actually spelled S-O-A-Y S-H-E-E-P.

The Ask-A-Biologist podcast is produced on the campus of Arizona State University and is recorded in the Grassroots Studio, housed in the School of Life Sciences which is an academic unit of the College of Liberal Arts and Sciences.

Remember, even though our program is not broadcast live, you can still send us your questions about biology using our companion website. The address is askabiologist.asu.edu or you can just Google the words “Ask A Biologist”. I'm Dr. Biology.

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