Erin Welsh	"Soon after my attention had been directed to the liver and its associated structures, I found in the blood of the portal vein a number of long, white helminths which with the naked eye I considered to be nematodes but soon recognized as something new. A look into the microscope revealed a splendid Distomum with a flat body and a spiral tail at least 10 times as long as the body. I have not yet reported the new stages of my portal vein worm. It did not, as I had expected, develop into an old wives tale but into something more wonderful, a trematode with divided sects.
	I performed an autopsy on a boy who died of meningitis. Upon opening the urinary bladder we found lentil to pea-sized soft, spongy excrescences. When I cut through the largest of the excrescences, a white thread adhered to the knife. Examining it more closely I recognized our Distomum haematobium. I searched the depth of the incision and pulled out several more the areas of the bladder mucosa where the earliest stages of the tumors appeared were covered with viscous, clear mucus containing large numbers of Distomum haematobium eggs, singly or in clumps.
	When I showed Dr. Lautner the Distomum haematobium found in the bladder he remarked that he too had seen the eggs while studying the pathologic changes of the bladder but had not been able to explain them. He and Dr. Griesinger encouraged me to examine the pathologic changes of the bladder which were so similar to those found in dysenteric degenerations of the intestine. Further investigations in this country which I shall continue zealously as well as those being carried out in Europe, investigations to which I invite my colleagues, will have to decide whether Distomum haematobium stands in the same relation to dysentery as Acarus scabiei does to the itch."
TPWKY	(This Podcast Will Kill You intro theme)
Erin Allmann Updyke	All right then.
Erin Welsh	So that was from excerpts from letters from Theodor Bilharz to his supervisor von Siebold while conducting research in Egypt.
Erin Allmann Updyke	Oh.
Erin Welsh	And this was essentially the discovery of Schistosoma haematobium.
Erin Allmann Updyke	The subject of today's episode.
Erin Welsh	One of the subjects, schistosomiasis in general. Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	Yeah.
Erin Welsh	Welcome to schistosomiasis.
Erin Allmann Updyke	Schistosomiasis. My first true love of disease.
Erin Welsh	(laughs) I like the qualifier there. Not just true love?

Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah I'm excited too, I mean we love a good multi-host parasite.
Erin Allmann Updyke	Yeah we do.
Erin Welsh	It's fascinating, the ecology's there, it typically has some long history.
Erin Allmann Updyke	Ooh I can't wait to hear the history because I know nothing about it.
Erin Welsh	Oh man, I'm very excited about this. This is like a full, rich history. I didn't have to color in the edges with some other external histories.
Erin Allmann Updyke	Blood products, etc.
Erin Welsh	Hey now.
Erin Allmann Updyke	That was great.
Erin Welsh	No, true. Okay so what are we drinking this week?
Erin Allmann Updyke	We're drinking Just A Fluke.
Erin Welsh	Because also schistosomes are known as flukes.
Erin Allmann Updyke	Flukes, yeah. It's a type of flatworm.
Erin Welsh	Blood flukes, yeah. And in Just A Fluke is pomegranate juice, vodka, club soda, mint simple syrup, maybe a little bit of lime juice, and then you garnish with some pomegranate seeds if we can find them from the store.
Erin Allmann Updyke	Fabulous. And as always we'll post the full recipe for this quarantini as well as our nonalcoholic placeborita on our social media and our website so you can check it out there.
Erin Welsh	Yeah. Now let's dive into schisto.
Erin Allmann Updyke	After this quick break.
TPWKY	(transition theme)
Erin Allmann Updyke	So schistosomiasis, also called bilharzia because as you mentioned from our firsthand account, the person who discovered it.
Erin Welsh	Yeah. Theodor Bilharz.
Erin Allmann Updyke	Can we call him Teddy? Do you think he went by Teddy?
Erin Welsh	I have no way of knowing. There probably is Google actually.

Erin Allmann Updyke	Teddy Bilharz. That's a cute name.
Erin Welsh	Yeah, I like it. I like the name Teddy.
Erin Allmann Updyke	So schistosomiasis aka bilharzia is caused by a worm, we haven't done a ton of worms so this is exciting. It's a flatworm and specifically one that's called a fluke, that's the type of worm that it is.
Erin Welsh	Why is it called a fluke?
Erin Allmann Updyke	That's a good question that I don't know.
Erin Welsh	Okay.
Erin Allmann Updyke	I feel like that's a history question.
Erin Welsh	Oh dang it, how dare you. (laughs)
Erin Allmann Updyke	So there are a number of different species of schistosomes that infect humans. The three most common are Schistosoma mansoni, japonicum, and haematobium. There are a few other species as well that are less common and they all have the same basic life cycle and overriding general pathways by which they travel through the human body and cause disease but they do cause slightly different diseases, especially between Schistosoma mansoni, japonicum, and haematobium, it's kind of like the special one. So what we're gonna do is talk about the general life cycle and pathway first as a group, like all the schistosomes, and then we'll talk about the symptoms and we'll talk specifically about the differences between them. Does that sound good?
Erin Welsh	Sounds great. Also I just looked up 'fluke' etymology.
Erin Allmann Updyke	Oh, tell me.
Erin Welsh	And apparently the Old English word 'floc' means flatfish and so the worms were called that because they resembled flatfish.
Erin Allmann Updyke	Little flounders. I can see that.
Erin Welsh	Yeah.
Erin Allmann Updyke	Cool. Thanks Erin, for answering your own question. All right so like we mentioned briefly one of the reasons that Erin and I get excited about a parasite like this is that it has a very complex life cycle and transmission cycle. So it goes a little something like this. I'm simplifying this a little bit but this is the general overview, okay. So we'll start with the eggs because you have to start somewhere in the cycle. So the eggs are present in the environment and they hatch in freshwater, okay. And out of these eggs hatch these little miracidia is what they're called but we'll call them baby schisto, okay.
Erin Welsh	Okay.

Erin Allmann Updyke	So baby schisto have all these little cilia around their edges which act like swimmers so that they can swim through their environment. Erin, I wrote they swim their way into a crab. Why did I write crab? (laughs)
Erin Welsh	Oh my god.
Erin Allmann Updyke	That is incorrect.
Erin Welsh	That is incorrect.
Erin Allmann Updyke	That is 100% incorrect, I can't believe I wrote 'crab'. How funny. So with these little swimmers they swim their way through freshwater into a snail, okay. And it depends on what species of schistosome, what species of snail they go into but they all make their way into snails. And inside these snails the baby schistos begin to multiply asexually.
Erin Welsh	So that's really interesting.
Erin Allmann Updyke	It is.
Erin Welsh	That's really wild. I started to talk as you were finishing that sentence. Also how do they get into the snail? Do they penetrate the snail's body?
Erin Allmann Updyke	Yep, little fleshy parts.
Erin Welsh	Okay. So they replicate asexually which is wild considering in the firsthand account we learn that there's-
Erin Allmann Updyke	Oh Erin, we'll get there. Don't you worry. These are baby schistos, okay?
Erin Welsh	These are the baby schisto. I won't talk again.
Erin Allmann Updyke	We're going through life stage by life stage.
Erin Welsh	Okay.
Erin Allmann Updyke	So the baby schistos swam their way into a snail. They begin to replicate asexually, so multiply and multiply. And then they change into what are called cercariae and these are kind of like a kid schisto, okay. Kiddo schistos. They look kind of like sperms, okay.
Erin Welsh	Okay.
Erin Allmann Updyke	Not quite like a sperm but sperm-esque, they have a head and a tail that they use for swimming. So these kiddo schistos, spermy-looking things, swim, burrow their way back out of the snail and are released again into freshwater and then they use that tail to swim around through freshwater.
Erin Welsh	Over how many days or how long do they replicate in the snail?

Erin Allmann Updyke	I knew you were gonna ask that question, so let me tell you. The eggs, they can live in the environment for up to 7 days and then once the baby schistos make it into the snail it takes 4-6 weeks before they start shedding the kiddo schistos, there cercariae.
Erin Welsh	Wow, that's a long time.
Erin Allmann Updyke	It is. And now these cercariae can live in the environment for up to 72 hours.
Erin Welsh	That's a short time.
Erin Allmann Updyke	That's a short time. They're swimming around in freshwater and now here you come as a human mammal, walking around for a nice walk through these freshwater ponds or whatever. You're obviously barefoot because you would want to get your shoes wet and these little kiddo schistos see you, swim right up, and burrow their way through your skin and into your foot. Okay?
Erin Welsh	Okay.
Erin Allmann Updyke	All right. Okay. So now these little spermy cercaria have wormed their way into your body, okay, and then they're gonna change yet again. That spermy tail is gonna fall off and they are going to start to swim in your body, a mammal body, and make their way into your bloodstream. So now you can think of them kind of as teenagers, these are called schistosomula at this point.
Erin Welsh	Okay.
Erin Allmann Updyke	So they're like the sperm without the tail, just a little head part. Okay?
Erin Welsh	Okay.
Erin Allmann Updyke	So inside of you they make their way as many parasites do into your bloodstream, either directly through your little capillaries or through your lymphatic system first. Then they're going to travel - this is where it gets really fun, it's already fun cause how complicated this is. They travel through your venous system and remember your veins are what carry the deoxygenated blood back to your heart, right. So they're gonna travel through your veins to the right side of your heart. The right side of your heart is gonna pump these teenage schistos out into your lungs where they can then cross the capillaries and travel to the arterials which go back to the left side of your heart. And then your heart can pump them out yet again to the rest of your body.
Erin Welsh	Whoa.
Erin Allmann Updyke	And where they go from there is actually they make their way from your heart to your liver.
Erin Welsh	Okay.
Erin Allmann Updyke	This is a very complicated route, okay? They've entered your foot, they travel through your bloodstream, make their way to your lungs in order to get to your heart in order to get to your liver.
Erin Welsh	Okay. So it's kind of like it almost follows the route of the hookworm up until the liver part.

Erin Allmann Updyke	Yeah, exactly, yeah.
Erin Welsh	Or no it's before the liver part, to the lungs.
Erin Allmann Updyke	Yeah, to the lungs.
Erin Welsh	Okay.
Erin Allmann Updyke	Hookworms also make it to your lungs but then they make you cough and then you swallow them to get into your intestine.
Erin Welsh	Right.
Erin Allmann Updyke	So these guys go a different way. In your lungs they stay in your bloodstream. So they're basically just riding your blood flow all the way to your liver, that's their target destination for now. Okay? Then in your liver, and this is all the different species of schistosoma do this, okay.
Erin Welsh	Okay.
Erin Allmann Updyke	They make their way to your liver and then they're going to... Like your liver has so much blood flow, lots of veins, lots of arteries all in there and so in your liver they're gonna leave the arterial system yet again and make their way back into the veins in your liver. And that is where they're going to mature into full-fledged adult schistosomes. And like you mentioned in the firsthand account, they now have male and female schistos, okay. I don't know whether you could identify them previously but at this point as adults there are male schistosomes and female schistosomes. And then just like on Love Island UK-
Erin Welsh	Yes! (laughs)
Erin Allmann Updyke	They're going to couple up, okay, and sleep in the same bed together. Just kidding.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	What happens is the female schistosome literally wedges into a canal in the male schistosome called a gynecophoral canal. And then as a pair they travel together to their final destination.
Erin Welsh	Okay.
Erin Allmann Updyke	For Schistosoma mansoni and japonicum this final destination is the venous plexus around your intestines, the mesenteric veins. For Schistosoma haematobium it's the venous plexus around your bladder.
Erin Welsh	Okay.
Erin Allmann Updyke	I don't know why, I can see on your face you're about to ask me that.
Erin Welsh	I was. (laughs)

Erin Allmann Updyke	Yeah. It's a very interesting question as to why most species of Schistosoma tend to go to the veins around your intestines but haematobium goes to your bladder, it's a really interesting question that I don't know the answer to. But that is where they go. And then they live their lives as adults schistosomes where the female just lays eggs and eggs and eggs and eggs, so many eggs. And then what has to happen for them to complete their life cycle is these eggs have to make their way out of your body. So the way that they do that if they're in the veins around your intestine is those eggs will burrow through those veins into your intestine and you poop them out. If they're in your bladder they have to burrow their way all the way through your bladder which is a really thick organ, like it has a thick wall.
Erin Welsh	Cool.
Erin Allmann Updyke	Into your bladder and then you pee them out.
Erin Welsh	Okay.
Erin Allmann Updyke	Okay?
Erin Welsh	Is there ever any recoupling?
Erin Allmann Updyke	(British accent) Recoupling? Erin I practiced for like 10 minutes last night how to say 'couple up' and I think I still did a terrible job of it.
Erin Welsh	(laughs) Do you mean you watched 10 episodes of Love Island UK?
Erin Allmann Updyke	I literally sat with Brett saying the words 'couple up' for 10 solid minutes trying to get a good accent. Anyways.
Erin Welsh	Time well spent.
Erin Allmann Updyke	So that's the life cycle of Schistosoma. Cool?
Erin Welsh	Cool.
Erin Allmann Updyke	They can live in your body, these adult worms, you haven't asked me but let me tell you, for 3-10 years in your body.
Erin Welsh	That's impressive.
Erin Allmann Updyke	Just laying eggs, laying eggs, laying eggs. Okay?
Erin Welsh	That also makes it very difficult to get rid of environmental Schistosoma.
Erin Allmann Updyke	Do you wanna know what? The theoretical reproductive potential of one schistosome pair is 600 billion schistosomes.
Erin Welsh	Oh my gosh.

Erin Allmann Updyke	Because not only are the adults living in you shedding for years but one single miracidium that infects a snail can shed thousands of cercaria every day for months. They live in the snail for months.
Erin Welsh	That is incredible.
Erin Allmann Updyke	I know!
Erin Welsh	Whoa.
Erin Allmann Updyke	Yep. Yeah, it's incredible. And it does, it makes control of this very, very difficult.
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay so let's talk about the pathophysiology of how this... We know how it moves through your body but how does it actually cause symptoms? How does it actually make you sick? What's really important to keep in mind about schistosomiasis is that the symptoms that we see from this disease are not from the worms themselves, they're from the eggs. And they're also not even necessarily from the eggs doing what eggs are supposed to do which is leave your body through your poop or pee but the symptoms are caused by what happens when the eggs don't leave your body.
Erin Welsh	Really?
Erin Allmann Updyke	Yes. The fact that the eggs have to cross through, so they have to leave your veins right, they're living in the veins around your intestines or around your bladder. They have to penetrate through your vein walls and either into your bowels or your bladder. So you can imagine that this causes inflammation, right. They have to make holes in your veins and your bowel or bladder wall to make their way into the lumen of these organs. So in the case of the bowels in your intestines, what can happen is they can leave essentially little holes behind. So you can get microtears, microperforations, you can get intestinal bleeding. Any time you damage the wall of the intestine you can mess up its absorptive capacity so you can have malabsorption which means diarrhea and also potentially malnutrition because of this. Because you have bleeding from these little ulcerations you can end up with anemia especially in children who are already prone to anemia.
Erin Welsh	Yep.
Erin Allmann Updyke	Okay. So that's in the intestine. In the bladder what can happen really commonly is that the bladder wall is very thick, and this can happen in the bowels as well but especially in the bladder because of how thick it is, the eggs don't always penetrate all the way through so they can get stuck in the wall of the bladder. And what happens when the eggs get stuck in the wall of your tissue essentially is it causes a massive inflammatory response in your body. And your body tries to wall off this egg. Like your body recognizes this egg doesn't belong here, I'm gonna wall it off, and it forms what's called a granuloma which is basically inflammatory cells and tissue and debris walling off this egg. It's the same thing that we saw in tuberculosis, is what happens in your lungs.
Erin Welsh	Oh!
Erin Allmann Updyke	Yeah. So that happens as well in schistosomiasis. And in the bladder wall this can cause chronic inflammation, so one of the hallmark symptoms is bleeding in your pee, so hematuria.

Erin Welsh	Yeah.
Erin Allmann Updyke	And that's from actual penetration through but also from this chronic inflammation that happens in the wall of your bladder. And then the other thing that can happen is that if you think about which direction blood flows in your veins, blood is flowing away from most of your organs in your veins, right. So the blood in the veins around your intestines is not flowing into the intestine, it's flowing away from the intestine. But the eggs are trying to get into the intestine, so they're swimming against the current.
Erin Welsh	Okay.
Erin Allmann Updyke	They don't all make it. So some of them get swept up backwards and where they go is the liver because that's where those veins drain to is the liver, that's where they came from, right.
Erin Welsh	Oh, yeah.
Erin Allmann Updyke	So then they can get lodged in the liver and also the spleen because a lot of blood flow drains into the spleen as well. So then you have the same thing happening that happened in the wall of the bladder, these granulomas forming, this intense inflammation in the liver and the spleen. So this can cause hepatosplenomegaly, so that means enlargement of the liver and the spleen.
Erin Welsh	Wait, we just talked about this and I said it was a great word.
Erin Allmann Updyke	Yeah we did. Yeah you did, yeah.
Erin Welsh	Which episode?
Erin Allmann Updyke	Let's see...
Erin Welsh	Was it hep C?
Erin Allmann Updyke	No because hep C doesn't cause spleen... Dengue? Dengue.
Erin Welsh	It was dengue, okay.
Erin Allmann Updyke	Yeah, dengue.
Erin Welsh	Cool.
Erin Allmann Updyke	Yeah. So fun.
Erin Welsh	Connections!

Erin Allmann Updyke	Yep. So it can cause hepatosplenomegaly. It can also cause what we did talk about with hepatitis C which is fibrosis of the liver especially. Now anytime that you have veins being clogged like we talked about in the hep C episode you can have portal hypertension. So the veins are being clogged so the pressure is building up on the backend so you can see all the same symptoms that you see with other chronic liver disease like ascites, fluid being filled up in your belly, you can get esophageal varices, so varicose veins in your esophagus which can cause massive bleeding if they rupture.
Erin Welsh	Oh my gosh, yeah.
Erin Allmann Updyke	Yeah. Isn't that fascinating?
Erin Welsh	It is.
Erin Allmann Updyke	So that's kind of like the pathophysiology of how and why it causes the disease that it causes. It's not the worms themselves, it's the eggs getting lodged in places and then our bodies mounting a massive immune response to try and wall these eggs off. Okay?
Erin Welsh	Fascinating.
Erin Allmann Updyke	Okay so then let's talk about the actual symptoms, we've kind of touched on them but we'll go through the stages of infection, okay.
Erin Welsh	Okay.
Erin Allmann Updyke	So super acutely, like hours after you get infected, especially the first time you ever get infected, you're right, there is symptoms that happen right away from the cercaria themselves and that is an itch where those little spermies penetrate your body, okay. This is sometimes called swimmer's itch.
Erin Welsh	It's also really funny to me that you're calling them little spermies because of something that I'll talk about in the history section.
Erin Allmann Updyke	Oh really?
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay. So yeah, you can get a rash, it's sometimes called swimmer's itch because again this is from freshwater ponds and things like that is where they live. And it'll be blistery, it'll be itchy but it's generally self-limited and it kind of goes away over time.
Erin Welsh	Right.
Erin Allmann Updyke	Then there is an acute disease that can happen in a number of weeks, usually like 2-10 weeks after infection. It tends to only really happen with Schistosoma japonicum infection but it also can happen in travelers who get infected with Schistosoma mansoni and haematobium but it doesn't tend to happen in people who live in areas where this disease is endemic with the other two species, if that makes sense. Okay. And so this acute disease essentially is your body mounting a hypersensitivity reaction to all the worms swimming through your bloodstream and making their way, that long travel down to the veins of your intestine or your bladder. It's your body seeing those worms swimming and mounting a response to it.

Erin Welsh	Okay.
Erin Allmann Updyke	So again it is the worms but it's also not the worms, it's your body reacting to the worms. And so the symptoms that you see are the same kind of general inflammatory symptoms that we see with a lot of diseases. Fever, fatigue, maybe muscle pains, things like that. If you were to test someone's blood at this time, what you would see is something called eosinophilia which is I think another fun word, if we're talking about fun words.
Erin Welsh	It's a great word.
Erin Allmann Updyke	So that means an elevation in the number of eosinophils which is a specific type of white blood cell that we have that we use to fight off parasitic infections. So it's your body going, 'Hey, I know that there is a parasite, a worm here in my body and I'm trying to fight it off,' which I think is so cool.
Erin Welsh	It's very cool. Cause it just shows how important parasites have been to u throughout our evolution.
Erin Allmann Updyke	Right? We have a whole line of blood cells that are specifically for parasites. Ugh, it's so cool.
Erin Welsh	It's very cool.
Erin Allmann Updyke	And then the other thing that you'd see if you took a chest X-ray of someone with this acute schisto reaction, you would see patchiness on chest X-ray and that's likely because the worms have made their way through your lungs and that causes some inflammation in your lungs as well.
Erin Welsh	Okay.
Erin Allmann Updyke	Okay.
Erin Welsh	But this is just 2-10 weeks.
Erin Allmann Updyke	This is just 2-10 weeks, this is also called Katayama fever, if I'm pronouncing that right. But that's what it's called. And yeah, that's sort of the acute... In endemic areas where Schistosoma mansoni and haematobium are the primary causes, this isn't a disease you tend to see very often.
Erin Welsh	Right.
Erin Allmann Updyke	Which is very interesting. So the majority of problems associated with schistosomiasis are in fact the chronic infection from the eggs.
Erin Welsh	Of course.

Erin Allmann Updyke	And so we've kind of already talked about what those symptoms are but we'll kind of just go through system by system to talk about what you actually see symptom-wise. So in your intestine when you have these eggs burrowing their way through into your intestine wall, you're gonna have symptoms associated with intestinal pain, abdominal pain. I mentioned you can get micro ulcerations in your intestinal wall which can cause bleeding, so you can get diarrhea either bloody or non-bloody diarrhea. In kids especially this can lead to malnutrition if you think about the intestinal wall being damaged, not being able to absorb all the nutrients that you need, on top of that having diarrhea, you can have malabsorption problems.
Erin Welsh	And anemia.
Erin Allmann Updyke	Exactly, you can also get anemia.
Erin Welsh	Yeah.
Erin Allmann Updyke	Especially in children. So that's the intestinal symptoms. When those eggs make their way up into your liver you can have all those hepatic symptoms that we mentioned already, so ascites, portal hypertension, liver fibrosis, all of that kind of stuff. In your urinary tract, blood urine, hematuria is kind of the hallmark sign of schistosomiasis especially in children.
Erin Welsh	Okay. Especially in children.
Erin Allmann Updyke	Yeah, in endemic areas if there is a kid with bloody urine, it's schistosomiasis essentially.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	What's very interesting is that in adults chronic infection with Schistosoma haematobium that affects the urinary tract is associated with an increased risk of bladder cancer.
Erin Welsh	Because of the inflammation essentially?
Erin Allmann Updyke	Yeah, it's thought that it's because of the inflammation. At least one thing I read said it's also possible that just the action of these eggs constantly going through your walls can make your bladder more susceptible to other carcinogens like smoking and things like that.
Erin Welsh	Oh, okay.
Erin Allmann Updyke	So it's not entirely clear whether it's like... But overall yeah, it's inflammation, right.
Erin Welsh	Yeah, right, right.
Erin Allmann Updyke	Yeah. And now here's the other really important thing about Schistosoma haematobium. So it's living in the veins around your bladder. Your bladder is in your pelvis which means that this can also affect other organs in your pelvis. And so this can cause what's called genitourinary schistosomiasis.
Erin Welsh	Yeah.

Erin Allmann Updyke	So it can affect the prostate, the seminal vesicles, so you can see things like hematospermia, so bloody semen. It can also result in very substantial cervical lesions, so the cervix is the bottom part of your uterus, top part of your vagina. This can cause very substantial cervical lesions, vaginal lesions, and what's really important is that this type of genitourinary schistosomiasis is associated with an increased risk of HIV infection and transmission.
Erin Welsh	Yes. Yeah.
Erin Allmann Updyke	Because of these lesions, you have open wounds, you have increased inflammatory cells, and so it's easier for HIV to be transmitted. So that's really important.
Erin Welsh	I had no idea about these other manifestations of disease until I was reading a review paper about the history of it and I scrolled to page 10 and it was just like picture after picture of urogenital schistosomiasis and yeah.
Erin Allmann Updyke	Yeah. It's terrible, it's horrible.
Erin Welsh	It's horrible.
Erin Allmann Updyke	Now because this is something that's in your blood it can technically also cause disease anywhere that your blood goes which is to say the rest of your whole body as well. So these eggs can also end up traveling all the way back to your lungs which can cause the same kind of granulomatous changes that we saw in everywhere else, in the liver, in the bladder, etc. So that can end up causing what's called pulmonary hypertension, so think of the increased pressure in the portal veins of your liver, the same thing can happen in your lungs.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	If you have an increase in pressure in your lungs, that causes a backup of pressure onto the right side of your heart which can cause right-sided heart failure which is called cor pulmonale.
Erin Welsh	Okay so does worm burden - my favorite phrase - relate to these symptoms or the increase of risks for bladder cancer and HIV?
Erin Allmann Updyke	Absolutely it does.
Erin Welsh	Okay.
Erin Allmann Updyke	Because we are talking about eggs.
Erin Welsh	Right.
Erin Allmann Updyke	So the more eggs you have in your body, the more symptoms that you're going to have and the more inflammation that you're gonna have. So the more worm pairs that you have, the more eggs they're going to be releasing, absolutely.
Erin Welsh	What is the average worm burden in endemic areas?
Erin Allmann Updyke	That's such a good question, I don't know. I'm gonna look it up.

Erin Welsh	Okay.
Erin Allmann Updyke	That's a really important question. It's high, I know that. But the other place that this can also affect is your nervous system.
Erin Welsh	I was wondering, does it go into your brain?
Erin Allmann Updyke	It can, yeah. It can cross your blood-brain barrier potentially, these eggs, cause they have enzymes that let them break down barriers right, that's how it makes its way into your bowels. So it can break its way into your central nervous system and cause neruoschistosomiasis which can cause seizures, other neurodegenerative type symptoms. Yeah, it's gnarly. That's schistosomiasis.
Erin Welsh	Wow. That's a very complicated story.
Erin Allmann Updyke	Super, super complicated.
Erin Welsh	And a lot of bad manifestations, obviously.
Erin Allmann Updyke	Yeah, it's a really gnarly disease.
Erin Welsh	Yeah.
Erin Allmann Updyke	What the heck, Erin?
Erin Welsh	What the heck.
Erin Allmann Updyke	Where did this thing come from? How did it get here? And why did it take us 45 minutes to talk about?
Erin Welsh	Oh good god. Well let's dive into the very long history of schistosomiasis right after this break.
Erin Allmann Updyke	Awesome.
TPWKY	(transition theme)
Erin Welsh	After hearing about the biology I'm even more excited to talk about the history because the history has all the fun things. It's got mummies, imperialism, a little bit of climate change, Philogenes, it's got everything.
Erin Allmann Updyke	That's everything you can ask for in an episode of TPWKY.
Erin Welsh	Right. Okay so you asked how did we get here. But I wanna change that question a little bit by asking and hopefully answering, how did we get from there to here? But first what is 'there'?
Erin Allmann Updyke	Ooh, okay.
Erin Welsh	Basically where did schistosomes comes from and how did some of them become parasites of humans?

Erin Allmann Updyke	Yeah.
Erin Welsh	So you mentioned that schistosomes are a super diverse group, there is about 100 species and the majority of those actually infect birds and don't have anything to do with mammals. But of the ones that infect mammals which is around 23 species, 7 of those infect humans regularly with the 3 that you mentioned being the biggest causes of disease. Okay but the rest of them infect tons of species of mammals, like rodents, ungulates, etc. And some of the ones that infect humans vary in their specificity to humans. So for instance, Schistosoma japonicum - ja-poh-nicum, that how you been saying it?
Erin Allmann Updyke	I said ja-pawn-icum but I don't know.
Erin Welsh	Schistosoma japonicum which has an Asian origin can infect a wide range of mammals which suggests that maybe only recently on an evolutionary time scale started infecting humans. But others which may have originated in Africa, that's sort of an asterisk, we don't really know, I'll talk about it.
Erin Allmann Updyke	Okay.
Erin Welsh	They seem much more human-specific and are even associated with human behavior that may enhance the possibility of transmission. So like peak infectivity coincides with the time of day and the time of year that bathing is most frequent in endemic areas. Answering the question where did schistosomes come from was a little bit more difficult than I expected because it turns out it doesn't seem entirely clear. Did they originate in Asia or in Africa? Don't really know. We can definitely rule out the Americas, Australia, Antarctica.
Erin Allmann Updyke	Antarctica, I'm glad we can rule that one out.
Erin Welsh	Because there isn't any fossil evidence of schistosomes, researchers have relied on a few other tools to try to trace the origins of the mammal-infecting schistosomes. So you know, you can do the genomic approach where you compare different genomes of different species to estimate when they diverged or split from one another and also you could use the evolutionary history of snail hosts or mammal hosts to estimate a timeline and geography of their history which is really cool. And so for a long time most people seem to believe than an African origin of the parasites was the most likely but recent research puts the origin in what is now Northern India. And they they say just that from there schistosomes first spread east to Central and Eastern Asia and then later spread west to Africa where they more recently diversified into the more human-specific species, Schistosoma mansoni and Schistosoma haematobium. That divergence occurred as much as 4 million years ago or as recently as 300,000 years ago. But again it's not entirely clear.
Erin Allmann Updyke	We don't know.
Erin Welsh	Yeah. But what's cool about this evolutionary history of schistosomes is that the evolution of a couple of species seems to coincide pretty well with human evolution when early humans or the ancestors of modern humans started spreading out all across the Savannah essentially. So regardless of where schistosomes as a group originated exactly, there was probably a longer association between humans and some of the parasites in Africa which led to the specialization of Schistosoma haematobium and Schistosoma mansoni in Africa and that's where you find the highest burdens typically.
Erin Allmann Updyke	So I was pronouncing that one wrong too, huh?

Erin Welsh	Which one?
Erin Allmann Updyke	Mansoni.
Erin Welsh	I don't know, I just said 'man-soh-nee'. What did you say?
Erin Allmann Updyke	Man-son-eye'.
Erin Welsh	Honestly I mean your guess is as good as mine.
Erin Allmann Updyke	People must hate me, I think.
Erin Welsh	No! People must hate our pronunciations.
Erin Allmann Updyke	Yeah.
Erin Welsh	Man-son-eye', 'man-soh-nee'. I don't know.
Erin Allmann Updyke	Man-soh-nee' sounds more better. (laughs)
Erin Welsh	(laughs) This is just how I was reading it in my head, so I don't know.
Erin Allmann Updyke	Yeah.
Erin Welsh	All right. Are you ready to talk Ancient Egypt?
Erin Allmann Updyke	Always, Erin. I live for it.
Erin Welsh	For hundreds of thousands of years, humans and schistosomes coexisted I guess in relative peace or as much relative peace as there could be. But that changed when humans began to settle in large communities and practice agriculture and domesticated animals for livestock. What's one of the things that is crucial for humans, their livestock, and their crops?
Erin Allmann Updyke	Water.
Erin Welsh	Exactly.
Erin Allmann Updyke	Yes!
Erin Welsh	And so when humans settled they pretty much always chose a place where they could reliably get fresh water.
Erin Allmann Updyke	Makes sense.

Erin Welsh	Yeah. And as the Sahara desert got drier and drier, humans in North Africa began to seek more hospitable lands and the Nile Valley was a pretty ideal place to form large, sedentary communities. So around 8000 years ago is when we see these earliest settlements. And just a few thousand years after that, these communities had developed extensive irrigation systems and canals to provide water for crops which is pretty amazing, the technology that they developed that was handed to them by ancient aliens. Just kidding.
Erin Allmann Updyke	(laughs)
Erin Welsh	Probably according to the History Channel. A lot of people had extensive contact with water probably every day. They used it for swimming, for bathing, sailing, fishing, and some trades like brick-making that required a water source. And what else needs water of course? Snails and schistosomes. And so these activities combined with the lack of sanitation perfectly set the stage for the proliferation of snails and of course the schistosomes themselves. And we see physical evidence for this in mummies from the time. Mummies!
Erin Allmann Updyke	Mummies!
Erin Welsh	The earliest known case of schistosomiasis actually appears in a mummy from modern day Northern Syria dating back to around 4000 BCE.
Erin Allmann Updyke	Wow.
Erin Welsh	Which is incredible. But schistosome infections in Ancient Egyptian mummies follow not that far behind. And so the first retrospective diagnosis of a disease in human remains thousands of years old happened around 1910 and it was a case of schistosomiasis in a 3000 year old Egyptian mummy.
Erin Allmann Updyke	In 1910 they were able to say... Wow.
Erin Welsh	In 1910. Yeah!
Erin Allmann Updyke	That's amazing.
Erin Welsh	So that's when paleoepidemiology got its start essentially.
Erin Allmann Updyke	Wow.
Erin Welsh	And so paleoepidemiological studies of mummies from the area on the border of Sudan and Egypt shows a 65% prevalence of schisto.
Erin Allmann Updyke	(gasps)
Erin Welsh	Right?
Erin Allmann Updyke	Everyone had it. Everyone!
Erin Welsh	Everyone had it!
Erin Allmann Updyke	Wow.

Erin Welsh	I mean hearing about the biology I'm like well how is that not 100%?
Erin Allmann Updyke	Yeah it's true. We can talk about it actually.
Erin Welsh	Ooh! This is a fun episode.
Erin Allmann Updyke	This is.
Erin Welsh	Okay. The finding of fossilized snails that are the host species in these areas and beyond, like into Mesopotamia and Palestine also suggest that the disease was there as well. What about any physical evidence in Eastern Asia?
Erin Allmann Updyke	Yeah.
Erin Welsh	So schistosome eggs of Schistosoma japonicum were found in a preserved corpse in China dating to 2100 BCE.
Erin Allmann Updyke	Wow.
Erin Welsh	So again, very old.
Erin Allmann Updyke	Long time ago.
Erin Welsh	And so yeah, we've got this physical evidence of schistosomes infecting humans going back thousands and thousands of years. So what's in the written record?
Erin Allmann Updyke	Yeah.
Erin Welsh	Let's start with Ancient Egypt.
Erin Allmann Updyke	Okay.
Erin Welsh	So I have to, because I say Ancient Egypt, I have to mention the-
Erin Allmann Updyke	Ebers Papyrus.
Erin Welsh	Yeah. So in the Ebers Papyrus there's a description of a disease that I actually mentioned in the hookworm episode called AAA disease, like the letter 'A' 3 times. And so egyptologists for a long time had thought this was likely referring to schistosomiasis since it seemed to have something to do with blood and urine and it said to avoid polluted water to prevent infection.
Erin Allmann Updyke	That's so amazing.
Erin Welsh	Well this interpretation has been disputed more recently.
Erin Allmann Updyke	Oh, okay.

Erin Welsh	Okay. Moving on, okay. So Herodotus observed that Egypt is the land where men menstruate which people have taken to mean hematuria which is caused by Schistosoma haematobium. Penile sheaths, so like protective sheaths for penises-
Erin Allmann Updyke	Like a condom kind of?
Erin Welsh	Essentially.
Erin Allmann Updyke	Okay.
Erin Welsh	These appear in early writings and illustrations in Ancient Egypt and people have suggested that they were used as a preventative against schisto since it was thought that the disease could enter the body through the penis.
Erin Allmann Updyke	Oh, that's too bad.
Erin Welsh	Yeah. But this interpretation has also been called into question. Anyway. And finally the last bit of evidence that has been called into question is that circumcision which is apparently of Egyptian origin, I didn't know that.
Erin Allmann Updyke	I didn't know that either.
Erin Welsh	Yeah. Circumcision was advocated as a way to prevent infection possibly of schistosomiasis.
Erin Allmann Updyke	That's really interesting though.
Erin Welsh	Yeah. So there's a relief picture from an Egyptian tomb from like 2400 BCE that shows someone performing circumcisions with the caption 'I will do you good.' But that also has been challenged.
Erin Allmann Updyke	Okay.
Erin Welsh	Okay. So basically in Ancient Egypt there are a lot of possible references to schistosomiasis but nothing that's absolutely accepted across the board.
Erin Allmann Updyke	Okay.
Erin Welsh	Except for the fact that it's in mummies, like that we know for sure.
Erin Allmann Updyke	Right. We know it's was there but writing-wise we don't know what they're talking about.
Erin Welsh	Exactly.
Erin Allmann Updyke	Okay.
Erin Welsh	Now onto the bible.
Erin Allmann Updyke	Ooh.

Erin Welsh	Does Jericho ring a bell?
Erin Allmann Updyke	For sure.
Erin Welsh	The battle of Jericho.
Erin Allmann Updyke	There's a song about it.
Erin Welsh	Exactly.
Erin Allmann Updyke	Yeah.
Erin Welsh	So Jericho was an old walled city, like one of the oldest in the world, 11,000 years old maybe.
Erin Allmann Updyke	Wow, wow.
Erin Welsh	In one passage of the bible Joshua was ordered to kill everyone in the city and then destroy the city itself. It ended with him cursing the city with low fertility which was thought to be caused by infected well water. And so a lot of people have said that this legend or belief or this story could refer to the fact that Schistosoma haematobium may obstruct fallopian tubes.
Erin Allmann Updyke	Yep. And seminal tubes as well, actually.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so the city was abandoned after its destruction and there's actually archeological evidence to support its abandonment. The curse on the town was removed when Elijah "went forth unto the spring of the waters and cast the salt in there, there shall not be from thence anymore death and barren land". And so they're saying oh, if you throw the salt in there you'll kill all the snails and then Schistosoma will... But also I feel like if you salt your drinking water it's not gonna be good.
Erin Allmann Updyke	It's not gonna be good for you.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	All right I promise I'm almost done with the ancient section. So we gotta move on to Ancient China though.
Erin Allmann Updyke	Of course.
Erin Welsh	So you mentioned Katayama disease and symptoms resembling this can be found in old Chinese medicine writings dating back to around 400 BCE. So that's all I got for that. But basically all of these little bits of evidence here and there suggest that schistosomiasis was widespread and probably pretty dang prevalent across much of the tropical and subtropical Old World.

Erin Allmann Updyke	Makes sense.
Erin Welsh	The New World seems to have been schisto-free until the slave trade began in the 16th century when Schistosoma mansoni was brought over. And so that species was able to establish where indigenous snail hosts could maintain the parasite's life cycle, so like Brazil, Suriname, Venezuela, and some Caribbean islands. All right so now we're caught up on the origins of schistosomes and the evidence for human infection in antiquity. But when did people discover the parasite? So like that firsthand account.
Erin Allmann Updyke	Yeah, right.
Erin Welsh	Well there are descriptions of a disease resembling some of the manifestations of schistosomiasis in Italy in the 16th century but no one really took much note of that. And it wasn't really until Napoleon's army invaded Egypt in 1798 that a French physician with the army noted how men in Egypt menstruate and how many of the French troops also had blood in their urine and pain in their bladder. And then about 50 years later researchers on two separate continents began to take a closer look at this disease. In Japan in 1847 a researcher named Dr. Yoshinao Fuji described what he assumed was a new disease. So quote: "During the past 2 or 3 years farmers have had small eruptions on their legs when they entered the water to cultivate the rice field. The eruptions are unendurably painful and itchy. Cows and horses also show the same symptoms. Most of the residents suffer from this disease." So that-
Erin Allmann Updyke	Sounds like schisto.
Erin Welsh	Sounds like schisto. The acute schisto at least.
Erin Allmann Updyke	Right.
Erin Welsh	And so one of the counties that was heavily affected by this disease was Katayama which is what gave the disease its name in Japan to indicate a new infection with schistosomes. It would be decades though before the parasite causing this Katayama disease was discovered in Japan. In 1851 a guy named Theodor Bilharz, which we talked about.
Erin Allmann Updyke	Teddy B!
Erin Welsh	Teddy B was working as an assistant professor at a hospital in Cairo when he observed this trematode in the portal vein of a young guy and so this is what was in the firsthand account. But he thought that this might have something to do with both the bloody urine and also dysentery, both of which were common throughout Egypt. And this is what actually got the attention of a lot of people, his descriptions and his suggestion of a link between those diseases and the parasite itself.
Erin Allmann Updyke	Okay.
Erin Welsh	This is like in 1851, yeah, 1850s.
Erin Allmann Updyke	Okay.

Erin Welsh	And people started trying to figure out the transmission cycle of this parasite but were thwarted partly because Bilharz didn't realize that the morphological differences he was seeing in the worms were because they were different species and partly because another leading researcher was adamant that there was no intermediate host for the parasite.
Erin Allmann Updyke	Why would you be so adamant about that?
Erin Welsh	Part of it was like I think hookworm and other worms that showed... Yeah, I know. But he had a lot of conviction which is a dangerous thing in science when you close your mind off. During the 60 years following Bilharz' discovery, many researchers tried to pick apart the puzzle of this parasite including its transmission cycle, how it entered the body, and the question of how many species were actually present infecting humans. And this was a pretty feared disease by colonists who had moved to affected regions. So British troops stationed in Egypt in the early 1900s were told to wear a condom while bathing so as not to get infected. It's not gonna help you at all.
Erin Allmann Updyke	It's not gonna do anything.
Erin Welsh	No. Eventually in 1915 a researcher named Robert Leiper showed experimentally that snails are the intermediate host of schistosomes and also showed how the adult worms mature in mammals.
Erin Allmann Updyke	To be fair it's amazing that people figured that out because it is such a complicated life cycle.
Erin Welsh	It's incredibly complicated.
Erin Allmann Updyke	Like as much as it seems wild to be adamant that there is no intermediate host, it's also wild that they figured out what the intermediate host was and they figured out this complex life cycle so long ago.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	Like it's really incredible.
Erin Welsh	Absolutely. Yeah, you'd think what would lead you to look at snails for instance?
Erin Allmann Updyke	Yeah.
Erin Welsh	So yeah, it is cool. So 1915 was pretty much when okay, we can finally get to the nitty gritty of all the different stages of the parasite and take a closer look at the intermediate hosts. Bilharz though unfortunately wouldn't live to see the life cycle figured out because he died only 11 years after his discovery of the worms of typhoid fever.
Erin Allmann Updyke	Ugh. At least it wasn't schisto. I thought it was gonna be schisto.
Erin Welsh	I wonder if he had schisto. Probably.
Erin Allmann Updyke	Aw that's sad, though.
Erin Welsh	Oh I have a quick question. Can you get schisto from ingesting contaminated water?

Erin Allmann Updyke	Good question. Not as far as I know.
Erin Welsh	Okay, it's just through contact.
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay.
Erin Allmann Updyke	Not as far as I know.
Erin Welsh	Okay. So Bilharz' work I think is actually pretty impressive considering that he was making a connection between a microscopic parasite and disease symptoms before germ theory was really a thing which is pretty cool. And his significant contributions to the study of schistosomes is why schistosomiasis was also called bilharzia or bilharziasis. But that's less common.
Erin Allmann Updyke	That's harder to say.
Erin Welsh	It is much harder, at least for us.
Erin Allmann Updyke	Yeah.
Erin Welsh	And actually it is still called bilharzia in many parts of the world. But schistosome was proposed first from the Greek words for divided and body. But other names for the disease include red water fever, snail fever, and big belly.
Erin Allmann Updyke	Big belly. That's from the ascites.
Erin Welsh	Yeah. While the debates for the parasite's transmission and life cycle were going on, the parasites themselves were experiencing a huge growth in prevalence especially in Egypt. Instead of basin or surface irrigation, so that's when the land is flooded to soak the crops and that's an old method of irrigation and allowed for one crop harvest along the Nile. But then perennial irrigation was introduced in Egypt and that allowed for water to be flowing year round which was great news for cotton which became the country's primary export but it also meant torturous working conditions and a steady source of snail and human hosts for schistosomes. Studies looking at how this new irrigation method increased schistosomiasis prevalence estimate anywhere from a tenfold increase to a growth from 1-3% prevalence to 75-80% prevalence.
Erin Allmann Updyke	Wow.
Erin Welsh	So it just like exploded in terms of prevalence.
Erin Allmann Updyke	Dang.
Erin Welsh	Oh yeah. The enormous growth of interest in schistosomes in the late 1800s and through WWII didn't just happen in a vacuum, it wasn't just driven by curiosity. In the case of schistosomes the motive to understand the disease was essentially imperialism.
Erin Allmann Updyke	As it often is.

Erin Welsh	As it often is, yeah. Tropical medicine as a field essentially began so that the tropical regions of the world could be made suitable for white people to inhabit and invest in.
Erin Allmann Updyke	Yeah.
Erin Welsh	Empire building essentially. Like the search for malaria transmission treatment and yellow fever prevention are two perfect examples of this that we've talked about on those episodes.
Erin Allmann Updyke	Yeah.
Erin Welsh	And there's even a line in a scientific article in the British medical journal from 1897 that says, quote: "Get rid of or avoid these disease germs and we get rid of a principal obstacle to the colonization of the tropics by Europeans."
Erin Allmann Updyke	Wow. Just straight up. Wow. There's so much anger brewing in me.
Erin Welsh	Yeah. The good news is that today we have a lot of studies of neglected tropical diseases that are motivated not by colonization but by wanting to make the world a better place. Or at least that's what the researchers want to do.
Erin Allmann Updyke	Is that why there's no funding for it though?
Erin Welsh	Exactly, yeah. So the researchers who are working on it, they want to make the world a better place. The funding agencies don't.
Erin Allmann Updyke	Right.
Erin Welsh	But also random piece of trivia here, the first graduate school of parasitology in the US was established at the University of Illinois in 1909.
Erin Allmann Updyke	I didn't know that!
Erin Welsh	Yeah. There's no longer a graduate school of parasitology.
Erin Allmann Updyke	I was gonna say. There's some of us here but not a lot of people studying parasites anymore it seems like comparatively.
Erin Welsh	Comparatively, yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	So the Boer War in South Africa, many British troops were stationed there and they became infected and incapacitated by schisto. And the presence of British troops in Egypt during the late 1800s and early 1900s, these directly led to the discoveries that I talked about. This is why people had such a vested interest in figuring out what was going on with the parasite's life cycle.
Erin Allmann Updyke	So imperialism and war, as usual.

Erin Welsh	Imperialism and war. So increasing efficiency and control in Egypt meant reducing the prevalence of schistosomes but primarily by reducing it in British troops. So once Leiper made the link between the snail and the schistosome, he proposed that if you control the snail, you control the schistosome and he recommended drying out the canals for a bit every year to kill the snails. This method of control doesn't actually work all that well since all you would need is a few snails to keep pumping out millions of parasites.
Erin Allmann Updyke	Thousands per snail, per day, from one... Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	It's such a harder thing to try and do, to control the snails.
Erin Welsh	Yep. But that was the primary control strategy for decades and is still I think a practice in some places.
Erin Allmann Updyke	I mean it's still I think an important component of everything but it's definitely not gonna be the only thing, that's not gonna do it.
Erin Welsh	It is. Yeah. And this aiming just for the snails kind of shows again how early tropical medicine was concerned only with the parasites or pathogens themselves without considering how cultural or behavioral practices may have an impact on disease transmission. Water filtration was also proposed but this was limited to British troops because setting up infrastructure to get clean water going everywhere was way too expensive in their minds, so let's just focus on the important people. And it also might have been that the discovery of an effective treatment for schistosomiasis discouraged any infrastructural changes to prevent the disease.
	In 1918 antimony tartrate, so tartar emetic, was found to be relatively successful in treating schisto which is around 70% cured. But it was also a poison so you had to be careful you didn't die. And the doses given to infected people were extreme. They also had to be given out over a period of 30 days so you had to return to a clinic every few days. And as you can imagine the proportion of people who actually completed the course of treatment was pretty low because a day of going to the clinic meant a day of lost wages and also potential poisoning.
Erin Allmann Updyke	Right.
Erin Welsh	And that's something that is still so very relevant today in terms of reducing the barriers for treatment or for just healthcare overall.
Erin Allmann Updyke	Yeah, healthcare access.
Erin Welsh	Let's not make it a decision between making the money that you need to live and having good health. Anyway. So researchers then were like, 'Okay, well we need an easier solution for reducing the parasite.' And so that's one of the reasons why snail killing continued at such a large scale. And the first large scale efforts to reduce snails throughout Egypt did seem to offer at least a short term reduction in snail populations and it was striking enough that in 1939 it was declared that schistosomiasis could be eliminated from Egypt in 25 years by clearing the canals.
Erin Allmann Updyke	I'm sorry, this was in what year?
Erin Welsh	1939!

Erin Allmann Updyke	1939. 25 years. Cool, cool, cool.
Erin Welsh	25 years.
Erin Allmann Updyke	How'd that work out?
Erin Welsh	That did not happen. Not at all. (laughs) Many of the public health directives in these tropical countries that were overseen by European imperialist countries, these were aimed towards controlling infectious disease either through infrastructure improvements limited to citizens of whatever European country or through widespread treatment campaigns. But it became obvious that neither of these tactics would result in a lasting improvement in actual public health. So gradually sanitation campaigns and improved living and working conditions were put in place. But this wasn't motivated just by, 'Oh we wanna make the world a better place again'. The ruling countries simply realized that a healthy workforce is more efficient and productive. And that's where a lot of the effort ended was as long as you got them well enough to work, then you leave, you drop it all. Often the medical officer of a mine for instance was seen as almost this missionary savior of the quote "savage" or uncivilized natives, pulling them out of the filth and disease to which they had been accustomed. But in reality the prevalence of many of these diseases in tropical countries increased tremendously during imperialist rule.
Erin Allmann Updyke	Of course.
Erin Welsh	I mean scurvy accounted, I'm getting a little bit outside of schisto but for example, scurvy accounted for 13.5% of all deaths in a mine in what is now Zimbabwe in 1908. Scurvy, which we talked about and which could have been prevented. Tuberculosis, pneumonia, silicosis, and of course schistosomiasis became huge problems in these mines among other diseases. And it wasn't just that crowded and unsanitary conditions promoted the spread of schistosomiasis, it was also the nature of the work itself. Sugar plantations and cotton growing both meant exposure to contaminated water and prevalences reached above 50% in many places. But the link between these conditions and disease wasn't really recognized at least publicly.
	But instead the sentiment was much more that the indigenous populations were acting as a disease reservoir, putting the white colonists in harm's way. And you can see this come through in the way that schistosomiasis is discussed in some of the public health reports in South Africa in the early 1900s. Schistosomiasis, quote, "seems well under control among Europeans though of course the natives are commonly infected," end quote. And attacking the disease, quote, "might help to free the country of infection and enable us to bathe safely."
Erin Allmann Updyke	Ugh.
Erin Welsh	Throughout the 1930s the focus on tropical medicine declined in the two main empire builders, so Britain and the US. But then WWII broke out which meant that those Europeans or Americans stationed in the tropical war zones would face the scourge of the diseases there. In terms of numbers, things like malaria and STIs far outweighed schisto infections in American troops but one campaign in the Philippines saw and explosion of schisto cases. Medical researchers kind of leapt on this outbreak and the funding that was provided for it to conduct research into schisto, the stages of disease like acute vs chronic, and treatment strategies. And this came at a pretty key time in the history of tropical medicine which was a field that was almost dying around the same time as imperialism was on the decline. So remember that 1939 prediction that schistosomiasis could be eradicated within 25 years?
Erin Allmann Updyke	Yeah.

Erin Welsh	Yeah. Well the snail population did seem to be declining but the schisto, no. A bunch of kids born after the eradication campaign began were screened for the parasite and the prevalence of the parasite was found to be 63%. Incredibly high. And in other more rural villages that number was over 95%.
Erin Allmann Updyke	Wow.
Erin Welsh	So obviously something was wrong. The eradication campaign recognized this and changed their name from the Bilharzia Snail Destruction Section to the Bilharzia Snail Control Section.
Erin Allmann Updyke	Also Snail Destruction Section is a gnarly name.
Erin Welsh	(laughs) Total destruction of snails!
Erin Allmann Updyke	Meeting them at a bar after work like, 'Oh what do you do?' Oh I just work for the Snail Destruction Section!
Erin Welsh	I want that on my business card.
Erin Allmann Updyke	Me too, I want like an embroidery on a zippered jacket.
Erin Welsh	Yeah the people working in these destruction and control sections, they couldn't answer how low the infection prevalence had to be in snails in order to break the cycle of transmission in humans.
Erin Allmann Updyke	Right.
Erin Welsh	So how could they even direct the campaign effectively?
Erin Allmann Updyke	Cannot.
Erin Welsh	Cannot. Meanwhile Egypt was not the only country dealing with incredibly high prevalences of schistosomiasis. China faced a similar situation and a mass campaign against the disease was started by the Nine Man Schistosomiasis Subcommittee, which are like the best names for these-
Erin Allmann Updyke	Yeah.
Erin Welsh	Starting in 1958. This set up prevention and treatment units across the country as well as research institutes to study the parasite. Treatment regimens were shortened to just a few days but it seems that the majority of the campaign's efforts were concentrated in reducing the snail host. Latrines were repaired, swamp land drained, snails buried, grass burned, and chemicals applied. Within a year or two several counties were announcing that they had eradicated schistosomiasis.
Erin Allmann Updyke	Excellent.

Erin Welsh	Mao Zedong wrote a poem called 'Farewell to the God of Plague' in response to this news and you can go read the poem in a book that I'll mention. But anyway, you can probably find it online. Anyway. The campaign against schistosomiasis seemed to be incredibly successful if you believe the claims about the progress made. But was schisto actually eradicated in these counties? Probably not but it does seem that substantial progress had been made in the prevalence of infection, obviously I'm sure you'll talk about what the prevalence is today. But one of the main problems and maybe something that's affecting the parasite today is that other mammals, especially cattle, were the main source of schistosome eggs in the environment.
Erin Allmann Updyke	Right.
Erin Welsh	And as far as I read, cattle themselves were not a target for treatment. So in the decades following WWII, interest in schistosomiasis grew for a number of reasons. One was the fear that soldiers returning back to the US or Britain would carry with them the parasites that could establish in native snail populations. Another was the fear of a looming food crisis. If enough food was going to be produced globally, people in the most productive agricultural regions had to be healthy enough to work but irrigation and dams had only led to an increase in schistosomiasis prevalence. For example in Ghana in 1965, a lake was created after damming a river. Within a year the snail host of Schistosoma haematobium had appeared and two years after that the prevalence of schistosomiasis was 50% in the population living around the lake.
Erin Allmann Updyke	Yeah, dams are not great.
Erin Welsh	Not great for schisto. So another reason for this increased interest was simply the increase in cases. In 1951 schistosomiasis had been declared next in importance to malaria among the world's tropical diseases.
Erin Allmann Updyke	I think it remains.
Erin Welsh	I think it does.
Erin Allmann Updyke	Yeah.
Erin Welsh	Which has been sort of contended in terms of is it truly the second most important.
Erin Allmann Updyke	We'll talk about it.
Erin Welsh	Yeah, okay. But the control programs kind of went like this. First, kill the snails. Oh that didn't work, all right well let's try treating people. Oh, that didn't work either because people can't afford to miss a ton of work to go get a shot? And also side note, so this is making another connection with the hepatitis C episode, these tartar emetic campaigns in Egypt throughout the 1950s to the 18980s, these were huge campaigns to get the treatment for schistosomiasis. They tended to reuse needles to save money and this led to a massive spread of hep C which was only discovered decades later.
Erin Allmann Updyke	Wow. Oh my gosh.
Erin Welsh	I think even now Egypt has one of the highest prevalences of hepatitis C infections.
Erin Allmann Updyke	Oh wow.

Erin Welsh	So how do we improve the treatments?
Erin Allmann Updyke	Yeah.
Erin Welsh	Or maybe we do a combination of treatment and molluscicides. But so far it doesn't really seem like any of these strategies have been super successful if the hundreds of millions of infections today is any indication. I'm sure you'll talk about it.
Erin Allmann Updyke	Mm-hmm.
Erin Welsh	Okay. I'm wrapping up now but I wanna say that before researching this episode I hadn't really considered how a possible negative consequence of germ theory was that people kind of stopped considering the social aspects of diseases. So there was a pathogen or a parasite or a vector and so the research concentrated more on understanding or controlling or treating those aspects rather than the underlying causes contributing to not just one specific disease but a whole suite of them. So before it was recognized that tuberculosis was caused by a bacterium it was known that crowded conditions and this and that, and so instead of focusing on treating the disease itself, let's treat some of the underlying issues associated with its spread or establishment. I mean obviously germ theory was hugely important but it is interesting how these social aspects were neglected.
Erin Allmann Updyke	Yeah.
Erin Welsh	Building that knowledge of the pathogen and parasite biology and treatments is obviously hugely important but it does seem to have come at a cost to social medicine, so like how social factors contribute to disease, especially for these neglected tropical diseases. And these were researched and described by western scientists through their lens and the vast majority of those doing the research did not have any knowledge of local customs, knowledge, or beliefs which may have given them not only a more full picture of the disease they were studying but also clues to its control. And I'm primarily referring to Schistosoma in Africa when talking about this.
Erin Allmann Updyke	Yeah.
Erin Welsh	And then later in South America. And so over the past few decades there has been a push towards social medicine and constructing a fuller picture of these diseases which are so multifaceted. But the disproportionate disease burden around the globe definitely shows that there is still so much work to be done. Plus the looming specter of climate change, cause I had to sneak it in there-
Erin Allmann Updyke	Yeah!
Erin Welsh	Means that the distribution and prevalence of schistosomiasis will likely change in ways that are gonna be difficult to predict. Since the African continent has the vast majority of schistosomiasis infections and is one of the most vulnerable regions for climate change and climate instability, there's a big push for predictive modeling for what the disease is going to look like. But that's the future and there's still a whole lot of work that needs to be done. So I'm ready to hear about what's going on with schisto in the world today.
Erin Allmann Updyke	I'm ready to tell you, right after this break.
TPWKY	(transition theme)

Erin Allmann Updyke	So schistosomiasis today. The World Health Organization considers it of course a neglected tropical disease which we've talked about a number of these in the past. It is estimated that globally nearly 800 million people are at risk of infection.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	Yeah. At risk of infection. And it's thought that about 250 million people are infected worldwide.
Erin Welsh	Wow.
Erin Allmann Updyke	And about 200 million of these people live on the African continent. So yeah, that's pretty massive. And you asked earlier about worm burden, so let's circle back to that. I don't know the exact numbers like how many worms do people get infected with but by and large children have the highest worm burdens and are the most affected. And one thing that I think is really interesting is that it used to be thought that is was entirely behavioral, kids play in the water, they run around, that's how they get infected whereas adults have different behavioral patterns and so they are infected at less of a burden. But there's more research that shows that there's also likely a strong immunological component to this because you do build up immunity slowly over time.
Erin Welsh	Interesting.
Erin Allmann Updyke	So that first of all is important because we'll talk in a minute about the potential for vaccination. If you can't build up immunity to this then there's no point in a vaccine, it wouldn't work. But we can build immunity to it, it just takes a really long time and we don't know exactly what the best targets are necessarily. So it's thought that that's part of the reason why we see less of a burden and less egg shedding in adults than we do in children.
Erin Welsh	Okay.
Erin Allmann Updyke	The adults who tend to have the highest burdens are people who are frequently exposed to freshwater sources so if you fish for a living, if you work in flooded rice paddies and things like that for a living, occupational exposure is where adults tend to get infected.
Erin Welsh	Right.
Erin Allmann Updyke	So yeah, I think that's something important to keep in mind, that we used to think it was entirely behavioral but it's likely not entirely behavioral. But in addition to just the number of people infected, we know that this is a chronic disease and it causes these chronic symptoms and so when we look at something like schistosomiasis, one of the metrics that people use to estimate the overall burden are what we call disability-adjusted life years which we've talked about, DALYs. And trying to get a handle on the DALYs for schistosomiasis is really difficult. We don't have really solid numbers on this, surprise, surprise.
Erin Welsh	Why though?
Erin Allmann Updyke	I think because it's kind of hard to estimate how much of an effect infection has on people.
Erin Welsh	Well I guess because it's probably not... Like often there are coinfections with a lot of other things too, so separating those out, yeah.

Erin Allmann Updyke	Absolutely. Absolutely. Coinfection is going to be huge but then also like the greater the worm burden is going to make a difference on how severe your infection is, so like infection severity is gonna range, how often you get reinfected, if you have access to treatment, things like that. So it's complicated. So estimates kind of are all over the place. 2016 global burden of disease estimated that it's about 1.9 million DALYs, so disability-adjusted life years.
Erin Welsh	Wow.
Erin Allmann Updyke	But there have been some other analyses that suggested much higher estimates. And that's I think if you include the fact that there is undernutrition, anemia.
Erin Welsh	Right, which I feel like you should cause that's manifestations of disease.
Erin Allmann Updyke	You should. You absolutely should. And so this where I actually wanna touch on something that is really important with a disease like schistosomiasis, a neglected tropical disease. And that is this cycle of poverty, right. I feel like we've talked about this in bits and pieces before but with something like schistosomiasis it's really important to touch on just how huge of an impact socioeconomics have on this disease and how much of an impact this disease can have on socioeconomics, right. So a disease like schistosomiasis that causes chronic and severe symptoms, especially in children, this can cause malnutrition, impaired growth, and compromised cognitive development in children especially when you consider coinfection, generalized undernutrition, and lack of access to nutrition and things like that on top of this. Okay? Then in adults this illness can lead to the reduced ability to work which can have profound impacts on economics, especially because of how widespread it is. So on a population level, a disease like schistosomiasis takes a huge impact, it has a huge impact on a population's and an individual's socioeconomic status.
Erin Welsh	Right.
Erin Allmann Updyke	Then when you combine that with poor sanitation and poor water quality which means opportunity for reinfection and continued exposure which means continued disease, you have further reduced productivity, further reducing a person's ability to move out of poverty.
Erin Welsh	It's a feedback loop.
Erin Allmann Updyke	And basically perpetuating that cycle, it's a feedback loop.
Erin Welsh	Yeah. And it's the same thing that we see also with hookworm and with many other geohelminths basically, many other of these intestinal parasites or neglected tropical diseases.
Erin Allmann Updyke	Absolutely. Right.
Erin Welsh	That's one of the hallmarks of a neglected tropical disease.
Erin Allmann Updyke	Exactly. Especially these ones that are chronic like this. Yeah so in that way schistosomiasis, we have a huge long way to go. The mainstay of control at this point is mass drug administration, so treating entire populations of people even if you don't know for sure if they're infected. So essentially the World Health Organization can go into an area and see what proportion of children are symptomatic or have for example hematuria or eggs in their stool and if more than 50% of children in an area are infected which is a very high proportion, then everyone in that area will be treated.

Erin Welsh	Yeah.
Erin Allmann Updyke	And the treatment now, there's only one drug really that's approved for use, we can talk about the problems with that but it's called praziquantel. It's effective, asterisk, it's effective and so you can administer this to entire groups of people and essentially wipe out adult worms from that population. But there's the asterisk. This drug is only effective against adult worms so it does nothing if the worms that are in your body are still in that teenage stage, larval stage.
Erin Welsh	Right.
Erin Allmann Updyke	It does nothing for the eggs that are already in your body, right, those are the ones that are causing a lot of the symptoms that we see, and it does nothing for the environmental aspect of it, right, so it does nothing to prevent reinfection.
Erin Welsh	How long is this treatment? Is it just a one time thing?
Erin Allmann Updyke	It is, it's a one time dose which is great. Pretty effective at this point.
Erin Welsh	Is there any resistance?
Erin Allmann Updyke	That's why I said 'at this point'. (laughs)
Erin Welsh	Ah.
Erin Allmann Updyke	So as with any drug there is certainly concern for drug resistance. There isn't at this point a lot of evidence for resistance in the field, so it seems to still be pretty effective in the field. There is some evidence in mouse models and I think this is really interesting and terrifying, there's evidence in mouse models that immature schistosomes, so like the teenage versions in your liver that are exposed to praziquantel are more likely to be resistant as adults and that this tends to increase resistance through generations. So because it doesn't kill those larval stages in mouse models, if those larval stages are exposed to this drug, as adults they're more likely to be resistant.
Erin Welsh	How does that work mechanistically?
Erin Allmann Updyke	Probably some kind of epigenetics thing.
Erin Welsh	Okay.
Erin Allmann Updyke	It's like turning on or off genes that they might already have in place.
Erin Welsh	That's really interesting.
Erin Allmann Updyke	Yeah. It's only in mouse models so it's unclear whether this is happening in real life.
Erin Welsh	Right.
Erin Allmann Updyke	There isn't at this point a lot of evidence for resistance in human populations with this drug, it's still an effective drug.

Erin Welsh	Okay, good.
Erin Allmann Updyke	Yep. But it also can't be used for chemoprophylaxis because it doesn't do anything for those larval stages, it doesn't prevent you from getting infected in any way, and it has a really short half-life. So it basically is like you take one dose of this drug, it kills the adult worms, end of story. That's the end.
Erin Welsh	Cool.
Erin Allmann Updyke	Okay. So we need something better is pretty much the long and short of it, right. So there's a lot of work being done to try and develop a vaccine in part by none other than our good friend-
Erin Welsh	Peter Hotez?
Erin Allmann Updyke	Yeah! Peter Hotez! Dr. Peter Hotez. His group in Texas as well as a number of other groups are working on vaccines. There are a number of challenges largely in that we don't sort of develop classical immunity to this parasite the way that we do to other viruses or bacteria kind of a thing. So it's a more difficult target essentially. But basically there's a lot of mathematical modeling that show that any vaccine that can overall reduce egg output and can last, so can actually prevent reinfection and prevent egg output from going up again, can massively help to interrupt transmission.
Erin Welsh	I mean that makes sense, yeah.
Erin Allmann Updyke	Right. So that's kind of gonna be one of the main things going forward is trying to develop a vaccine that can do that. There are at least three vaccines right now in clinical trials, they are component vaccines so they're made up of specific antigens of Schistosoma mansoni along with adjuvants because one of the big things is that because this is a parasite that we know can elicit an immune response, it takes a very long time. So we have to include adjuvants in these vaccines to elicit a stronger immune response so that your body can actually then fight off any further infection with this parasite. Does that make sense?
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	So there's a long way to go but there is a lot of really great work being done by people to try and develop a vaccine for this which is great.
Erin Welsh	That's awesome.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah, cool. It's always good to hear after a very depressing history section and a little bit daunting, not even daunting but horrifying numbers of people infected around the world, some promising future for the disease that we talk about.
Erin Allmann Updyke	Yeah and World Health Organization I will say has a lot of goals in terms of trying to reduce morbidity and mortality from schistosomiasis. So they really are trying to get praziquantel, the drug, to as many people as possible. In 2018 about 40% of people who needed treatment were actually reached and about 62% of children were being treated who needed to get treated.

Erin Welsh	Okay.
Erin Allmann Updyke	So we still have a ways to go there but again there are people really working hard to try and get people access to drugs as well as develop vaccines for this horrible disease.
Erin Welsh	Yeah. Truly.
Erin Allmann Updyke	So yeah. That's schistosomiasis.
Erin Welsh	A good turn for tropical medicine.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's changed its intent and that's great.
Erin Allmann Updyke	Yeah. So, sources?
Erin Welsh	Sources. I want to shout out first of all a book called 'Bilharzia: A History of Imperial Tropical Medicine' by John Farley, fantastic book, really thorough, very fascinating, great resource. And then I also want to shout out a few other papers that I read. 'Where do human schistosomes come from?' By Claude Combes, 1990. By Di Bella et al 2018, 'History of schistosomiasis in humans from Egyptian medical papyri to molecular biology on mummies'. And finally by Mahmoud 2004, 'Schistosomiasis: from antiquity to the present'. And I've got a whole bunch more that I'll post on the website.
Erin Allmann Updyke	If you would like a really, really comprehensive overview of schistosomiasis biology and ecology there's a great primer in Nature Reviews: Disease Primers by Donald McManus from 2018. And then I have a number of other review articles and papers about the vaccine development. We'll post all of our sources on our website thispodcastwillkillyou.com under the EPISODES tab where you can find all our sources for this and every single episode we've ever done. So check those out.
Erin Welsh	Yeah. Thank you so much for listening and for letting us do this podcast cause it's the most fun thing and honestly I can't believe that we get to do it.
Erin Allmann Updyke	It's so fun. And thank you to Bloodmobile for the music in this episode and all of our episodes.
Erin Welsh	And finally until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!