

Marsha Howe

My name's Marsha, I live in the UK as you can tell from my accent. (laughs) And I've had sickle cell for the longest time I can remember. My parents found out when I was about 6 years old. My mother knew she had the trait but my dad didn't know that he carried the trait and obviously my older sister was born and she just had a trait, so my mom was like, 'Okay fine, she got that from me.' But when I came about I was born with another sort of illness on top of sickle cell which is called B6 deficiency, so it kind of masked the sickle cell. So over the many years growing up I was becoming sick, they couldn't quite work out, and then it was when my younger sister was born they said, you know, let's retest them for sickle cell and that's when they found out that I had the full blown disease.

I kind of understood I had an illness much later on, I would say when I was about 9, 8 or 9. Yes, I went to hospital appointments prior to that but it just didn't really sink in, I kind of let my parents deal with it all like, 'Okay well you manage my health, I'll manage being a child and playing with my friends and stuff like that.' I didn't really understand it til I think later on in my teenager years when I went to start to go to secondary school, that's when I started taking more control over my illness and saying okay well I have to eat right, I have to dress right, I have to make sure I get enough rest and not overstress myself because if I don't, these things can trigger off a crisis and I can be left out of school for weeks on end.

And it was only when I joined sort of like a big positive choir that I actually came out and a lot of my school friends, it was like, 'I did not know you had sickle cell.' I didn't know how to explain it to them in a way and I didn't know how they would receive me. I always think if I said it I would lose friends which I remember having a friend who said they don't wanna be my friend cause they felt they could catch sickle cell if they held my hand. And I was like it doesn't work that way unless you're born with it, it does not work that way. So I shielded myself so I wouldn't have to face that negativity and that hurt. Later on in my adult years I was like no, you know what? If you don't like me the way I am then that's fine, somebody else will, there's many people in this world that will. And I grew that confidence and was able to mentor or talk to other teenager girls and boys who were in my situation and say don't let sickle cell stop you from doing what you wanna do.

When I do get in a crisis and I'm in pain, the best was to describe it, it has to be like when you get a really bad cold and you have aches and pains and all of your body hurts on a 10 times worse scale than aches and pains when you've got a cold and you just want it to stop. And it's brought me to tears before many times and it's brought me to the parts where I'm like I don't wanna be here on this earth because I don't wanna experience this pain, why do I have to go through it? Why was I the unlucky one? And I did go through the phase of blaming my parents so to speak, saying like, 'You should have checked each other before you had me, why didn't you do this?' And your mind starts thinking loads of things of if I wasn't here, would I be in a better place or if I was born before my sister, would I be in a better place? And you just think many things.

Everyday you wake up, you don't know if it's gonna be a good day, if it's gonna be a bad day. And I think that affects your social life as well because you're forever canceling on your friends and it's the same with relationships. I've broken up with a lot of partners because they don't understand the extent of sickle cell, going into hospital, that's our last resort on our mind. We tend to not fight going into hospital but we wanna try and treat it the best we can at home. Sometimes we don't like going to hospitals because of the stigma that we get, we get looked upon as oh we're drug addicts or we're not really in pain, we're just here because we need a fix. And it's like I don't wanna be in hospital, this is the last place I wanna be.

Lucky enough my family are amazing, bless their hearts. I have snapped at them many times but it's not a case that I mean to, it's just a case of all I can feel is this pain and I don't wanna feel the pain anymore. I have apologized to them afterwards but now they kind of know my routine, when I say I'm in a crisis they don't ask silly questions, they're just like, 'Right, pain meds, heat pad or hot bath,' or 'It's that bad? Do you need to go to the hospital?' And obviously I've got a son who is fantastic, I call him a little doctor, the minute I say mummy's not feeling very well, he's on it with the pain meds, the hot cups of tea, the hot water bottle, everything he can think of to cheer me up. He'll put my favorite movie on and cuddles and just sit there with me. So he is literally amazing but because it's just me and him that live together, I feel like sometimes he feels his childhood got robbed and sometimes he feels like he can't be a child because he has to look after mummy and also be himself which I knew was quite hard.

That was the same thing when I knew when I was gonna have children, what impact would my health have on him? And for me, when I fell pregnant and after my pregnancy, that's when my sickle cell got worse. I had a minor stroke, more things were happening to my body where I felt like it was deteriorating. And that was not made aware to me when I was thinking about starting a family. So I'm now going over that hurdle of experiencing things where I feel that maybe I could've been made more aware of and given that option of what to do. But nevertheless he's still a blessing and I love him to pieces.

And I think now that I joined B Positive Choir, it's journey that you don't want to end. Singing for Britain's Got Talent, singing for the queen, Meghan, Prince Harry, Prince William, everyone was amazing. It was like I was living a dream, I had to keep saying pinch me, somebody pinch me, is that Meghan over there? No! So it was absolutely amazing and the way since we've come on that platform it's gone viral, I think it's got more awareness, everybody's starting to get involved and starting to be more clued up and taking notice of what sickle cell is and how they can go about helping to spread the awareness.

And I felt that it's a way that brings the community together as well cause in a choir there are many people who have the illness and we share our stories, everybody experiences sickle cell differently. So it's nice where we've become a big unit and we get to share it around the world which is amazing. And we have a laugh, we have a laugh and that's the main thing. Yes, you have your down days but also you have your good days. And everyone always says, 'How is it you're always smiling?' And I think I look at the positive that now I don't see sickle cell as a burden as I did before, I actually see it as a gift and a blessing to have because I can go out and spread the word about sickle cell and make friends. Yeah, I'm happy. Literally happy. I couldn't be any more happier. (laughs)

Sharif Tusubira

So my name is Sharif Tusubira. I was born in Kampala in Uganda, a small East African country. And I have sickle cell disease. So when I was born my mom and dad had a very sad love story. They gave birth to their baby boy, like all parents they were very excited to have a baby boy. I think after about 4 or 5 months after that I started to show up, I was very irritated, I was always crying and they told me I had swollen hands and we didn't know what was really going on. And my mom kept on going to different health centers until a time one doctor did say, 'You know what, we need to do a sickle cell test to be able to find out if this child has sickle cell.' So that was the change of their story because once she told my dad, they actually broke up and my dad left her because he's like, No, I'm not having any child who has sickle cell. In my family, we don't have sickle cell disease.'

So my mom ended up having to raise me as a single mother because my dad had left. During that time she was pretty scared about what was going on, she didn't know what was going on because at that time in the early 90s sickle cell wasn't really a very big thing. Most people who have sickle cell today in Uganda, you find that over 90% of the babies who are born with sickle cell died before their 5th birthday. So this is mostly because we don't have a comprehensive follow up program that you're gonna be diagnosed and good and go to a sickle cell center and be followed up, receive all the care. All that has not been there, if it has it's started to come up I think in the last 1 or 2, 3 years we're starting to see sickle cell centers across the country in Uganda.

So during that time when she was pretty alone, pretty scared, she named me Tusuubira. So my second name is Sharif Tusuubira, Tusuubira means 'we hope'. So the reason she chose the name Tusuubira was mostly because she of the fact she wanted to have a way to have some hope in the heart because if everyone around you is trying to say your baby's gonna die, every mom would be scared. But as a child growing up I didn't know what was going on. Yes, I'd have pain and cry and ask what's going on. My mom did not really have a way of explaining it to me until I think 6 or 7 years when I got to play and kids who come to play with me would say, 'Temuzanya naye mulwadde' which means in my local language 'do not play with him, he's sick'. So that's where I started to realize that there's something different about me. So that was my kind of childhood experience.

And this was the case whereby I'll be in the pit trying to kick the ball and I feel pain in my leg, feel pain in my hand and sometimes I just couldn't walk. My friends would have to carry me home. I'd go and ask my mom what's going on? Why me? Why am I feeling this way? I remember there was a time growing up I asked her for a knife so I could cut off my hand and cut off my leg because it was bringing too much pain for me. And they're like, 'No, you can't do that, you can't just cut off the leg because you're in too much pain.' But even then yes, I would feel very stigmatized and feel very bad about it.

And when I went to school it was actually different when we were at school because at school in the rainy seasons, extreme seasons, I'd be in pain and I couldn't go to school, so you'd miss like two weeks or three weeks of school. And the teacher has to say, 'Where has he been?' And so often my mom would have to explain, 'You know what, he has sickle cell. If he tells you his hands are sick, he can't write, it's fine. You have to understand.' But it was really hard for the teachers to understand because like I said this disease is mostly unknown. Even teachers are like, 'This kid just has an excuse, every time I want him to come and draw on the blackboard he's saying his hand is hurting. I want him to be part of the class activity, he's saying he feels pain in his leg and feels pain in there.' So that was another issue.

Because of my sickle cell I had complications like jaundice in my eyes and had a distended belly. So those things made me look more of an outlier. Yes, you look like everyone else but your eyes are pretty yellow so that's a thing that you have to explain to everyone, why are your eyes yellow? I didn't know how much to break it down but I would say yes, I have sickle cell, it's a blood disease, that's all I'd say. When I'd get sick and had a school nurse I would get care from the nurse. So high school was a much better experience. So during my second year in the university, I did get sick and I got sick and I think I missed almost three or four weeks of school. So everyone was asking, 'Where's Sharif?' And that's the time I was dating a very beautiful woman. And when I got sick, I lay in hospital and she tells me, 'You know what, I can't be with you because of your sickle cell. I mean I've never seen myself with someone with sickle cell.' That was a turning point for me.

So that was my driving thought now to make a change in not only my life but in the life of all those people living with sickle cell, so that they don't have to go through what I have gone through. So it was me, myself, Ashiraf, and two other people, Evelyn and another guy Salim, we agreed to create an organization called Sickle Cell Network Uganda, it was the first sickle cell nonprofit that we registered. Because of my background and stigma and the experience I had, one of the first things we implemented was having sickle cell as a training. When I looked at my background of laboratory technology and the fact in our market you could have people test for HIV, I thought to myself I think we should be able to test for sickle cell.

We started out at all our community events, we'd have a team of laboratory people do the sickle cell screening, our counselors to do the counseling so that people could understand what it means if you are trait, what it means if you have sickle cell, all those things. And after two years of this our local Minister of Health actually did accept and took this program, it's now been rolled out and several health centers have these rapid sickle cell testing kits, people now have access to sickle cell screening tests, wherever they are.

So in Uganda we have a tribe called Buganda tribe, it makes up the biggest portion of the population. But we didn't have a local name for sickle cell and this is not only the Buganda but most tribes in Uganda do not actually have a local name for sickle cell. And the indicator for this means that if you don't have a local name for something, it means you're not talking about it. If you're not talking about it then that explains all the stigma. So because we don't talk about it, there's no name. But the biggest win for me as an advocate is the fact that the kingdom gave us a local name for sickle cell, they did say now we pronounce that sickle cell anemia as Nalubiri. At least now someone who's uneducated, somebody who has never been to school can have a word that they can know to mean sickle cell and that in a way helps us break the stigma because then people can be able to talk about it in their mother tongue.

Looking back on how the journey has come from the time when we introduced community sickle cell screening, from the time when we have a local name, to the fact that we have not been to support the emergence of so many sickle cell nonprofits here. For example, at the time when we started there was only one nonprofit in Uganda working with sickle cell called Sickle Cell Association of Uganda. Today as I speak, we have over 25 CBOs, community-based organizations, all working for sickle cell in local communities. I think in 2019 I decided you know what, I've been an advocate for the past few years, I think I need to think of something, that's how I thought of coming back to grad school and I decided to come back to the US for my grad school.

So I came back, I went to the University of Kansas as a PhD student. When I came to the US, I was here doing a lot of hearing a lot of the racial bias in terms of sickle cell and that absolutely never happened to me until one time I think in May, I go to the ER. I had a lot of pain, I was actually very sick. I had a lot of pain, I spent the whole day in the ER, they give me all the pain meds, I was still in pain, and guess what happened to me there? There the doctor says, 'You are fine. We have checked everything, you're very normal. So we can't admit you.' Of all of the driving factors in terms of why as advocates living in the US we need to come out and promote more awareness about sickle cell such that the doctors will have more understanding.

I think one of the key important aspects may not be so much a big deal in the US but still a big deal in the world, the fact whereby people are not understanding and accepting sickle cell, having all these myths and beliefs. So it still goes back to awareness and helping people understand that this is like any other blood disease, if you can take good care of yourself, you can have a comprehensive follow up, if you can do whatever we can do to stay healthy, then I can live like anybody else, I shouldn't worry about that, I shouldn't worry that I'll not be able to meet my dreams. My story started out because of a heartbreak, because of a sad love story I ended up being a sickle cell advocate. Today I was able to find love, I'm married to Sophia and have two kids and they're part of my support system to keep me healthy and strong and going. So I appreciate them and everyone who is supporting me. Thank you.

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

Thank you so much Marsha and Sharif for sharing your stories with us, we really, really appreciate it. And we wanna tell you a bit more about our amazing guests. Marsha started her blog My Life With Sickle Cell in 2016 and has since been recognized for her awareness-raising efforts by appearing on TV programs, radio shows, newspapers, you name it. And in her firsthand she mentioned being a member of the B Positive Choir which is a choir made up of people with sickle cell disease or those who have friends or family members affected. And the B Positive Choir has made amazing strides in raising awareness of sickle cell disease as well as encouraging blood donations. And also as you heard they were on Britain's Got Talent and performed in front of the Royal Family which is pretty dang cool.

Erin Allmann Updyke

That's amazing. Our other incredible guest, Sharif, has been instrumental in a number of different advocacy and outreach efforts which you heard a bit about in his firsthand, including launching the East Africa Sickle Cell Alliance, working with the Pan African Sickle Cell Federation International, and serving as the first executive director of the Uganda Sickle Cell Rescue Foundation.

Erin Welsh

That's incredible.

Erin Allmann Updyke

So amazing. Sharif's amazing advocacy and outreach efforts have been recognized by many organizations. In 2017 he was named a Mandela Washington Fellow through the Young African Leaders Initiative, in 2018 he became a Telemachus Fellow under the Global Thinkers Forum, and this year, 2020, he was named the International Sickle Cell Advocate of the Year. No big deal.

Erin Welsh

No big deal.

Erin Allmann Updyke

And he's just casually also getting his PhD studying quantitative genetics at the University of Kansas, like you do.

Erin Welsh

Just casually getting a major degree.

Erin Allmann Updyke

Right? Oh my goodness.

Erin Welsh

That's amazing. We will provide links to both Marsha and Sharif's websites and social media handles on our website thispodcastwillkillyou.com and in our show notes if you'd like to learn more about these awesome humans and their work.

Erin Allmann Updyke

Yeah.

Erin Welsh: Hi, I'm Erin Welsh.

Erin Allmann Updyke: And I'm Erin Allmann Updyke.

Erin Welsh: And this is This Podcast Will Kill You. This week we are, as you may have guessed-

Erin Allmann Updyke: You might have figured it out by now.

Erin Welsh: (laughs) Covering sickle cell disease!

Erin Allmann Updyke: Yeah. This is a big one obviously.

Erin Welsh: This is a huge one. And we've been wanting to do this one for a while and I'm very excited now that we're finally doing it because there's so much to it.

Erin Allmann Updyke: Yeah, absolutely. There is such fascinating biology, I can't wait to learn about the history. I have a feeling it's gonna be equal parts fascinating and infuriating. That's my guess.

Erin Welsh: Oh I would say maybe not even equal parts, I would say mostly infuriating.

Erin Allmann Updyke: Oh great. Cool, cool, cool. Great, yeah, awesome. Okay.

Erin Welsh: There are some shining moments but yeah.

Erin Allmann Updyke: But I can tell you that there are some very exciting things to talk about in the current events section for which we had the pleasure of speaking with a very special guest, Dr. Megan Hochstrasser, who is Education Programs Manager at Innovative Genomics Institute in Berkeley.

Erin Welsh: It's incredible. I'm sure that you may have heard the word CRISPR or genome editing at some point and been like what the heck is that? Don't worry, we're gonna get into it at least a little bit and it's going to make you so thrilled and make you feel like you're living in the future.

Erin Allmann Updyke: It's thrilling. But before we get into all of the thrilling things that we're gonna talk about today Erin, what time is it?

Erin Welsh: I believe Erin that it is quarantini time.

Erin Allmann Updyke: You would be correct about that. What are we drinking today?

Erin Welsh: We are drinking The Whitten.

Erin Allmann Updyke: Lovely.

Erin Welsh
Oh yes. And The Whitten is named for Dr. Charles Whitten who among many other amazing accomplishments was the cofounder of the Sickle Cell Disease Association of America and he made amazing strides in raising awareness of sickle cell throughout the 70s and 80s and into the 90s as well. And he also initiated a lot of programs that were designed to provide more opportunities for those underrepresented in medical fields to actually have medical school as an opportunity. So we wanted to name our quarantini to honor this amazing human in the tiniest possible way.

Erin Allmann Updyke
And to do so, what is in this quarantini exactly?

Erin Welsh
The Whitten is strawberry-infused tequila which is so good.

Erin Allmann Updyke
So good.

Erin Welsh
And also just really easy to do, it just takes patience. And lime juice and agave syrup.

Erin Allmann Updyke
Fabulous. We'll post the whole recipe for that quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and all of our social media channels, so make sure you're following us.

Erin Welsh
And we have one more piece of business before we get into the business of sickle cell.

Erin Allmann Updyke
Just a little one which is big news actually.

Erin Welsh
We have new merch.

Erin Allmann Updyke
New merch! We've been waiting, we're so excited.

Erin Welsh
We have some really fun, cool things like we'll just drop a few little hints. You want a hoodie? We got a hoodie.

Erin Allmann Updyke
Oh we got one!

Erin Welsh
You want some socks? We have socks.

Erin Allmann Updyke
Oh you need some socks to keep your toes warm!

Erin Welsh
Big shout out to Abigail Ervin-Penner whose always incredible artwork is featured on so many of these. Honestly I'm in love.

Erin Allmann Updyke
I can't wait to be TPWKY head to toe, baby.

Erin Welsh
I mean literally, literally head to toe.

Erin Allmann Updyke
Head to toe and for my sips. Yeah, okay.

Erin Welsh
If you would like to see this new merch you can head to thispodcastwillkillyou.com and click on the merch tab at the top of the screen.

Erin Allmann Updyke
All right, is that all of our business, Erin?

Erin Welsh

I believe so.

Erin Allmann Updyke

Well then, let's take a quick break and dive straight into the biology of sickle cell.

Erin Welsh

Let's do it.

TPWKY

(transition theme)

Erin Allmann Updyke

So sickle cell disease or SCD, I think it's often taught as sickle cell anemia, right, this one particular illness. But in fact sickle cell disease is a group of disorders of red blood cells. And it's a genetic disease which means it's inherited, so it's caused by a mutation. But as we'll see, it's not just one single mutation and there's not just one single manifestation. So we're gonna start from the very beginning before we even get into sickle cell disease itself and talk about blood. Cool?

Erin Welsh

Yes.

Erin Allmann Updyke

Okay, good.

Erin Welsh

We've talked about blood before a little bit.

Erin Allmann Updyke

We have but we've never talked about this. We have talked about... When have we talked about blood?

Erin Welsh

Hepatitis C.

Erin Allmann Updyke

Oh yeah, this is a totally different blood discussion, okay.

Erin Welsh

Okay.

Erin Allmann Updyke

So what we're gonna talk specifically about is in our red blood cells the protein that is actually responsible for carrying oxygen and that protein is hemoglobin. Okay? So hemoglobin a protein that's made up of four polypeptides, two pairs of polypeptides, and these four polypeptides or strings of amino acids form the protein that's in our red blood cells that actually carries oxygen which obviously our tissues need in order to survive. So in most adult red blood cells, hemoglobin is made up of two alpha chains, alphas, and two beta chains. So alpha-alpha, beta-beta. Okay?

Erin Welsh

Sounds good.

Erin Allmann Updyke

Now we also have some other forms of hemoglobin, like you can have two alpha chains and two delta chains, that's another kind of adult hemoglobin. And then in a fetus, before we are born, the majority of our hemoglobin is actually two alpha chains and two gamma chains and that's called fetal hemoglobin.

Erin Welsh

Why?

Erin Allmann Updyke

Great question, so glad you asked. So you know how fetuses are grown inside and all of their blood comes from mom, right? So that means that all of the blood that a fetus is getting is already partially deoxygenated, it doesn't have as much oxygen as the blood in our bloodstream cause we're breathing in air. So because of that, fetal hemoglobin has to actually bind oxygen more tightly than adult hemoglobin because it has to be able to get all of that oxygen out of mom's blood. Does that make sense? Okay. Now remember that because it's going to become very important in our discussion of sickle cell later, okay.

Erin Welsh

Okay.

Erin Allmann Updyke

So now we understand hemoglobin inside normal adult red blood cells. So what does that mean for sickle cell disease? Why did I tell you all that? Turns out the sickle cell disease is produced by a single amino acid change, if anyone cares it's a glutamic acid to valine, in that beta hemoglobin chain. So it's a single mutation in beta hemoglobin that results in what's called sickled beta hemoglobin, so HbS instead of HbA for adult. That is the change that if you have two copies of that mutated beta-globin gene, you have sickle cell anemia, the disease caused by two copies of these sickle cell genes. So what happens if you have these sickle cell versions of beta hemoglobin? Well what happens is that in your red blood cells at low oxygen concentrations, like low overall oxygen concentrations in your blood, the hemoglobin forms a polymer, so multiple subunits, like multiple little globules of hemoglobin protein will link together inside the red blood cell and form a linear chain.

Erin Welsh

Like a little string of beads?

Erin Allmann Updyke

Like a little string of beads, exactly. And this becomes rigid and causes a deformation in the whole red blood cell so that it kinda sucks in on itself and becomes sickle-shaped or like a crescent moon shape. So a normal adult red blood cell, even a fetal red blood cell, is shaped kind of like a donut, like you know the things you go down the lazy river in, those inflatable tubes with the mesh in the middle so your butt doesn't fall through? You know what I'm talking about?

Erin Welsh

Oh I've never had one that had the mesh but sure.

Erin Allmann Updyke

The fancy version, okay. So that's kind of what a normal red blood cell looks like. When you have two copies of this sickle cell beta hemoglobin chain, all of your hemoglobins line up in the red blood cell and sickle it, so instead of that nice donut you have a C-shaped red blood cell. And that is kind of the core problem that results from two copies of this sickle cell gene. Okay, it's just a different shape of your red blood cell. Why is that so bad? So these sickled cells are very rigid, okay. Normal red blood cells are kind of like an inflatable donut, they're kind of squishy and squashy, okay? So as they move through your blood vessels from larger vessels to smaller vessels like your capillaries, they can squash and deform and scooch through small vessels and then pop back out on the other side. Sickled cells are more rigid so they can't do that as well.

So what happens is these cells can start to get stuck especially in small vessels, okay. But it's not just the rigidness of the sickled red blood cells. So it turns out that once a red blood cell sickles like this, they're also literally stickier, like proteins on the outside of them become more sticky so that they get stuck to the walls of your vessels and they get stuck to other white blood cells and things that are rolling along in your vessels, okay. And imagine what happens if you have a bunch of cells starting to stick to one another inside of your blood vessels.

Erin Welsh

Well you'd get a blood clot.

Erin Allmann Updyke

You're gonna get a blood clot, exactly. And so kind of the hallmark of sickle cell disease that's we'll talk a little more about in a minute when we talk about the symptoms are what's called vaso-occlusive crises. So you literally have occlusion or blockage of your vessels, small vessels like capillaries but even larger vessels like in your brain, leading to stroke.

Erin Welsh

That sounds terrible.

Erin Allmann Updyke

It's not great, that's for sure. And there's more, okay. So now we know that they sickled cells, they get more sticky, they can get stuck in places. But on top of that, red blood cells only sickle at lower oxygen concentrations so for the most part in your arteries, even if you have sickle cell disease, your red blood cells are gonna be a normal shape. It's not until you reach the capillaries or the veins where oxygen concentration is lower, that the hemoglobin will form those chains and then cause the red blood cell to sickle. But this is reversible, but there's two problems with it. First of all this tends to happen in microvessels like your capillaries and small veins because that's where both oxygen concentration is low and you have slow flow, so the red blood cell's in there for a long time comparatively. And so those two things combined lead to sickling and in small vessels if you sickle and you get stuck, then you can block those small vessels directly.

Erin Welsh

Gotcha.

Erin Allmann Updyke

Now another thing happens. Over time this constant sickling and unsickling, sickling and unsickling causes damage to the red blood cell membrane itself, so like the outer shell of the red blood cell. And this can cause an irreversible sickling, so now it's just stuck sickled all the time. And those sickled cells in particular are very, very sticky. So that can cause sticking on the inside of vessel walls and to white blood cells in larger vessels which can eventually lead to blockage of even larger vessels, not just small ones.

Erin Welsh

Right and it seems like the white blood cell thing then will play a role in immune system function?

Erin Allmann Updyke

Oh you're so accurate, Erin.

Erin Welsh

Here's a question.

Erin Allmann Updyke

Yeah?

Erin Welsh

And maybe it's jumping the gun.

Erin Allmann Updyke

Okay.

Erin Welsh

But your body, as we talked about in the hepatitis C episode, your body makes new red blood cells very frequently and so what does it do? Does it attack the sickled cells in any way or what is their lifespan?

Erin Allmann Updyke

I'm so glad that you asked Erin, it's totally jumping the gun but it's the perfect question, I love it. So yeah, okay. I'm gonna answer that question in a couple parts, okay. So first of all you're right that white blood cells and things play a big role and overall even though this is technically a disease of just red blood cells right, it's just hemoglobin being messed up, it's not just a disease that affects your red blood cells. Overall there's an increase in inflammation and inflammatory state in sickle cell disease and the more inflammation, so the higher people's leukocyte counts or white blood cell counts, the worse off their disease tends to be. And as we'll see there's huge variation in disease severity and that's one factor that plays a role. Now in terms of how long these blood cells last, that's a perfect question to ask. A normal healthy red blood cell has a lifespan of about 120 days. In someone with sickle cell disease, that lifespan is reduced by over 75%. So some estimates that I saw we're the lifespan of a red blood cell in a person with sickle cell disease, so that's two copies of that sickle cell gene is about 16 days.

Erin Welsh

Oh wow. And so even if your body is producing blood, it's not enough to make up for the loss.

Erin Allmann Updyke

You're getting the perfect... Yes, 100%. So there's two ways that you get anemia. One like you said, you just can't make enough because you need to constantly make more red blood cells and more red blood cells. But on top of that, as those cells sickle and unsickle and become damaged, that leads to hemolysis, so red blood cells actually breaking open within your vasculature. So not only can you have anemia from lack of production, you can also have a hemolytic anemia, so breaking open those red blood cells. Now that leads to even more problems because when you burst open red blood cells, all that hemoglobin that's inside those red blood cells is now released into the bloodstream and this causes a whole host of biochemistry reactions I'm not gonna get into but one thing that it does is it scavenges up all of the nitric oxide which is an important molecule that helps with things like vasodilation.

So as your hemoglobin sucks up all the nitric oxide, now you have increased vasoconstriction as well as damage to the epithelium of the lining of your blood vessels which causes even more stickiness, okay. So it's like this horrible feedback loop, if that makes sense, where you have smaller vessels because you have less nitric oxide, you have damage to the inner layer which increases the stickiness, you have inflammation so there's white blood cells rolling around, picking things up, and it's bad, it's a mess, okay.

Erin Welsh

Yeah that's like from one amino acid substitution.

Erin Allmann Updyke

One.

Erin Welsh

These systemic problems.

Erin Allmann Updyke

It's fascinating that you can have so many effects from one single... And I mean it's a single nucleotide, it's a single base pair change.

Erin Welsh

Right, right.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah, man.

Erin Allmann Updyke

Okay so let's talk about what these symptoms then look like, so now we know what's happening in your blood vessels and it kind of all boils down to increased inflammation and blocking your vessels, okay. So I said this already but the main complication are these vaso-occlusive crises and so these can manifest as you can probably imagine in so many different ways depending on what vessels are getting blocked up. So in small children, especially tiny babies like under the age of 2, the most common presentation is when the small blood vessels in their hands and feet get clogged up, this causes swelling of the hands and the feet. And this is really, really painful as well because you're literally blocking blood flow to your hands and feet. And so in small babies that for example didn't have a newborn screen done, so they're parents maybe didn't know that they had sickle cell anemia, this is a really common way that they would come into the emergency room and be identified as having sickle cell anemia.

Erin Welsh

Okay. Is there treatment for that aspect of it or is it...?

Erin Allmann Updyke

So we'll talk about treatment more later but for the most part not really.

Erin Welsh

Okay. God.

Erin Allmann Updyke

Yeah, yeah. Okay. So then as you can imagine, as you get older, these pain crises, these vaso-occlusive crises, just kind of keep happening and they can happen almost anywhere. So it's very common for people to come in with massive, massive amounts of pain without any kind of, you can't see anything wrong with them because it's these tiny blood vessels in your abdomen or your legs, in your arms, anywhere that get clogged up. This causes a huge amount of pain. If you imagine a heart attack happens when you have a blockage of blood flow to your heart, heart attacks are extremely painful. This is happening in small vessels throughout somebody's body during a sickle cell crisis. This is a disease that is I think often very misunderstood and the pain I think can be minimized by people because it's not visible, it's another kind of disease like we've talked about before where you don't look sick necessarily. And so I think it's really important to get across just how debilitating the pain associated with these can be.

Erin Welsh

It's funny that you're using the phrase invisible and visible because that's my theme when I talk about the history of it.

Erin Allmann Updyke

Yeah, yeah. It's bad. Okay so then you also can have additional symptoms or sort of more specific symptoms depending on where you have these blockages. It can happen in people that have a penis, it can happen and you can get what's called priapism which is a long lasting and very painful erection. If it happens in the blood vessels under your skin especially in your legs which is really common, it can cause chronic ulcers, so open wounds on your legs that are unable to heal because they're not getting good blood flow over time. If it happens in your eyes it can lead to blindness because the vessels in your retina become blocked.

Erin Welsh

God.

Erin Allmann Updyke

It can happen in your bones and this is very serious because your bones are also alive, they need blood flow, so when you block off the vessels to your bones you get what's called avascular necrosis, so that means tissue death because of lack of blood flow. So your bone marrow will literally die.

Erin Welsh

Oh my god.

Erin Allmann Updyke

Yep. So that's pretty bad as you can imagine, that can also lead you susceptible to osteomyelitis which is infection of your bone, like a bacterial infection of your bone because you don't have good blood flow to that bone. It can happen in your spleen which is very common and with your spleen, kind of two different things can happen. So you can have what's called an acute splenic crisis, so all of a sudden blood flow to your spleen gets blocked, this can cause your spleen to enlarge very rapidly and that can kill you, that alone can kill you. Your spleen is an organ where a ton of blood flows through it because it's a lymphatic organ, so all of your white blood cells kind of hang out in your spleen and are responsible for gobbling up bacteria and cleaning your bloodstream of infection, okay. So because it has such huge volumes of blood flow, if you block that blood flow then you can die just from that alone. But it can also happen and it commonly does happen where over time, small vessels get blocked little by little in your spleen, leading to long term death of your spleen, what's called autoinfarction.

Erin Welsh

Right.

Erin Allmann Updyke

So that a person, even though they have a spleen in their body, it's essentially nonfunctional, it's like you removed it. So that leaves you very susceptible to infection especially bacterial infections because you don't have a spleen to take care of all those bacteria. So it's very common for peoples, especially young children, to die not from sickle cell anemia or sickle cell disease itself but from an overwhelming bacterial infection cause their spleen is nonfunctional.

Erin Welsh

God.

Erin Allmann Updyke

Another really horrible outcome would be stroke. And this is especially what is so tragic is that stroke is very common in young kids with sickle cell anemia. And so that's essentially not just from small vessels being blocked but from larger blood vessels in your brain that can get blocked. And then overall the most common cause of death and the second most common cause of emergency room visit for someone with sickle cell anemia at least in this country is what's called acute chest syndrome or ACS. And this is when you essentially get those crises in your lungs.

Erin Welsh

Oh my god.

Erin Allmann Updyke

Yeah. And what is awful and also very interesting about ACS is that the trigger for that can be almost anything. So it doesn't necessarily start with just these sickled cells blocking blood vessels, it can be a viral infection that causes inflammation that then triggers all these events. It could be an asthma attack, because you can have asthma and sickle cell, that triggers all these events. It can be fat embolism because if you have for exactly necrosis of your bones, your bone marrow is full of fat. Little pieces of that fat can break off and travel to your lungs and then those little emboli they're called can cause a blockage that can then trigger all these downstream effects. So acute chest syndrome, ACS, it's basically a triad of extreme chest pain, infiltrates, so fluid and junk all over your lungs, and then what's called arterial hypoxemia, so not able to get oxygen in your arteries because of all this fluid and junk in your lungs.

Erin Welsh

Oh my gosh. This is horrible.

Erin Allmann Updyke

It's really, really awful. So yeah, that's kind of the overall symptom picture of what happens with sickle cell anemia, or sickle cell disease.

Erin Welsh

And so these happen, like you talked about, these tend to happen at different stages of someone's life. So why is that? Is it just a matter of your body growing and certain things growing at certain times more?

Erin Allmann Updyke

Yeah, it's a really good question. I don't fully know but it is the case that people tend to present differently at different ages. So like in very young kids the first presentation might be that hand and foot swelling, right, in a very young baby. As they get older, especially under 5, it's very common to have bacterial infections that can end up becoming very serious. Then at a certain age stroke is a common manifestation. And then after that these pain crises and acute chest syndrome.

Erin Welsh

Right. Oh my gosh.

Erin Allmann Updyke

Yeah. And then on top of that like we said kind of already, you have kinda chronic anemia, so not enough red blood cells, this hemolysis which leads to fatigue, it leads to jaundice, you can have gallstones very commonly because of all this hemoglobin in your bloodstream it can cause the formation of gallstones, so you can have huge pain from that. It's very bad. Kidney failure is really common if you block the bloodstream to your kidneys, you can have kidney failure and that's really common. I mean it's everything, it's anywhere that your blood flows.

Erin Welsh

I mean anywhere blood flows, yeah.

Erin Allmann Updyke

Exactly.

Erin Welsh

Geez.

Erin Allmann Updyke

And what I also want to mention that I think is often glossed over is the huge amount of mental and behavioral health complications for this, depression and anxiety are very, very high among people living with sickle cell because they have chronic pain. Not only are they living with chronic pain, not only so they have a reduced life expectancy, they're frequently in the emergency room, they're frequently being hospitalized, that's a massive amount of financial cost that's incurred, and on top of that there's a longstanding history of medical professionals not believing or not taking seriously the pain that you're in. So yeah, this is a very, it's a single mutation that leads to so very many complications.

Erin Welsh

Oh yeah, oh yeah.

Erin Allmann Updyke

Yeah. Well is it a single mutation? There's my transition. Okay so all of that is kind of the description of sickle cell anemia which is when you have two copies of that mutated beta-globin gene so that you have messed up hemoglobin. That's not the only way that you can have sickle cell disease. There are a number of other mutations that can result in sickle cell disease that is usually less severe than sickle cell anemia although in some cases it's almost as severe. So if you have one copy of the sickle, like HbS, that sickle cell allele, and then you have one copy of a beta-thalassemia allele. So beta-thalassemia is something most people might have heard of or thalassemia maybe you've heard of. This is another entirely separate mutation of your beta-globin gene.

Erin Welsh

Right.

Erin Allmann Updyke

You can have one copy of HbS and one copy of beta-thalassemia, then you kind of have thalassemia and you kind of have sickle cell disease, you have a combination of both. So typically your symptoms aren't gonna be as severe as someone with two copies of sickle cell but you're still gonna have some of that, you can still have some cells that sickle essentially. Okay?

Erin Welsh

Gotcha, yeah.

Erin Allmann Updyke: There's another gene called HbC that's like another form of sickle cell, so you can be HbS-HbC, that's a whole other one. There's another type of thalassemia called alpha-thalassemia so that's where those alpha polypeptides are messed up rather than the betas in your hemoglobin. And that typically leads to actually a less severe form of sickle cell anemia or of sickle cell disease.

Erin Welsh: Why? What's the difference between the alpha and the beta that it would be a different severity?

Erin Allmann Updyke: This is very complicated but it's actually because instead of only two copies of alpha, we have four copies of alpha.

Erin Welsh: Okay.

Erin Allmann Updyke: So if you have just one mutation, you still have three good copies.

Erin Welsh: Gotcha.

Erin Allmann Updyke: So what's I think really kind of important... It's a good question, I'm glad you asked that Erin. What's important about this is that if you have one copy of this HbS, this sickle cell allele, you're still gonna make that messed up beta hemoglobin but you'll make enough normal that you won't have these sickling events. Okay? You make enough normal hemoglobin that they can't form those chains and sickle unless you have extremely low oxygen concentrations, okay? So in rare instances you can still get sickling but in general it's gonna be a lot less, it's not gonna be nearly as many of your red blood cells. If you have two copies, all you make is a messed up beta hemoglobin. So all of your red blood cells have this messed up hemoglobin, okay.

Erin Welsh: Right. And this is where the language around it is so important to remember, like the difference between sickle cell disease, sickle cell trait, and sickle cell anemia.

Erin Allmann Updyke: Exactly.

Erin Welsh: And that's led to a lot of confusion in the history of it as I'll talk about.

Erin Allmann Updyke: Yeah. And so sickle cell trait would be if you have one copy of HbS and one copy of a normal HbA or normal adult hemoglobin.

Erin Welsh: Right, right.

Erin Allmann Updyke: Oh gosh. So yeah, okay. I think that's all about those types of things. What else do you wanna know about the biology, Erin? I've got more for ya.

Erin Welsh: Well I wanna know about treatments.

Erin Allmann Updyke: Okay, let's talk about it. It's not great.

Erin Welsh: Okay.

Erin Allmann Updyke

There are some good things. So remember how especially for young kids the most common cause of death is overwhelming bacterial infection. So in many countries in the world we now screen for sickle cell disease in newborns and if you identify somebody with sickle cell disease, you can start treating them prophylactically, so before they ever get sick, with penicillin. So these kids get penicillin just everyday for like the first 5 years of their life. So that has reduced the death rate to less than 3% compared to over 25%.

Erin Welsh

That's great.

Erin Allmann Updyke

So that's great. Vaccinating babies is massively helpful in preventing overwhelming infection because we have vaccines for a lot of the things that commonly cause infection in these kids. But beyond that, so that's kind of like we can prevent kids from dying at a very young age from sickle cell. But beyond that we really have cruddy treatment for sickle cell disease and sickle cell anemia. If somebody comes in with one of these acute crises of pain, there's not much more to do besides pain control which I'm sure you'll talk more about later, so many problems. You can give transfusions, so you can do an exchange transfusion where you take out their blood and give them new blood essentially, so that can decrease the amount of sickled cells in their blood which can be very helpful. But the only actual treatment, like drug that we have, is hydroxyurea, which this is so fascinating, we have no idea how it does this but what it does is it increases the amount of that fetal hemoglobin, that gamma hemoglobin. I see your confused face, Erin.

Erin Welsh

Yeah. How? Why? How?

Erin Allmann Updyke

Okay, I can't answer.

Erin Welsh

Do we have any amount of gamma hemoglobin just circulating at any given time?

Erin Allmann Updyke

Yes.

Erin Welsh

Oh okay.

Erin Allmann Updyke

And great question, potentially yes. and there's massive amounts of variation in how much fetal hemoglobin a non sickle cell diseased person produces. And even within someone with sickle cell disease, how much fetal hemoglobin they have correlates to how severe their disease is. So the more fetal hemoglobin, the less severe their disease tends to be. So giving somebody hydroxyurea increases the production of fetal hemoglobin, decreases the severity of disease.

Erin Welsh

That's fascinating.

Erin Allmann Updyke

Fascinating.

Erin Welsh

And I have a question.

Erin Allmann Updyke

Okay.

Erin Welsh

Do you know is there any sort of elevational or altitudinal gradient in terms of let's say populations whose ancestral history has been mostly high elevation, so they produce more gamma hemoglobin than those at lower elevations?

Erin Allmann Updyke

That's such a good question and I can't remember. That is such a good question, Erin. I can't remember. I don't know if people tend to have higher fetal hemoglobin but there are certainly adaptations in populations that have lived for a long time at high altitudes where their hemoglobin has a higher affinity, so it binds tighter to oxygen the way that fetal hemoglobin does, the same way.

Erin Welsh

Yeah. Interesting.

Erin Allmann Updyke

Yeah. There's so much more to the whole oxygen thing and altitude, we can't get into it but yeah.

Erin Welsh

I know. I mean we really should do an episode on blood.

Erin Allmann Updyke

Ooh!

Erin Welsh

Because I also want to talk about blood groups at some point.

Erin Allmann Updyke

Oh I know, we've never done that, that would be super fun. I'd love to talk about blood even more. Okay. People will be experts by then because we did it in hepatitis and now we're doing hemoglobin, it's cool. Okay so that's hydroxyurea, so that is considered a disease-modifying agent, it's the only one we have because it actually improves your functioning essentially by increasing the amount of fetal hemoglobin. But the only "cure", and I'm gonna put that in air quotes, is bone marrow transplant.

Erin Welsh

But that has its own suite of problems.

Erin Allmann Updyke

Absolutely, always does. Yeah so it has to be a perfectly or very well-matched donor which is very difficult to find, it requires that you wipe out somebody's entire bone marrow first which leaves them very susceptible to infection, then once you put in the new bone marrow you can have auto rejection, etc. And so because the severity of sickle cell disease and sickle cell anemia ranges so much, transplants are not generally done except in very severe cases and even then only in high income countries like the US or the UK. So it's very rare essentially which is problematic since that's the only curative treatment that we have.

Erin Welsh

Right. And it's curative as in it's done forever.

Erin Allmann Updyke

Yeah, as long as your body doesn't reject it, then yes.

Erin Welsh

Yeah, wow.

Erin Allmann Updyke

You have brand new bone marrow so you no longer make these sickle cells. You could still pass that on, right, if you have a kid they could have either sickle cell trait or sickle cell anemia. But yeah, you would be cured. Yeah. I think that's all the major things I wanted to talk about for the biology.

Erin Welsh

Okay. Gosh, this is a big one.

Erin Allmann Updyke

It's a big one. Erin, where did this come from? Why does anyone have to live with sickle cell disease? And what the heck is up with this mutation? Tell me about it.

Erin Welsh

Okay, as soon as we take a short break.

TPWKY

(transition theme)

Erin Welsh

Okay so to tell the history of sickle cell trait and sickle cell anemia, for this I'm gonna concentrate primarily on the HbS form, not talk about thalassemia, this is just about sickle cell anemia and sickle cell trait. I think that the best place to start is in the name itself because aside from being one of my favorite things to learn about and talk about for any disease, it can also be incredibly revealing especially in the case of sickle cell. Because the name tell us not only what those who named it saw and what was important to them in describing this disease but it also makes us consider what discovery is, like what does discovery mean and how often that term is misapplied to something that could more accurately be called a development.

Erin Allmann Updyke

Ooh.

Erin Welsh

So when the term 'sickle cell anemia' was first used by western medicine in 1922, named by Dr. Verne Rheem Mason, the medical field was still in the midst of this big rush of new technology and new theories and new hypotheses that led to enormous leaps forward in the understanding of disease, both infectious and noninfectious.

Erin Allmann Updyke

Okay.

Erin Welsh

And with huge improvements in microscopic, surgical, and other medical tools, physicians could now get a much more detailed look at what was going on inside the human body. And among other things, this led to a shift in how diagnoses were made. So previously doctors may have had to rely solely on symptoms of disease as described by the patient but with these new tools it allowed for measurements and observation, so the art of medicine was becoming a science. And this is something that we've kind of talked about before.

Erin Allmann Updyke

Yeah.

Erin Welsh

And the vast increase in knowledge of medicine in the human body also changed the medical field in terms of specialization because with the volume of information that was growing day by day, it was nearly impossible for one person to learn it all and retain it all. And so there was not only the capacity but also the need for specialists in certain fields.

Erin Allmann Updyke

Okay, interesting.

Erin Welsh

And so both of these shifts were enormously beneficial to the people being treated because with an accurate diagnosis you had a greater chance of getting appropriate treatment and care. But there were also some unintended consequences. So in some ways medicine became more about the body and less about the person and the heightened attention paid to measurements or direct observation could sometimes take away from the experience of the person receiving treatment and this is reflected in the naming of sickle cell anemia. As you mentioned, the term 'sickle cell' describes the shape of the affected cells which is a direct result of the mutated allele and it was given that name by the physicians who first observed these types of cells under a microscope. But the condition, the experience of sickle cell anemia had been known long before the 1900s, thousands of years before, and people who lived in areas of high prevalence, notably in parts of Africa, had names for the disease as well. And I have a list of these names but I don't want to butcher them entirely but one of the commonalities of these names is they have sort of this onomatopoeia, this onomatopoeic rhythm to them.

Erin Allmann Updyke

Ooh.

Erin Welsh: And that's because it represented the repetitive, gnawing pain of sickle cell anemia rather than the cellular morphology.

Erin Allmann Updyke: Right, so it's like a description of what people were going through, not just what the cell looks like.

Erin Welsh: Exactly.

Erin Allmann Updyke: Fascinating.

Erin Welsh: And there was also another name that was reported in the African medical literature in the late 1800s, it was a term 'Ogbanjes' meaning 'children who come and go' which is in reference to the high childhood mortality.

Erin Allmann Updyke: Yeah.

Erin Welsh: And so yeah, these names describe someone's experience with the disease and perhaps how they would define it rather than a cellular observation which was completely removed from the experience. I mean if you think about it, if you have sickle cell anemia, you are probably familiar with these extremely painful episodes characteristic of the disease but you may have never seen your own sickle-shaped cells under a microscope.

Erin Allmann Updyke: Right.

Erin Welsh: So I just think that was a very... Yeah.

Erin Allmann Updyke: I love that Erin, that's so, so interesting and important. And I don't think I ever would have thought about it quite honestly.

Erin Welsh: Well this is not my observation, this is something I read in a book, but I think it did make me think about other diseases that we have talked about and there is a lot of meaning in a name whether it's specific to a location, and we've talked about the issues with that, or whether it's this very clinical, detached way, objective way of looking at a condition. There are some other ones that are more about the experience itself like dengue I remember may have some link to the painful bone-breaking sensation.

Erin Allmann Updyke: Yeah. That's very interesting.

Erin Welsh: It's interesting.

Erin Allmann Updyke: Yeah.

Erin Welsh: And also as the author of one of the books I read pointed out, the sharp contrast between the visible, the sickle-shaped cells, and the invisible, the excruciating pain endured in the various names of sickle cell anemia, in many ways it mirrors the history of the disease, particularly throughout the 20th and 21st centuries in the US.

Erin Allmann Updyke: Ooh.

Erin Welsh

Okay. So though there were some brief descriptions of what was likely sickle cell anemia since the mid 1800s, the first clinical description of the disease was made in 1904 by the University of Chicago physician James Herrick who reported, quote, "peculiar, elongated, and sickle-shaped red blood corpuscles" in a 20 year old patient of his named Walter Clement Noel who was originally from Grenada and the only person of African descent to be accepted into the Chicago College of Dental Surgery that year.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. So Noel had some ulcers on his leg and described painful episodes and other symptoms of anemia and so Herrick drew some blood and gave it to his intern named Ernest Irons to check it out. And Irons made the actual observation, like that description, but Herrick reported his findings at a conference in 1910 and then Irons was given no credit.

Erin Allmann Updyke

As per usual.

Erin Welsh

As per usual. And although Walter Clement Noel recovered from his illness after his visit to Herrick, he did die at a young age, 32, of pneumonia, 12 years after that visit. And this first description of sickle cell anemia was closely followed by many others who noted that it primarily affected black Americans of African descent, these were all American physicians, and that complications arising from the condition often led to death at an early age. And despite these warning bells going, 'Hey, we have a serious disease here on our hands, maybe we should learn more about it and how to treat it,' sickle cell anemia remained largely invisible for a couple of decades before finally gaining some recognition in the 1930s.

Erin Allmann Updyke

Wow.

Erin Welsh

Okay so why was sickle cell anemia obscured for so long?

Erin Allmann Updyke

I can guess.

Erin Welsh

There are many reasons. Part of it was the pre-antibiotic high prevalence of acute infectious diseases and also pre-vaccine, some of which mimicked the symptoms of sickle cell anemia such as malaria and made it more difficult to see this disease underneath. And when antibiotics, vaccines, and infectious disease control policies were implemented in the early decades of the 20th century, other chronic diseases became much more visible.

Erin Allmann Updyke

So it was like kids were just getting sick and dying from sickle cell anemia before they knew that it was because of sickle cell anemia.

Erin Welsh

Exactly.

Erin Allmann Updyke

Okay, that makes sense.

Erin Welsh

Exactly. But of course the other enormous component was the inherent racism in medicine.

Erin Allmann Updyke

Yep.

Erin Welsh Higher rates of disease, higher infant mortality, and lower life expectancies overall in black American compared to white Americans was dismissed by the vast majority of those in the medical field which of course were primarily white was either evidence for biological basis of race or they said this is just indicating that there's large widespread ignorance of medical practices.

Erin Allmann Updyke Oh geez.

Erin Welsh And essentially the fact that black Americans faced worse health outcomes was seen as normal, as an inevitability.

Erin Allmann Updyke I would say unfortunately that still is-

Erin Welsh The bias of medicine?

Erin Allmann Updyke Oh yeah.

Erin Welsh Oh yeah, yeah. And this false concept of racial superiority in biology is so long standing and insidious and is still, like we talked about, very present today in medicine.

Erin Allmann Updyke Yeah.

Erin Welsh So following the American Civil War, some opponents of emancipation claimed that the black race would die out and that the high rates of disease and poverty among black people were evidence that enslavement was a good thing. And these paternalistic beliefs bled into policy, policies which were designed to uphold these divisions of class and privilege and prevent any movements across those invisible but very real lines. In addition there was the bigger issue of how risks of disease overall were perceived. So in much of the American South for instance, discussions about disease were framed as the dangers posed by black people rather than the dangers the diseases posed to black people.

Erin Allmann Updyke What?

Erin Welsh So something that I've talked about before in the context of syphilis, tuberculosis, hookworm, and so on.

Erin Allmann Updyke Yeah.

Erin Welsh So high rates of disease among black people were not seen as worrisome because they were directly damaging the health and shortening life expectancy of black people, it was more, 'Oh well we don't want white people to get sick from black people'.

Erin Allmann Updyke Right.

Erin Welsh That is where the focus primarily was.

Erin Allmann Updyke Right, how can we prevent white people from getting sick with what the black people have?

Erin Welsh Exactly.

Erin Allmann Updyke

Yeah. Ugh.

Erin Welsh

Yeah. And this shaped policy and attitudes toward public health and access to healthcare. Basically the only way a public health policy was going to be enacted or research funds awarded was if the disease affected or threatened to affect white Americans in some way. Okay and so when antibiotics and vaccines became more widely available throughout the 1930s and 40s, the widespread prevalence of chronic diseases such as sickle cell anemia was revealed. At the same time the commodification of health and people's bodies had really ramped up. And what I mean by that is that basically alongside the medical developments of the late 19th century and early 20th century, people's health and bodies began to be assigned a monetary value. How much did this procedure cost? How much did that medicine cost? How much did someone's poor health limit their productive output?

Erin Allmann Updyke

Right. Disability-adjusted life years.

Erin Welsh

Yeah, right. The medical profession contributed to this not just through the exchange of money for treatment but also by assigning intrinsic values to certain conditions. People with rare diseases were seen as valuable to the medical profession. Hospitals in poverty-stricken, densely populated urban areas were considered to be great places to get experience and training as a medical student. And the term 'clinical material' was frequently used as a way to even further remove the person from the medical experience, as in whatever general hospital supplied an adequate amount of clinical material to train students at not one but two medical schools.

Erin Allmann Updyke

I'm sorry, so clinical material meaning humans?

Erin Welsh

Humans, yeah.

Erin Allmann Updyke

Wow.

Erin Welsh

Humans or different cases or different surgeries. And this is still today.

Erin Allmann Updyke

It really is.

Erin Welsh

It's very much like, 'Oh you should get experience there because you're likely to see more of these diseases.'

Erin Allmann Updyke

The amount of times I heard, 'Oh we've got really interesting pathology at this residency program.' I'm like wow, that's horrible for the people in that area. But yeah.

Erin Welsh

Yeah. And employers also played a large role and continue to play a large role in the commodification of health. Maximize profits and productivity by ensuring your employees are well enough to work. And of course if their health can't be improved, consider dropping them. Against this backdrop of this enormous growth of medical knowledge, reduction of infectious disease, and commodification of health and disease, awareness of sickle cell anemia rose greatly. And in the coming decades, this fame would grow to become in some ways a double-edged sword. So on the one hand the adoption of sickle cell anemia throughout the 1950s, 60s, 70s as a cause by many social groups and the increase in research funding for it led to a great deal of important knowledge being gained and in raising awareness overall.

Researchers fascinated by the puzzle that the disease posed, not necessarily by the people experiencing the disease, they had uncovered that certain conditions like low oxygen and high acidity could induce sickling of cells and they had also observed that sickling could also result in people who did not have the disease but were relatives of those that did. In 1949 two papers published nearly simultaneously by Dr. James Neel and Col. E. A. Beet presented the hypothesis that the disease was an autosomal recessive trait, meaning that it was inherited, and like you said the two copies were required for disease to be present. I also wanna note that, once again discovery vs development, that the inheritability of sickle cell anemia had long been recognized in some groups where the disease was especially prevalent such as among certain populations in Ghana.

Erin Allmann Updyke

Makes sense.

Erin Welsh

Yeah. And also in 1949, Dr. Harvey Itano and Dr. Linus Pauling demonstrated that the sickling was caused by an abnormality in the hemoglobin molecule, prompting them to call it a molecular disease. I think it might actually be the first disease described as a molecular disease. A few years later the individual amino acid substitution leading to the structural change in hemoglobin was identified, teaching researchers that single mutation could be responsible for this whole suite of systemic effects on the body.

Erin Allmann Updyke

Yeah, which is pretty incredible.

Erin Welsh

Oh yeah. But a huge shift in the notion of representation of sickle cell trait or that sickle cell, that mutated allele as a disease condition came about with the hypothesis first floated in the mid 1940s that the sickle cell trait, so again one copy of that mutated allele, actually provided a level of protection against the falciparum malaria parasite, giving insight into why the allele was present at relatively high rates despite its deleterious effects.

Erin Allmann Updyke

Right.

Erin Welsh

And so this is an example of what is called a balanced polymorphism and this turned the dichotomy or this long standing dogma of normal equals good and abnormal equals bad on its head.

Erin Allmann Updyke

Yeah, it's why the term 'normal' is stupid.

Erin Welsh

Yeah. It's inadequate.

Erin Allmann Updyke

Yeah, I mean what is normal? And sometimes it's hard, like I don't know what other word to use but it's not a good word in medicine.

Erin Welsh

I know. We need to improve our vocabulary for that.

Erin Allmann Updyke

Yeah.

Erin Welsh

But these scientific breakthroughs, particularly in its labeling as a molecular disease and all the hype that that generated, it got a lot of researchers super excited to jump on the sickle cell train which was also pulled forward by the increasing interconnectedness of hospitals, research institutions, public health departments, and outreach groups. And this wealth of new information about the nature of sickle cell trait and sickle cell anemia did not though necessarily translate directly into lives saved. Because in much of the South, racial segregation still prohibited black Americans from seeking care at the highest funded hospitals which were of course white only.

Erin Allmann Updyke

Yeah. Wow.

Erin Welsh

In addition, and here comes the other side of that double-edged sword, despite these advancements in the understanding of the disease, outside of academia such as in political discussions or debates, clear knowledge about the exact nature of sickle cell anemia lagged far behind, especially in understanding the difference between sickle cell trait and sickle cell anemia. For instance during WWII a controversial debate arose about whether sickle cell trait, so having the one copy, posed a threat to the health of soldiers who had the trait. In other words posed a threat to war efforts.

Erin Allmann Updyke

Oh gosh.

Erin Welsh

Suddenly this disease that had been invisible for so long was now visible and could be used to discriminate against those with the disease or even just the trait. After four people in the Marine Corps with sickle cell trait died after a training exercise at a high elevation, strict limits were placed on whether those with sickle cell trait could become pilots, either in the Armed Forces or commercial airlines or hold other positions. So not just in Armed Forces, so there's huge restrictions placed on that but also in other parts of the workforce, so like flight attendants. There was a lot of issues with health insurance carriers dropping people who were found to have sickle cell trait or sickle cell anemia.

Erin Allmann Updyke

Oh my god.

Erin Welsh

And so these restrictions were instances of racial discrimination.

Erin Allmann Updyke

Yeah.

Erin Welsh

Since the overwhelming majority of those forbidden from entering the Armed Forces for instance due to sickle cell trait were black.

Erin Allmann Updyke

Right.

Erin Welsh

And class action lawsuits led to the removal of some of these restrictions but only decades after they were first put in place.

Erin Allmann Updyke

Oh my god.

Erin Welsh

But of course just because restrictions are gone does not mean the racial discrimination in the workplace was gone and whether it was because the parent of a child with sickle cell anemia was more likely to miss work or if they themselves were affected, there was simply no shortage of ways for people to be discriminated against. Into the 1960s and 1970s, sickle cell trait and sickle cell anemia moved or was pulled even further into the spotlight. In academic circles, sickle cell became the focus of narratives that interwove biology, anthropology, and history to explain whatever story was the goal of the author. And these narratives were sometimes criticized for their tendency to make sweeping generalizations about entire groups of people or entire places or for forcing the facts to fit the story, making it sort of a just so story. Other researchers finally began talking about how sickle cell disease and inadequate medical care may lead to poverty rather than poverty being the cause of disease and ill health.

Erin Allmann Updyke

Yeah.

Erin Welsh

And understanding more of the cycle of poverty and access to healthcare. And in the sociopolitical sphere, sickle cell disease took on new meaning during the civil rights movement of the 1960s. It was held by some civil rights groups to be symbolic of the longstanding invisible or ignored pain and suffering experienced by so many who had long been racially discriminated against and whose access to healthcare had always been restricted. Despite the increased awareness of sickle cell, it still lagged behind other genetic diseases in terms of funding, particularly those that disproportionately affected white people such as cystic fibrosis.

Erin Allmann Updyke

Oh yeah.

Erin Welsh

So for example in 1967 there were roughly the same new number of cases of cystic fibrosis and sickle cell anemia but the difference in funding from volunteer organizations was staggering. For cystic fibrosis these organizations raised 1.9 million dollars and for sickle cell that number was 50,000.

Erin Allmann Updyke

Do you want some current numbers or do you want me to tell you those later because they're not any better.

Erin Welsh

Tell me those later because yeah, I'm sure that they're not any better at all.

Erin Allmann Updyke

Yep.

Erin Welsh

Yep. But there was a lot of charitable work being done and awareness efforts that were made. So the Black Panther Party among other groups organized and created a massive network of healthcare centers across the country where one of the goals was to raise sickle cell awareness and funding. Dr. Charles Whitten, for whom our drink is named, started the Sickle Cell Detection and Information Center in Detroit in 1971 and also helped found the Sickle Cell Disease Association of America which has been instrumental not only in their educational efforts but also in assisting families who have been impacted by sickle cell disease. And also he did a lot of work in terms of lowering barriers for people who were underrepresented in medicine to be able to go to medical school and have that as an option. Federal funds also poured in as Nixon signed into law the Sickle Cell Anemia Control Act in 1972. And so this act included increased funds for research as well as healthcare for those impacted. It also required genetic screening to be voluntary rather than mandatory which had been a huge issue previously cause that just paved the way for discrimination.

Erin Allmann Updyke

Yeah.

Erin Welsh

And it also included support for reproductive counseling. And during the 70s our understanding of the disease itself became more nuanced as well. So first new research about the possible origins of the allele showed that it likely emerged in four different mutational events between 70,000 and 150,000 years ago, three events that took place in Africa, and a fourth that took place in either Saudi Arabia or Central India. This allele emerged in different places around the world, it's not just from one origin event. Secondly there was the growing awareness of other hemoglobin disorders and the fact that sickle cell trait was found in non-black people as well which threw some complexity into the discussion in the 70s. Representation of sickle cell anemia in popular media also increased as characters with the disease were featured in a couple of movies or TV episodes and magazines featured articles about the condition. But once again, here comes the other side of that double-edged sword.

Erin Allmann Updyke

Yeah.

Erin Welsh

The prominence of sickle cell anemia in political discussions of this time meant that some politicians felt as though they could use the disease to symbolize whatever they wanted in order to drive their own narrative about race relations in the US. And sometimes that was used to bring about real positive change but other times it was twisted to halt forward progress. Let's take genetic screening and reproductive counseling as an example.

Erin Allmann Updyke

Okay.

Erin Welsh

The push for genetic screening for sickle cell anemia and sickle cell trait came at a time when genetic screening in general had greatly increased and when discussion of reproductive rights was at the forefront, especially issues of birth control and abortion. Genetic screening to look for sickle cell trait or sickle cell anemia, although it was helpful in terms of getting people the medical attention that they may need, it often did an inadequate job of explaining what exactly the difference between sickle cell trait and sickle cell anemia was. And this inadequate explanation may have been unintentional or intentional at times it appears. So people who had the trait, just one copy of the allele, were often openly discouraged from having children and urged to have abortions or undergo sterilization, procedures that we sometimes made free as an incentive.

Erin Allmann Updyke

Ugh.

Erin Welsh

Yeah. And then the concept of mandatory screening for this and other genetic disorders was floated and Linus Pauling, the Nobel Prize winner and whose name I mentioned earlier as being the scientist, he suggested that everyone who had the sickle cell trait should have it tattooed on their forehead so that when they see another person with the tattoo, they can avoid falling in love and wanting to have children with them.

Erin Allmann Updyke

What?

Erin Welsh

Mm-hmm. And these acts, these discussions of course resulted in accusations of restricting black fertility, racial genocide, and new eugenics and rightfully so.

Erin Allmann Updyke

Yeah. That's what it sounds like to me.

Erin Welsh

Oh yeah. And this misleading reproductive counseling for sickle cell was just one way that reproductive restrictions were intentionally or forcefully placed upon black people. I really recommend 'Killing The Black Body' by Dorothy Roberts to read more about that topic. And so before wrapping up with the history of sickle cell in the 1980s and 1990s, I wanna read a quote by the author of 'Dying in the City of the Blues' that I think does a really good job of summing up the 1970s and sickle cell perfectly. "The story of sickle cell disease in the early 1970s also revealed the ways in which the political process both channeled and deflected the popular activism of the time. It was a time of grudging recognition of the black experience but it proved difficult to translate that awareness directly into health policy without creating enormous new stigmatizing burdens for black Americans and without fostering growing cynicism about racial politics."

Erin Allmann Updyke

Yep.

Erin Welsh

Yep. And so that brings us to the 1980s and 1990s. I don't wanna step on your toes too much Erin about whatever you're gonna talk about, so I'm just gonna go over a few big developments or patterns that emerged during this time with regard to sickle cell that I have a feeling you'll talk more about.

Erin Allmann Updyke

Okay, let's see.

Erin Welsh

Yeah. So as you mentioned, pain management is a huge component of sickle cell anemia and the sympathy for people with sickle cell that seemed characteristic of the 1960s and 1970s kind of gave way to this disturbing trend of cynicism and stigma.

Erin Allmann Updyke

Yeah.

Erin Welsh

More and more healthcare providers seemed to simply not believe that people with sickle cell anemia were experiencing a true painful episode and there were increasing reports of healthcare providers accusing their sickle cell anemia patients of faking it, of exhibiting drug-seeking behavior and correspondingly limiting the pain medication prescribed. And earlier when you talked about the different timeline of when at different ages you're more likely to experience one symptom over another, the increase in painful episodes in late adolescence and early adulthood also made this whole thing worse. They were like, 'Oh well you're a young adult, you're just seeking drugs so I'm not gonna give you any.'

Erin Allmann Updyke

Oh my god.

Erin Welsh

And this is despite the fact that there was research indicating that this wasn't going on, that people with sickle cell anemia were just as worried about their own narcotic consumption or pain medication consumption as anyone else and it didn't seem to make a difference.

Erin Allmann Updyke

Yeah.

Erin Welsh

It seemed to be like this belief that became so embraced and so difficult to get rid of.

Erin Allmann Updyke

It's so frustrating that in so many papers that you read it's still something that is mentioned. Like, 'Oh you often have to use opioids to treat pain which can lead to addiction.' It's like that's true in anyone and there's no higher rates of opioid addiction in people with sickle cell anemia than in the general population. There just isn't. It's infuriating that you'd be withholding treatment that is necessary.

Erin Welsh	Yeah. There was also something that was mentioned in this book about how there was research indicating that opioid addiction starting from hospital treatments or medical treatments is extraordinarily low, that is not the way that the vast majority of opioid addictions begin. But despite all this, this enormous bias still remains. I mean this is a larger issue, the invisibility of pain in medicine. We can't measure it and I think that makes people trust it less, trust the person less. And it sort of goes back to what I was saying earlier about how medicine became more about the body and measurements and these things that you could put on a chart, then it became about the person's experience itself.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	Yeah. But in this context what this meant, this increasing disbelief, was that people with sickle cell anemia were at renewed risk for their pain, their experience to once again be neglected, ignored, and made invisible. And this persists today, this issue.
Erin Allmann Updyke	Yeah.
Erin Welsh	And these decades also brought the promise of many different therapies for sickle cell anemia such as hydroxyurea, as you mentioned, and bone marrow transplantation which didn't necessarily uphold the shiny promises that had been made about them in their first introduction. But I'm really hopeful to hear more about new approaches. But I wanna end now again with another quote, again from Keith Wailoo, the author of 'Dying in the City of the Blues'. "For liberals, moderates, and conservatives alike, the history of neglect and the disease's chronic painful character seem to reflect white America's neglect and misunderstanding of black health concerns and demanded attention. The disease became a multipurpose metaphor, a proxy in social, economic, and political debates about a wide range of seemingly unrelated issues." Okay Erin, bring me up to speed on what's going on with sickle cell today.
Erin Allmann Updyke	Okay. Let's take a quick break first.
TPWKY	(transition theme)
Erin Allmann Updyke	All right. So we'll talk first about numbers, how many people are being affected by sickle cell in the US and in the world today and then we'll touch a little bit more on why that is and the malaria connection cause I do think that's a really interesting part of the story. And then we talk about current research. Does that sound good?
Erin Welsh	Sounds great.
Erin Allmann Updyke	Okay. So we'll talk first about the US and then globally. So in the US, newborn screening is conducted since 2006 or 2007 across the board in all states plus Puerto Rico and the US Virgin Islands, so we know the rates of sickle cell allele in the population, so having one copy of sickle cell trait. Okay? So overall in the US in 2010 the incidence was 15 per 1000 babies born.
Erin Welsh	Trait.
Erin Allmann Updyke	Trait, okay. But this is a huge range from 73 per 1000 among black newborns to 2 per 1000 in Asian, Native Hawaiian, and Pacific Islander newborns, 3 in white babies and 7 per 1000 in Hispanic newborns.
Erin Welsh	And this is voluntary or mandatory screening?

Erin Allmann Updyke

So newborn screening is generally, it's universal. I think it is possible to opt out of it but in general it's universal and kind of recommended. I think most of the time they don't wanna let you leave the hospital without newborn screening. Cause it doesn't only screen for sickle cell, this screens for a whole bunch of different... We talked about this in the cystic fibrosis episode as well.

Erin Welsh

Right, right.

Erin Allmann Updyke

Because you're also identifying then those newborns with sickle cell anemia. But what's interesting is that it's actually hard to get a number on the number of babies in the US born with sickle cell anemia which I think is interesting. So let's talk about the whole globe. How many people are born every year with sickle cell anemia? Globally estimates are about 300,000, just over 300,000 babies born every year with sickle cell anemia.

Erin Welsh

That's a huge number.

Erin Allmann Updyke

It's a massive number. And I want to point out that that number is the number of babies born with sickle cell HbSS. But remember that there are other ways that you can have sickle cell anemia right, you could have it with one copy of HbS and one copy of beta-thalassemia, you could have it with one copy of HbS and one copy of HbC. Those aren't included in that estimate of 300,000.

Erin Welsh

Okay.

Erin Allmann Updyke

So it's thought that that total number accounts for about 70% of the total amount of sickle cell disease, so that whole range of clinical disease worldwide. And it's also estimated that about half of these babies worldwide are born in Nigeria, the Democratic Republic of Congo, and India and that in many parts of Sub-Saharan Africa, sickle cell anemia might be responsible for as much as 6% of all childhood mortality. 6%.

Erin Welsh

Oh my god.

Erin Allmann Updyke

Just from sickle cell anemia. Because in many places in many parts of the world, under 5 mortality from sickle cell anemia, so dying before your 5th birthday, can be as high as 50-90% which is atrocious.

Erin Welsh

Wow.

Erin Allmann Updyke

Yeah.

Erin Welsh

Wow, yeah.

Erin Allmann Updyke

Yeah. And that's because if babies aren't identified by newborn screening then they don't receive penicillin prophylaxis or they don't receive adequate vaccinations, then it's very common that they will die from overwhelming infection before they turn 5. So that's why newborn screening is so important and has been so helpful. It's only worth screening if you can do something about it, right. So we screen for things that we can prevent death if we identify them early and so that's what we can do with newborn screening.

Erin Welsh

Yeah. And this is in general newborn screening or any kind of genetic screening is such a touchy issue because it can so easily lead to who has that information and how can they use it against you?

Erin Allmann Updyke: Absolutely. Plus it gets into so many things of so if you identify a newborn with a genetic trait that had to come from either mom or dad, right, so now you know that either mom or dad has this, maybe they didn't want to know that. The ethics of all of that is wide-ranging and more than we can talk about in this episode.

Erin Welsh: Yes, yes.

Erin Allmann Updyke: But identifying babies with sickle cell anemia prevents them from dying so in that way it's extremely important and helpful. But despite the fact that this is a very common disease and a very common trait among the population, like you said funding discrepancies remain which is why to date we have only one disease-modifying treatment that is hydroxyurea. So I wanna talk, I wanna give some more specific numbers. You mentioned them from I think the 60s and 70s so let's talk about the last decade from 2008-2018.

Erin Welsh: Good, I was hoping you would do this.

Erin Allmann Updyke: This paper just came out in March of this year. So we'll compare federal funding per person between cystic fibrosis which we did an episode on and sickle cell disease. So cystic fibrosis is another genetic disorder, it's also identified on newborn screens, it's also the most common genetic disorder among white babies. So compared with cystic fibrosis per person with the disease in the US, cystic fibrosis received \$2800 in federal funding compared to \$800 for sickle cell.

Erin Welsh: Wow.

Erin Allmann Updyke: That's \$2000 more. It gets even worse if you look at charitable foundation expenditures.

Erin Welsh: Oh yeah.

Erin Allmann Updyke: Cystic fibrosis, \$7600 per person with cystic fibrosis compared to \$100 for sickle cell.

Erin Welsh: Oh my god.

Erin Allmann Updyke: This directly leads to a discrepancy in the number of new drug approvals.

Erin Welsh: Yeah.

Erin Allmann Updyke: In that same time period, four new drugs were approved for cystic fibrosis, one for sickle cell.

Erin Welsh: It just trickles down and down and down. You have the research money, you have treatment accessibility, you have new treatments being developed, you have healthcare, access to healthcare, all of these different components to it.

Erin Allmann Updyke: Yeah. And so to put a specific number too on the difference in terms of overall prevalence of sickle cell vs cystic fibrosis in the US, this paper reported the US birthrate of sickle cell disease is 1 in 365 black babies.

Erin Welsh: That's a high rate.

Erin Allmann Updyke

It's very high, it's scary high. For cystic fibrosis it's 1 in 2500 white babies. Which is also you could say very high. But 1 in 365 is a lot higher.

Erin Welsh

But yeah, when you put the numbers side by side it's not surprising but it is appalling that there's such unequal support and funds.

Erin Allmann Updyke

Yeah. And so I think it kind of leads to a really important question about why is it that this is such a prevalent disease because a lot of times when we have genetic diseases that are recessive, so you have to have two copies of that allele, in theory evolutionarily that allele, that mutation should die out, right. If it's so bad that if you have two copies of it you end up dying before the age of 5, you're not gonna be reproducing, so you're not gonna be passing on that allele. So why is it at such high prevalence in the black population? Here's why or at least what we think. It turns out that if you have one copy of this allele, it's very protective against dying from malaria. It's very protective against severe infection with Plasmodium falciparum malaria. So in regions where Plasmodium falciparum malaria, so that one species of malaria is very, very prevalent, the prevalence of this specific mutation is also very prevalent.

What I think is so interesting is we've shown this epidemiologically in so many, many studies just how massive the protection is but there's still not a clear molecular answer as to how one copy of this allele protects you against dying from malaria. Overall it seems like if you have some of that HbS beta hemoglobin then your cells can eventually sickle and then those cells that are infected with Plasmodium, the Plasmodium doesn't replicate. So essentially malaria can't grow as well in those cells for a number of different reasons that we still don't fully understand.

Erin Welsh

Right. But it's only in the cells that have sickled?

Erin Allmann Updyke

Yeah. And so it turns out that infected cells tend to sequester in certain organs that have low oxygen concentration.

Erin Welsh

Right, so the spleen or something.

Erin Allmann Updyke

Yeah, spleen and liver. So then those cells end up sickling because of that. So whereas normally if you just have one copy, your cells wouldn't sickle very often but these infected cells get sequestered under low oxygen concentration and then end up sickling and then the plasmodium can't replicate.

Erin Welsh

That's really interesting.

Erin Allmann Updyke

Yeah, it's pretty interesting. So I'll post a paper, one of the more recent papers I found going into more detail on that if you're interested. But yeah, so then I guess the question is where do we go from here? And even though we only get 100 or 800 research dollars per 2800 for cystic fibrosis, is there research going on about more treatments? And the answer is yes. There's actually some pretty exciting in terms of technology treatments on the horizon. So we have a very special guest on today to talk about the wonderful world of genome editing and specifically CRISPR as it relates to treatment options for sickle cell disease and other genetic disorders. So let me introduce Dr. Megan Hochstrasser, the Education Programs Manager at Innovative Genomics Institute in Berkeley who's here to tell us in much greater detail than I ever could what CRISPR is, a little bit about genome editing and what that even means, how we can use it for diseases like sickle cell, what some of the drawbacks might be, and how far away we are from technology like this being in everyone's life.

Erin Welsh

Excellent.

Megan Hochstrasser

My name is Megan Hochstrasser and I work for the Innovative Genomics Institute or IGI at UC Berkeley. I am the Education Program Manager so I basically try to talk to people about all of the research that our institute does and the science behind it and help them understand what it means and what it's all about. So the IGI or the Innovative Genomics Institute is a partnership between UC Berkeley and UC San Francisco, so we're a nonprofit research group doing academic research, trying to use genetic engineering tools like CRISPR to solve big world problems. So we work in biomedicine and human health, we work in sustainable agriculture, and we basically try to improve CRISPR-based and other technologies that are used to manipulate DNA in different ways, improve the tools and then apply them to solve different problems.

Erin Allmann Updyke

Oh my gosh, that's amazing.

Megan Hochstrasser

Good.

Erin Allmann Updyke

That is so cool. So could you start off just by telling us what exactly CRISPR is? I think that people have heard that term but a lot of us don't know what it means.

Megan Hochstrasser

Sure. I mean I got my PhD studying CRISPR and I still am behind the times in understanding every little bit about it, it's really complicated. And actually there's new CRISPR tools and CRISPR news like every other day, so it's hard to keep up with. But at the core, CRISPR in the most basic terms is a way of changing DNA, so it's a tool that scientists can use to make targeted, precise changes in the sequence of DNA that's in a living cell or an organism. So this is really impactful because previously we were kind of limited to making synthetic DNA in a tube or something in the lab and kind of adding that to a cell or breeding two plants together to try to change the DNA in the progeny plant, the child plant. But now we can take something that is alive like a human being, make changes in their cells to change the DNA sequence, and they will continue to be alive. So that's the a really amazing advancement actually. So genome editing is actually the bigger category. So CRISPR is one type of genome editing tool.

Erin Welsh

I feel like I'm living in the future.

Erin Allmann Updyke

It is.

Erin Welsh

It's incredible. So specifically in this episode we're focusing on sickle cell disease and recently in the news there was stories about using genome editing to treat sickle cell disease and could you maybe walk us through how that is done? Like in the case of sickle cell, how CRISPR was used to treat the disease?

Megan Hochstrasser

Sure, yeah. So it's been a really exciting time to be in the CRISPR field because I was there kind of before it was used as a genome editing tool and I was just interested in what it's normally doing which I don't have to get into cause it's a long story but CRISPR actually comes from bacteria and it's just this system the bacteria use to fend off viruses that infect them which sounds so obscure and not interesting. But we were able to take this tool from bacteria and kind of steal it and use it for our own purposes. So I've been watching the development of this field since the very beginning and it's been amazing actually to see when patients like the person who's been covered in NPR who has sickle cell talking about how they have been essentially cured. And fingers crossed, it seems like she's really been cured of the disease. So it's been incredible to watch from the beginning, so it's very exciting.

I guess I would say there are two general approaches to using CRISPR to treat sickle cell disease and they're really different in a conceptual way. So the most straightforward way you can imagine to fix a genetic disease would be to go in and change whatever the mutated letter is in the DNA to the correct letter, right. And that's what our institute is trying to do for sickle cell disease, that's our approach is kind of conceptually straightforward and understandable. The approach being used to treat the patients who are now in the news for being treated for sickle cell disease with CRISPR is a little bit different. So instead of trying to fix the mutation in the hemoglobin gene that was causing their disease, instead those clinicians are editing cells to start producing something called fetal hemoglobin. So instead of fixing the broken hemoglobin, they actually turn back on this other hemoglobin that all of our cells have the instructions to make but is turned off. And that hemoglobin can compensate for the damaged one.

Erin Welsh

That is so amazing.

Erin Allmann Updyke

It so incredible, wow.

Erin Welsh

And a treatment like CRISPR, does it fall under the category of treatment or cure?

Megan Hochstrasser

Right. So in theory CRISPR could be a one-time fix for something like sickle cell disease. I think we're not gonna know how long things like this last until we actually try them in a person because we can test something in a mouse but mice live for a couple of years and then you don't know, right. So I think it remains to be seen how longlasting the effects are and it also remains to be seen whether or not there are side effects that will pop up later that we haven't been able to detect early on. But so far it seems like things are going well, again this is only two patients for which there are data but I think it's really promising. And that's what's exciting about genome editing in general to me is that you could do a one-time treatment because you're not treating the symptoms of a disease, you're not doing some kind of lateral approach to kind of helping the person but not actually fixing the underlying cause.

With genome editing we can in theory correct the underlying mutations, we can change someone's DNA in their cells and keep them from having any kind of symptoms, basically wiping out whatever the disease is. So it's super promising. I think one thing to note is that for some conditions, you've already done damage, just living with some of the genetic diseases that are out there like sickle cell causes a lot of damage to your tissues and there are things that you can't change once they've already happened, they're irreversible. But in theory with sickle cell you could stop future pain crises where the cells pile up and get stuck in a cell and cause really horrible pain and more damage. So you could kind of halt the progression of the disease permanently. But that still remains to be tested.

Erin Allmann Updyke

So I guess that kind of leads into our next question which is how close are we to this being something that is more commonly used beyond just a couple of patients?

Megan Hochstrasser

I think we're farther away than I would want to be, so I think it's gonna be a slow process. And this is something I have to deal with all the time when I'm talking to people who have various diseases or I'm giving public talks is that everyone wants their disease to be cured today or yesterday. And it's just a very, very slow process. So sickle cell is one of the most mechanically treatable diseases, so there's just details about the way it works that make it treatable using genetic engineering or genome editing and there are a couple of other conditions that are also possible to do with our current technologies and so they're coming first. But there are thousands of genetic diseases out there and all of those deserve to have some sort of treatment.

So I think it's gonna be probably a couple decades before we start having really common treatments using genome editing. Right now we have maybe three or four genetic diseases are in clinical trials using CRISPR and the clinical trial process takes years. But I think I would be shocked if you had told me when I was in graduate school that just 6 years later basically someone would be cured of a disease using CRISPR. I would be stunned, I wouldn't have thought that was possible. So I think it is moving very fast in scientific terms but it can be kind of slow in human terms.

Erin Welsh

Mm-hmm, that makes sense.

Erin Allmann Updyke

Yeah, yeah.

Erin Welsh

And so I guess speaking of clinical trials and why there might be potential for this to take a little bit longer than other traditional treatments, have there been observed any downsides to CRISPR either in the technology itself, whether it's expensive or sort of in the side effect kind of way?

Megan Hochstrasser

Yes, for sure. So I think as fast as we can move scientifically, we are still a long way from figuring out a societal level solution to rolling out CRISPR-based therapies. There's a big gap between a scientific solution to a disease and a societal solution because we can make the greatest scientific tool we can come up with that works really efficiently and it's accurate and there's no side effects but if we can't make that affordable or accessible to people, it's not going to have any impact. So the cost in particular of genetic therapies is a huge issue and something we talk about all the time at our institute and are trying to strategize and come up with ways to get around this. But it's enormously expensive.

So there's a similar technology called gene therapy that is a little bit different from CRISPR, you could kind of call CRISPR a gene therapy but at its base a gene therapy is using a virus to add in a gene. So instead of making a precise change in DNA like CRISPR, you're just throwing a gene in somewhere into the genome that will be helpful. And actually there is a gene therapy for sickle cell disease, you could throw in a healthy copy of the beta-globin or hemoglobin gene to help people and that under development. But gene therapies are kind of an emerging approach to genetic disease that have only recently started being approved by the FDA, so they've been in development for a couple decades now and are finally starting to reach patients or real people. But their price tags have been whopping. So they've been a couple hundred thousand dollars to million of dollars per treatment which is more money than I have. I don't know about you but that's a lot of money. (laughs)

And I think on the one hand we talked about how these approaches is they're fixing the underlying cause of the disease could be a single treatment. So if you compare the lifetime cost of treating something like sickle cell disease or beta-thalassemia or these other blood disorders, that's gonna be a lot of money. And in theory perhaps paying half a million dollars once is actually gonna be cheaper than the long term cost. But if you can't afford that up front, it's a moot point. And I think right now we're kind of trying to figure out if this is something that's gonna be covered by insurance companies. I think it's an issue in America that is kind of broader than the science but we've been trying to think if there are scientific solutions. So hopefully someone will figure out some social solutions to healthcare but in the meantime we're trying to figure out if there are ways that we can change the way we do the science that'll actually change the outcome when things are priced eventually. So that's one thing that we're working on that I'm kind of hopeful about.

One of the big issues with sickle cell disease that's going to make this so expensive is that we're doing all of this gene editing I'm talking about in patient cells that we've taken out of a patient, so we're not putting a shot in someone's arm or giving them a pill. We're taking their cells, extracting cells from their bone marrow, editing them in the lab, and then putting them back into the patient's body. And that's really complicated and expensive. It requires people with a lot of expertise to handle the cells and it just jacks up the price by a lot. And there's also this requirement in a lot of these cases for using a virus to deliver the CRISPR tools and manufacturing this virus is really expensive and difficult as well. So there are a lot of steps and compounding steps potentially that add costs. So we've been trying to think are there ways to do this in vivo? So instead of having to take cells out and put them back, can we just do a fix directly in a patient's body? So I think there are potential scientific solutions to some of these problems but they're really, really hard problems and they'll take a lot of investment.

You said you talked in this episode about kind of historic marginalization of people with sickle cell and the way there's racism in medicine manifests in this disease. I think one of the promising things that's been happening lately is 1) this kind of reckoning amongst the white scientific community and others about how black communities have been affected by the practice of science and government funding and medicine and all of that, and 2) we were recently told that NIH and Gates Foundation are now investing 100 million dollars towards doing in vivo therapies or potentially other therapies but particularly in vivo therapies using genome editing for sickle cell. So that's a huge investment of money that I think could make a really big difference of how we're able to treat this disease and actually making it an affordable treatment for people.

TPWKY

(transition theme)

Erin Welsh

What an awesome interview, thanks again so much Megan for taking the time to chat CRISPR and genome editing with us. We loved it. And Erin, we should definitely do an entire episode on CRISPR someday.

Erin Allmann Updyke

Oh yeah.

Erin Welsh

All right could we do sources?

Erin Allmann Updyke

Yes, absolutely.

Erin Welsh

Okay. So for my sources I read a few books, one is called 'Body and Soul: The Black Panther Party and the Fight Against Medical Discrimination' by Alondra Nelson. Also as I mentioned earlier, 'Killing the Black Body' by Dorothy Roberts and 'Dying in the City of the Blues' by Keith Wailoo. And also I have a few other books and papers that I will link to. A couple papers I want to shout out are by Steensma et al, 'Walter Clement Noel - first patient described with sickle cell disease' and by Barash in 1998, 'Sickle cell trait, policy, and research paradigms'.

Erin Allmann Updyke

Awesome. I read a few good book chapters that I will link to as well as there is a great sickle cell disease in Nature Review Disease Primers, that was from 2018 if you want just kind of a nice overview of the biology of sickle cell disease. And then if you want that paper on the comparison of funding between sickle cell and cystic fibrosis was by Faheem Farooq et al published in JAMA in 2020 just earlier this year. We post all of these sources as well as the sources from every one of our episodes on our website thispodcastwillkillyou.com, just click on the EPISODES tab.

Erin Welsh

Well thank you again so much to the amazing Marsha and Sharif for sharing their experiences with us and also to Megan for walking us through the incredibly cool world of CRISPR technology.

Erin Allmann Updyke

Yeah, thank you all so much. And thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Welsh

And thank you to you, listeners, for listening. We love you, we appreciate you, we hope you liked this episode.

Erin Allmann Updyke

Yeah, it was really fun so we hope you had fun too.

Erin Welsh

Until next time, wash your hands.

Erin Allmann Updyke

You filthy animals!