TPWKY	This is Exactly Right.
Su Wang	My name is Su Wang. I am a physician, I'm an MD-MPH. I'm the Medical Director for the Center for Asian Health & Viral Hepatitis Programs at the Kupferman Barnabas Medical center in New Jersey and I'm also just coming off a two year presidency for the World Hepatitis Alliance which is a nonprofit organization that represents patients living with viral hepatitis. And our goal is to harness the power of people living with viral hepatitis to achieve global elimination of viral hepatitis.
	I was diagnosed with hepatitis B in college. In my first year of college I went to donate blood right to do a good thing, donate blood. And shortly after I got a big fat envelope sent to my dorm and it said don't be worried, you don't have HIV but you do have hepatitis B. And I was a pre med student but honestly I didn't know anything about hep B. I called my sister, confided in her about this new diagnosis and she said, 'Oh didn't you know? Mom also has hep B.' And then I just remember thinking oh, who do I need to tell? And when I went back home I did go see a doctor and talked to her about it and I think she did blood work and basically said I was a carrier and there was nothing to worry about. So I honestly pushed it to the back burner, didn't want to think about it.
	So it didn't come up again until med school. I filled in all my med school forms and a lot of our employment forms and our screenings for working at a hospital, you do have to indicate your hep B vaccination and statuses. And I had indicated that I was a carrier and didn't hear anything about it. I didn't think anything of it and it's not until now that I've heard numerous people who are in med school found out to have hep B and actually they lose their acceptances to med school or they face quite a bit of what I would consider discrimination over their status. And it's happened to residents, it's happened to nurses, it's happened to dental students. So it is an issue of stigma and discrimination but I was fortunate it didn't happen to me and it kind of was in the back of my mind and I remember kind of when we learned about hepatitis, just kind of listening a little bit more attentively.
	And when I got to residency after med school I became really good friends with somebody. A friend of mine went into infectious disease and I had confided in her that I had Hepatitis B. And she told me, 'Oh make sure you see a doctor for it.' I hadn't seen a doctor in years at that point. So I went in to see somebody and they did my viral load and I did the ultrasound and everything was fine. It was very low, I didn't need medication. And at that point I remember I was engaged I think and so my friend had said, 'Oh make sure your fiance also gets tested.' And he ended up getting tested and needing to get vaccinated. So that was kind of the extent of how it impacted my life. And I had told him about it and I was happy that he didn't make a big deal out of it.
	And these are all points now looking back I realize I was fortunate and so many people around the world are not so fortunate to have a career that's not affected by it or a relationship that's not affected by it. There are a lot of people who lose their partners, they may get divorced, they may get disowned by family or unable to pursue the career they want to. So I didn't have any of that. And I got married and we got pregnant. I've had four kids and with each one of those kids, especially the first one, it did hit me that I know there's a chance that I could pass this infection on to my children and that definitely weighed heavily on me. Although I knew the research that because my viral load was low there would be very low chance of the infant developing hep B. But that's where I really all of a sudden felt like oh my gosh, this could really impact me personally.

And I'm happy to say that all four my kids are hep B free and that they don't have to live with this chronic disease and worry about risk of liver cancer and other things that other kids have to go through even now in this day and age. And so as a physician I didn't particularly have an inkling that I was going to do hepatitis work at all. And it wasn't until I moved to New York City after I finished my residency and I took a job with a community health center in Chinatown. So I began serving the largely Chinese community in Chinatown and learned so much more about hep B than I ever knew, that it's one of the most common infectious diseases around the world. Up to like 1 in 10 of our patients had hep B, it was as common as hypertension. And whereas I had seen specialists during residency, a lot of our patients could not afford to see a specialist and they weren't necessarily easily accessible. So many of us at the community health center learned to treat hep B along with hypertension, diabetes and other chronic diseases.

So during that time I really saw a lot of the difficulties that people face in getting care. And so I began really advocating and creating programs that would help people living with Hepatitis B to increase screening in the communities, linkage to care, all these things that can happen in a very complex medical system. We tried to create a program to kind of streamline and all of that. As I was getting more and more immersed in really providing the care that needs to happen, I really had the hat on, the physician hat, like this is what needs to be done, these are the interventions, this is the science behind it. I did not wear the patient hat at all in terms of what it meant for me and I kind of didn't feel like that was my role.

And it wasn't until somebody did an interview, actually I did an interview for CDC and it was the first time on camera that I said I'm actually living with hepatitis B myself. And at that point I had already occasionally mentioned it to patients. So if I was counseling a patient who had been newly diagnosed with hep B and I could see they were really distraught or felt really overwhelmed, I would share with them that I also was living with hep B, I was just like them, I had to go for a blood tests. And I think that really helped them see that it's possible to live a happy, healthy life and it's not a death sentence. So I was using that more often but I'd never spoken about it publicly. So it took me a while and what I've seen as a physician which I think as physicians we don't quite get is just how powerful that personal experience is. And I have only learned this through other people.

Somebody asked me to get involved with the World Hepatitis Alliance which is led by patients and through that on the board, the board is all patients who represent each of the WHO regions. And I heard specifically from a good friend of mine, who is now a good friend of mine, Dee Lee who represented the WPR region, the Western Pacific region. He told me all these stories of people who really had hep B drastically impact their life in ways that us in medicine don't measure, right. We measure the outcomes, we look at our morbidity, mortality, life expectancy, right? Cirrhosis, liver cancer. We don't look at outcomes in terms of somebody's quality of life.

When I hear these stories of how people have suffered with the burden of the disease even if they are... I mean as a doctor if you were to look at them, they would look healthy. You would tell them they're perfectly healthy, their liver enzymes are normal, their viral load is low, I only need to see you once a year, you're fine. In our mind we think it's nothing. If you were to then delve into how they feel about themselves and most patients won't even tell me that. So I know that what I see, what I glimpse in my exam room is just such a small part of what it means for them to live with the disease. And so it's beyond just keeping them from getting cirrhosis and liver cancer. Us in medicine, if our mission is to improve quality of life and decrease burden of disease on people's lives, we have to think outside just our biochemical tests.

	I think I've just learned that we can't afford to operate in our silos, right? The scientists cannot afford to operate in their silos only like publishing to the scientific community and having meetings that are only for scientists and medical researchers. But we have to get out of the box. We have to combine, the people living with the disease have to work in concert with the medical community if we're really going to make progress for elimination and for really alleviating the suffering of hep B on people's lives.
TPWKY	(TPWKY intro theme)
Erin Welsh	Thank you so much Dr Wang for sharing your story.
Erin Allmann Updyke	Thank you.
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.
Erin Allmann Updyke	Welcome to another episode.
Erin Welsh	Yes. Welcome, welcome. As you have probably gathered, we are going to be talking about another hepatitis virus, our second in the podcast history.
Erin Allmann Updyke	Our second one.
Erin Welsh	Yes. This one, hepatitis B.
Erin Allmann Updyke	Yeah. We started with C, now we're going to B.
Erin Welsh	What's next?
Erin Allmann Updyke	Well I am going to mention D.
Erin Welsh	I figured.
Erin Allmann Updyke	I think next will be A.
Erin Welsh	Yeah next will definitely be A. And then we'll have to do E. And then maybe by the time that comes out there'll be a few more that we can cover all in one.
Erin Allmann Updyke	Who knows? Quite possible.
Erin Welsh	Well Erin.
Erin Allmann Updyke	Yes?
Erin Welsh	What time is it?

Erin Allmann Updyke	It's quarantini time, Erin.
Erin Welsh	It is. And what are we drinking this week?
Erin Allmann Updyke	We're drinking The B Sting.
Erin Welsh	We are.
Erin Allmann Updyke	Hepatitis B.
Erin Welsh	Hepatitis B. And what is in The B Sting?
Erin Allmann Updyke	Well it's a lovely little bev. A ginger mint syrup, some lemon juice, club soda. If you're drinking alcohol, you could certainly put some gin in it.
Erin Welsh	That will be the little sting. But otherwise on its own it is delicious.
Erin Allmann Updyke	Very refreshing.
Erin Welsh	I just, I love it. And we will post the full recipe for this quarantini as well as our non alcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels.
Erin Allmann Updyke	On our website thispodcastwillkillyou.com you will find any and every of the things that you ever wanted to know about the podcast. You can find Bloodmobile who does all of our music and the link to their Spotify. You can find merch, all of our merch. You can find transcripts for all of our episodes. You can find a bookshop.org affiliate account and a Goodreads list.
Erin Welsh	You're doing great.
Erin Allmann Updyke	You can find all the sources for all of our episodes. Thanks, I need the encouragement. And you can find our Patreon. Whew.
Erin Welsh	Wow, that was impressive.
Erin Allmann Updyke	Thank you. Thanks.
Erin Welsh	I'm always relieved when I don't have to do it.
Erin Allmann Updyke	I always get really nervous and then I just power through.
Erin Welsh	I like it. It's like you get in the zone and then you're there. Well before we get into the episode, I wanted to mention one thing because endometriosis which is the last episode we released is still on my mind. Even though I've been reading a lot about hepatitis B, I still have these like little thoughts of endo that pop in. And I realized that there was like one more thing that I wanted to say. Also endometriosis, we've recorded it, it's not yet released. And so maybe people will have already said this by the time this comes out. It's sort of a weird time travel thing we're doing here.
Erin Allmann Updyke	Yeah.

Erin Welsh	But in the endometriosis episode we talked about how often complete or partial hysterectomy is recommended as like a cure for endometriosis which it isn't and which that can also add another dimension of pain and anguish to an already difficult disease. But I also think that another aspect to that that we didn't really touch on and I think it's important to mention is that there can also be a reluctance on the part of physicians to perform hysterectomies or even just tubal ligations, like getting your tubes tied, for whatever reason even if that reason is I don't want to have any children or any more children. A lot of people are just told, 'Oh, you're just too young, you might change your mind and want to have kids in the future.' And so really, that's sort of another way in which many times physicians don't fulfill the very basic requirement of listening to their patient and how the social and gender role of someone can be held as more important than what they want and their wishes.
Erin Allmann Updyke	Yeah.
Erin Welsh	Anyway that just kept like circulating in my head and I was like oh gosh, I need to say it. So yeah. Okay, got it out.
Erin Allmann Updyke	Yeah, that's an incredibly important point.
Erin Welsh	Okay.
Erin Allmann Updyke	All right.
Erin Welsh	Should we move on to the actual topic of today's episode?
Erin Allmann Updyke	Today's topic, hepatitis B. Let's take a quick break and then get into the biology.
TPWKY	(transition theme)
Erin Allmann Updyke	So like you mentioned Erin, this is our second hepatitis virus and I know for sure that during our hepatitis C episode we talked at least a little bit about how all the hepatiti. (laughs) All the hepatitis viruses are named not for anything that links the particular viruses together aside from the fact that they all predominantly affect the liver.
Erin Welsh	Right.
Erin Allmann Updyke	So there are five predominant viruses which we kind of already named at the beginning, A, B, C, D, and E. And today we're focusing on hepatitis B and I will mention hepatitis D. And you'll understand why in a minute if you don't already know the little interplay between hepatitis D and B. Alright, hepatitis B. It's in the family Hepadnaviridae which essentially just means viruses that affect the liver, no surprise.
Erin Welsh	Straightforward.
Erin Allmann Updyke	There's a lot of interesting things about the virology of hepatitis B and I'm probably not even going to do them justice. But here we try. Hepatitis B virus is a partially double-stranded DNA virus which is weird. So it has a genome that is like in a little circle and part of it is double-stranded and part of it is single-stranded which is very bizarre. Do you have a question already, Erin? I can see it on your face.

Erin Welsh	No. I mean yes but I'm waiting, I'm being patient.
Erin Allmann Updyke	Okay, we'll see if I have any answers. Hepatitis B virus has a lot of different genotypes that vary very widely in their overall geographic distribution. However as we mentioned up top and as we'll talk a lot about towards the end of this episode, this is a globally distributed, incredibly prevalent virus.
Erin Welsh	Incredibly prevalent.
Erin Allmann Updyke	Incredibly prevalent. And it's still as far as I can tell a little bit up for debate whether these different genotypes really vary in their tendency to cause chronic infection or in their overall disease course. A lot of sources I read said that yes, different genotypes kind of have different tendencies or characteristics and some said it's up for debate.
Erin Welsh	Okay.
Erin Allmann Updyke	But being a virus, this is of course a pathogen that has to find its way into our cells and being a virus that infects the liver, it's unsurprising that the primary cell type that it infects is our hepatocytes, our actual liver cells, not the blood vessels in our liver, not any of the other things around there but generally our liver cells.
Erin Welsh	The things that make up the meat of the liver.
Erin Allmann Updyke	Exactly. Also called the parenchyma of the liver. It's a fancy word for the meat. So hepatitis B is transmitted in very similar ways to hepatitis C as you may remember from several seasons ago now but with a few important caveats. So hepatitis B can be a bloodborne virus. So anything that involves the sharing of blood, whether that's contaminated needles in the healthcare setting or in intravenous drug use settings, it can be transmitted via blood transfusions and of course is something that we screen for to try and reduce the risk of that. But hepatitis B is also much more easily transmitted sexually compared to hepatitis C. It's present in so many bodily fluids.
Erin Welsh	Why is that?
Erin Allmann Updyke	It's a really good question. I imagine it is largely because hepatitis B is very, very infectious. As an example, according to WHO it's 50 to 100 times more infectious than HIV.
Erin Welsh	Whoa.
Erin Allmann Updyke	I know.
Erin Welsh	Do we know the reasons for that increased infectivity?
Erin Allmann Updyke	That's a very good question. I do not.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. And I don't also have numbers on the actual infectious dose, I couldn't find a solid answer on that either. I do know that it can persist in the environment for at least several days so I think it's a pretty hardy virus, so that might be part of it. Yeah.

Erin Welsh	Interesting. Okay so going back real quick to partially double-stranded, what's the implication of that in a virology sense?
Erin Allmann Updyke	So it's really interesting. Hepatitis B is one of the few viruses that's not an RNA virus but uses a reverse transcriptase in order to replicate its genome.
Erin Welsh	Okay.
Erin Allmann Updyke	So HIV is an RNA virus that relies on an enzyme reverse transcriptase to make a form of DNA in order to then replicate. And hep B also does even though it's a DNA virus.
Erin Welsh	That is so bizarre and so I definitely came across some of that in the evolution papers.
Erin Allmann Updyke	Yeah.
Erin Welsh	Because it kind of throws a wrench in things as to the mutation rates, the scale of the molecular clock, blah blah blah, all of that.
Erin Allmann Updyke	Right. Yeah. And it also, as I'll kind of talk a little bit more about later, it allows it to integrate into our genome in a way that then sets us up for both chronic infection and also potentially cancer, right, and cancer-causing mutations. Spoilers.
Erin Welsh	Do other viruses have this partially double-stranded DNA thing as well?
Erin Allmann Updyke	I don't know of any other human viruses but I know that there are other animal hepadnaviruses that do.
Erin Welsh	Right, okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	Those that's like the unifying feature of adenoviruses. Okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	Wow, cool.
Erin Allmann Updyke	Okay. So hepatitis B is also transmitted, back to that part of it, vertically at much higher rates. Let me tell you some numbers. The estimates that I read ranged from 40-90% of babies born to people living with hepatitis B, with chronic hepatitis B, will become infected with hepatitis if they are not treated.
Erin Welsh	Wow.
Erin Allmann Updyke	And this is in comparison to only 6% of people with hepatitis C will then transmit hepatitis C to their offspring.
Erin Welsh	What is the reason for that difference?
Erin Allmann Updyke	Again, I think it's largely just how infectious hepatitis B is.

Erin Welsh	Okay.
Erin Allmann Updyke	But here's something that I think is very interesting and important about this vertical transmission of hepatitis B. First of all a lot of times when we talk about vertical transmission, so from parent to offspring, it's when viruses or bacteria can cross the placenta and infect a fetus during pregnancy. That is not what happens in hepatitis B. The transmission is not transplacental. In the vast, vast majority of cases, it's happening during the process of childbirth and it's not happening during breastfeeding, it's not happening during pregnancy, crossing the placenta, it's happening specifically during the period of childbirth whether that birth happens vaginally or via C-section.
Erin Welsh	What?
Erin Allmann Updyke	There is some papers that suggest that C-section delivery is a slightly lower risk but it's not conclusive. And if you've ever seen a delivery of either kind, it kind of makes sense because neither one is really less bloody than the other and so many bodily fluids are being exchanged no matter what exit route a baby takes.
Erin Welsh	So it's just like the blood and bodily fluids aspect of it.
Erin Allmann Updyke	Blood and bodily fluids. It's thought that cervical secretions, so if a baby comes out vaginally and that's why maybe there's some thought that it's a slight higher risk but the data hasn't really borne that out necessarily. What?
Erin Welsh	That's very interesting.
Erin Allmann Updyke	I know because I didn't really realize that. I kind of thought that it was something that could be transmitted transplacentally.
Erin Welsh	Yeah.
Erin Allmann Updyke	But it's not and that is really important when we talk about how to treat and prevent hepatitis B infection. So let me keep going, shall I?
Erin Welsh	You shall.
Erin Allmann Updyke	So the incubation period of infection, the time from when someone gets infected to when they show symptoms can really range anywhere from 30 days to up to 6 months. And I think that this incubation period, even noting an incubation period is interesting because hepatitis B is a virus that can be entirely asymptomatic and chronic infection is generally defined as the persistence of a specific antigen, being able to detect Hepatitis B surface antigen for a period of at least 6 months. So it's interesting that you can also say the incubation period itself might be 6 months before you show symptoms but you also might never show symptoms.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	That makes it really difficult to calculate an incubation period.

Erin Allmann Updyke	Exactly. It sure does. So let's talk briefly about what the symptoms can be if people do have kind of an acute infection or symptoms with an initial infection. Most of the time of course it's completely asymptomatic or very minimally symptomatic. And it's important to note that some people can clear the virus entirely from their system after an acute infection whether they show symptoms or not but we'll talk about how that doesn't happen for a lot of people and who those people are and why. Okay, okay. But when symptoms do occur in the case of an acute infection, they really don't look any different from a lot of the other viruses and pathogens that affect our liver, including hepatitis C.
	So hepatitis B is less likely to cause acute liver failure completely but it can cause things like jaundice where your skin can become yellow or the whites of your eyes and your gums, things like that become yellowish. And this occurs because our liver is what conjugates and helps eliminate bilirubin from our bodies. And so without that process, bilirubin, which is a breakdown product of our red blood cells, builds up in our skin and our eyes and that's what turns us yellow. It then also causes a lot of nausea and vomiting from this build up of not just bilirubin but a lot of stuff in our system that our liver is supposed to filter out. It causes abdominal pain because your liver is inflamed and even though your liver itself doesn't have sensory innervation, this inflammation can reach the lining of the liver, the lining of the abdominal cavity and cause pretty severe abdominal pain.
	And then all of these toxins that can accumulate in your bloodstream can cause severe fatigue, it can cause a darkening of your urine as the bilirubin tries to be excreted through your urine instead of your poop and in very rare cases it can cause actual acute onset liver failure which can be fatal. But much more commonly liver failure happens as a progressive process of long term inflammation leading to cirrhosis and fibrosis and potentially hepatocellular carcinoma or cancer. So I want to focus on this chronic infection of hepatitis B because it's not only very interesting but it's also the most important part of this virus.
	So first of all, the likelihood of a chronic infection becoming established varies person to person and it's inversely related to the age at which you become exposed and infected. So for infants for, neonates who get infected vertically during birth, the likelihood of a chronic infection is over 90%. Over 90%. So that means that almost all babies that become infected at birth or shortly thereafter go on to have a chronic lifelong infection with a very significant risk of progression to fibrosis and or liver cancer.
Erin Welsh	So this inverse relationship, is it like a straight line or does it kind of have any sort of peaks and valleys?
Erin Allmann Updyke	It's not a straight line. It's a what do you call it? No, it's a jupe maybe?
Erin Welsh	Sigmoid?
Erin Allmann Updyke	What do you call it, a J? So let me just tell you numbers because I'm clearly not doing a good job shwooping. So infant neonate, 90% chance. A child if they get infected when they're young, like between ages 1-5, the risk of chronic infection is like 30%. So it's a pretty big drop. And then it's a little lower for older children and for adults, if you don't get infected until you're an adult, the risk of chronic infection is only about 2-5%, so substantially lower.
Erin Welsh	I mean, okay, I have to ask why. Obviously.

Erin Allmann Updyke	I'm glad you asked Erin, let's talk about it. But first let me also say that even though the risk of chronic infection if you get infected as an adult is low, the chronic infection itself and the prognosis of a chronic infection with hepatitis B in general is worse than, for example, the chronic infection of hepatitis C. And if you listened to our Hepatitis C episode then you remember hepatitis C is not a good virus, right? But in hepatitis C, the likelihood of a chronic infection is much higher for adults across the board. But the rate of, for example, liver cancer is very low, like 2.5% for people who have chronic hepatitis C, right?
Erin Welsh	Okay.
Erin Allmann Updyke	But much more people who get infected as adults with hep C go on to get chronic hep C.
Erin Welsh	That makes sense.
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay, in the numbers perspective.
Erin Allmann Updyke	Right. But for Hepatitis B, 15-40% of people who have chronic infection go on to have liver cancer, hepatocellular carcinoma. That's a huge percentage.
Erin Welsh	Yeah.
Erin Allmann Updyke	And again, 90% of infants who become infected go on to have chronic infection. So that's major.
Erin Welsh	That's a really disturbingly large number.
Erin Allmann Updyke	Right. Okay. So you asked why.
Erin Welsh	Yeah, I did.
Erin Allmann Updyke	In short, we don't fully know. It's always my answer.
Erin Welsh	I'm going to cross stitch that onto a pillow for you.
Erin Allmann Updyke	(laughs) I would love that pillow! Oh my gosh. Okay. But so the question of why are infants who get infected more likely than adults who get infected to go on to have a chronic infection? While we don't fully know the answer, it likely has to do with a few different factors that relate to the various phases of this chronic infection. So a chronic hepatitis B infection which is defined just as the persistence of the virus and detection of these viral antigens for at least 6 months in the bloodstream. After that point, like after that 6 months point, this isn't a static infection, it's very dynamic and it progresses through several different phases that can vary in their length and their severity.
	So the first phase is often known as immune tolerance and that's essentially when our body doesn't really do much about this infection, the virus is there. And one thing that it tends to do is integrate into our genome the way that - do you remember the other virus that does that, Erin?
Erin Welsh	HPV.

Erin Allmann Updyke	HPV, that's right. And as our cells replicate, so does this virus. But in the immune tolerance phase it doesn't cause much in the way of damage. Then there is the immune active phase. And in some papers they called this the immune clearance phase and this is really the meat of chronic hepatitis B infection. This is when our bodies are recognizing this virus, we are mounting an immune response to it and therefore we ourselves are causing a lot of inflammation and damage to our own liver cells. It's not the virus itself.
Erin Welsh	Okay, yeah.
Erin Allmann Updyke	And this is the phase where people are more likely to be symptomatic, like maybe have jaundice. But this is the phase where that inflammation is causing fibrosis which is damage to the liver due to that inflammation. That fibrosis can eventually lead to scarring or permanent damage, cirrhosis, and that can ultimately lead to liver cancer. And so this is the phase, the immune active phase, that the longer that somebody is in this phase, their immune system fighting the infection, the greater their risk of cancer.
Erin Welsh	Okay.
Erin Allmann Updyke	But there is another phase, just to get more complicated.
Erin Welsh	Okay. (laughs) All right.
Erin Allmann Updyke	And that's a so-called inactive phase wherein the virus is still there and we've maybe made some antibodies against that virus, so we're kind of at a standstill. But at any point people could still revert back to a more immune active infection like say if they became immunocompromised for some reason. And therefore the virus is still there and still posing a risk of cancer development.
Erin Welsh	Gotcha, that makes sense.
Erin Allmann Updyke	Yeah. So I know that that was a lot and it was really just a drive-by, the immunology of hep B infection is a lot more complicated, there's a lot more detail. But one of the things that's different among adults who get infected vs infants is that infants tend to have a very long immune tolerant phase whereas adults who have chronic hepatitis B, that is they get infected and aren't able to clear that infection right away, they tend to not really have an immune tolerant phase but rather progress directly to that active inflammatory chronic hepatitis infection.
Erin Welsh	Right, okay.
Erin Allmann Updyke	So that's a really big difference. And it's thought that during pregnancy viral particles or maternal antibodies or both are passing through to the fetus and then when that infant is born and exposed to hepatitis B, while they're not able to fight off that virus entirely the way most adults who are exposed can, they instead establish this relationship of tolerance that lends itself more easily to a chronic infection. Right?
Erin Welsh	Okay. So it's kind of like getting to know you and like, all right, I guess we'll just tolerate you know each other for a while.
Erin Allmann Updyke	Yeah. Right. But then eventually progress to the other phases of disease.

Erin Welsh	Right, okay. Interesting.
Erin Allmann Updyke	But that is generally hepatitis B virus.
Erin Welsh	So I have a question. You mentioned that... Okay, there are people who become infected and they cleared the virus, they develop antibodies, boom, they're in the category that you didn't discuss the later stages on for obvious reasons. And so these people now have a lifetime immunity to hepatitis B virus. What about different genotypes? Is there any sort of like genotype-dependent immunity where you can be infected with one genotype and then clear that and be exposed to another one and not clear that?
Erin Allmann Updyke	Great question, Erin. As far as everything that I have read, immunity to hepatitis B is immunity to hepatitis B across genotypes.
Erin Welsh	Okay. That's great news.
Erin Allmann Updyke	Exactly. It's really great news Erin because we in fact have a vaccine for hepatitis B, it is a recombinant vaccine that contains only the surface antigen of hepatitis B and that is what we make antibodies to.
Erin Welsh	I have a follow up question.
Erin Allmann Updyke	Okay.
Erin Welsh	If someone is chronically infected with one genotype of hepatitis B, can they become infected with another genotype of Hepatitis B?
Erin Allmann Updyke	Not as far as I know but do you know what they can become infected with?
Erin Welsh	Hepatitis D virus.
Erin Allmann Updyke	Hepatitis D. Thanks for the little intro there.
Erin Welsh	You're welcome, you're welcome.
Erin Allmann Updyke	I wanted to just very briefly mention hepatitis D because I don't think that we would ever do a full episode on it. I don't know, maybe I'm wrong. But delta hepatitis virus or hepatitis delta, hep D, it's a fascinating virus. This virus belongs to its entire own viral genus that doesn't have an actual family that it falls within and some people say it's not even really a virus, it's like something else entirely, it's a sub viral agent.
Erin Welsh	Whoa.
Erin Allmann Updyke	What?
Erin Welsh	It's like a virus of a virus?

Erin Allmann Updyke	Kind of. So hepatitis D has an RNA genome and it can replicate on its own inside of ourselves when it infects us and it does infect our liver cells but it can't actually infect our cells by itself. It relies on the surface proteins of hepatitis B virus in order to get into our cells and in order to be released from our cells. So hepatitis D is a virus that can only infect someone who has a chronic or acute hepatitis B infection.
Erin Welsh	I am really regretting right now not reading more about the evolutionary origins of hepatitis D. Because what on earth?
Erin Allmann Updyke	So maybe it does deserve its whole own episode.
Erin Welsh	Yeah.
Erin Allmann Updyke	That's that's literally all I have to say about it but it is very, very interesting.
Erin Welsh	Okay, so what about besides the vaccine? What about treatments? Are there antiviral treatments for hepatitis B virus or maybe hep B and hep D combined?
Erin Allmann Updyke	Yes. For hepatitis B there are. So there's a number of different treatments that we have actually, none of them can cure hepatitis B, they're all used to sort of manage it and to try and reduce the rate of inflammation and complications. But pegylated interferon which I think we talked about in our hep C episode possibly, but that's basically like an immune modulator you can think of it as. That can be used and has been used to treat hepatitis B. But there are also a number of antivirals that in many cases are used to treat HIV or were used to treat HIV and are now used to treat hep B. So yes, there are. Again none of them actually clear the infection but they all just sort of help to manage it.
Erin Welsh	Okay.
Erin Allmann Updyke	And what's really important about all of these is that because all of those different states, immune tolerance, immune active, inactive, these different phases of infection really vary person to person and how severe someone's symptoms might be, it really varies. So just because someone has an infection with chronic hepatitis B doesn't necessarily mean that they have to be on treatment if they're in a phase that isn't directly causing damage. Does that make sense?
Erin Welsh	Okay. Yeah, that's interesting.
Erin Allmann Updyke	At least as of now because the treatments that we do have are not without side effects and in a lot of cases they have quite a lot of side effects. So it requires a lot of careful monitoring and everything which makes it a lot harder to do quite honestly.
Erin Welsh	There's so much here about this virus that...
Erin Allmann Updyke	I know. So speaking of so much about this virus, Erin. Like what? Where did it come from? What the heck?
Erin Welsh	I will do my best to answer those questions but let's take a quick break first.
TPWKY	(transition theme)

Erin Welsh	All right, the story of Hepatitis B. I feel like in the last couple of episodes I've maybe deviated a bit from the normal history overview that I usually give. But don't worry, I'm going back to my roots for this one. I'm going to start with a bit of evolutionary history, mixing some early accounts of infectious hepatitis, then the fascinating story of its identification and then finally getting us to where we are today. The usual.
Erin Allmann Updyke	The usual. I love it.
Erin Welsh	But usual doesn't mean boring or straightforward especially in the case of hepatitis B. So beginning at the beginning, where does the hepatitis B virus come from? It turns out that the answer to that question has been a moving target for a number of years with new hypotheses introduced or old hypotheses overturned or tweaked to fit new findings as more about the evolutionary history of this virus has come to light. And this should come as no surprise really considering how widespread this virus is, how many genotypes there seem to be, how the virus can undergo recombination, the confusion about its partially double-stranded DNA, and how we don't really know exactly maybe the rate of evolution or mutation. There's been a lot of work on this, I was happily surprised to find, especially recently. And so I'm going to try to bring us up to speed on what the current consensus is, relying mostly on two papers that came out in 2021 about the origins and evolution of the hepatitis B virus. One by Locarnini et al and the other by Kocher et al.
	Like you said Erin, the hepatitis B virus belongs to the Hepadnaviridae family and in the years after the hepatitis B virus was first identified, researchers found viruses belonging to that family that infected birds, fish, reptiles and amphibians, other mammals, nonhuman primates, etc. Basically this is a lot bigger and a lot older of a virus family than we thought. And there are some estimates that it originated around 82 million years ago.
Erin Allmann Updyke	Whoa.
Erin Welsh	So like this thing was infecting birds-
Erin Allmann Updyke	Dinosaurs.
Erin Welsh	Essentially, yeah. Back when birds and dinosaurs were the same thing.
Erin Allmann Updyke	Yeah. (laughs)
Erin Welsh	That's probably not accurate but you know what I mean, 82 million years. Let's stick with that.
Erin Allmann Updyke	Yeah.
Erin Welsh	So from 82 million years ago, how did it get into modern humans? And on that there seems to be some debate. Surprise, surprise. For a long time it was thought that hepatitis B virus originated in Africa or for a while it was thought maybe the Americas and then it spilled over into humans possibly from a nonhuman primate and then dispersed. Maybe it was dispersing out of Africa following prehistoric patterns of human migrations. But more recently that assumption has been questioned. So one of the studies published in 2021 used hepatitis B virus detected in skeletal remains of 137 individuals found in Eurasia and the Americas and dating between 10,500 years ago and 400 years ago.
Erin Allmann Updyke	What?

Erin Welsh	That's some old viral DNA.
Erin Allmann Updyke	I just love it when you find things like this, Erin.
Erin Welsh	I know. This paper was really interesting, it also had the most authors of any paper I've ever seen, I think it was 170-something.
Erin Allmann Updyke	Oh my goodness. That's more than like the whole human genome paper.
Erin Welsh	(laughs) But I mean it makes sense because I'm assuming that there was a lot of collaboration across many different universities with all of these remains, skeletal remains.
Erin Allmann Updyke	Yeah.
Erin Welsh	So okay, anyway. So what this paper using all of these old skeletal remains with hepatitis B virus did is that they wanted to reconstruct the evolutionary history and dispersion of the virus. And what they propose is that the most recent common ancestor of the hepatitis B virus dates back to around 12,000 to 16,000 years ago which is more recent actually than was previously thought. And it places that most recent common ancestor in Eurasia where over the next hundreds and thousands of years it's spread across Eurasia into Africa through Europe and to the Americas. It seems like the emergence of the hepatitis B virus and some of its spread happened before the Neolithic Revolution which is when people began settling in larger groups and farming and so on.
	And if you think about it this completely makes sense because what are some of the transmission characteristics that hepatitis B has, right? People can be carriers, it can be transmitted to a baby at birth, can be spread during sexual contact or through blood, so like violent interactions or tattooing, even. There are many different ways that this virus can be transmitted and the fact that there are people who can carry it for long periods of time means that it doesn't need this critical population size in order to spread or persist in a population.
Erin Allmann Updyke	Right. Yeah.
Erin Welsh	So in that way it's a lot like a couple of the other viruses that we've talked about before like the herpes simplex virus or chickenpox virus.
Erin Allmann Updyke	Right.
Erin Welsh	But once people began settling in larger groups around 7000-8000 years ago, that meant of course more opportunities for transmission which led to an increase in the diversity of hepatitis B virus strains and the emergence of multiple genotypes or lineages. I'm not going to go into a ton of detail about this but the paper that I keep mentioning by Kocher et al actually traced the kind of rise and fall of different hepatitis B virus lineages. So one for instance seemed to be the prevailing lineage in Western Eurasia for like 4000 years but then it disappeared around 3300 years ago. It just went almost extinct. No idea why, maybe sampling bias, maybe a reduction in human population that kind of bottlenecked it or eliminated it. Or maybe it was intergenotype dynamics. Who knows?
Erin Allmann Updyke	So interesting, Erin.

Erin Welsh	I find this so fascinating. And this pattern of genotypes going extinct and shifts in the predominant genotype, it still happens today and we don't know for sure but maybe it's partially due to the fact that some genotypes may be associated with certain transmission routes I've seen. And maybe some of the genotypes vary in their ability to cause severe disease or in their ability to cause this persistent carrier state. And so that's I think why it's really important to understand the origins and the evolutionary history of a virus like the hepatitis B virus. It can tell us in part why we see some of the epidemiological patterns that we see today and it might be helpful for predicting what we could expect to see in the future. Okay, so we have this virus that has ancient roots and that had reached a global distribution a long time before the present day and I already mentioned that evidence of hepatitis B infection has been found in ancient human remains dating back thousands and thousands of years as well as just a couple thousand years as well as more recent. So basically it's kind of persisted in human populations for all of that time.
Erin Allmann Updyke	Right, yeah.
Erin Welsh	But were the people who were around back then aware of this? Like did they have any idea?
Erin Allmann Updyke	Were they? Did they?
Erin Welsh	Well probably in a sense. So jaundice which can be caused by many different things including the hepatitis B virus has long been recognized and described in ancient medical texts. I'll toss in the Hippocratic texts from around 400 BCE because it's an episode of This Podcast Will Kill You.
Erin Allmann Updyke	We always do that.
Erin Welsh	And outbreaks of jaundice were also written about. So one paper I read suggested that there was a description of what was likely infectious hepatitis dating back to the 8th century CE and it was sometimes called campaign jaundice because it seemed prevalent during times of war. Surprise, surprise. But switching from talking about the evolutionary history of the hepatitis B virus to the written human history part, it's tricky because of the existence of other hepatitis viruses. Hepatiti.
Erin Allmann Updyke	Hepatiti.
Erin Welsh	We can test human remains for hepatitis B virus specifically but we can't always know which hepatitis virus was causing whatever outbreak that was being described.
Erin Allmann Updyke	Right.
Erin Welsh	How likely was it that it was hepatitis B? In terms of outbreaks, I would guess actually that the hepatitis A virus which is transmitted fecal-orally may have been the culprit more often than not, especially in crowded or unsanitary conditions like war.
Erin Allmann Updyke	Yeah. And especially in any that were acute infections, right?
Erin Welsh	Yes, exactly.
Erin Allmann Updyke	Yeah.

Erin Welsh	But it's certainly possible that hepatitis B and other hepatitis viruses transmitted through blood or bodily fluids caused outbreaks especially as the use and reuse of needles became more popular around the middle of the 19th century.
Erin Allmann Updyke	Yeah.
Erin Welsh	So let's fast forward to then, the last decades of the 1800s.
Erin Allmann Updyke	Let's.
Erin Welsh	This is after the development of germ theory and after the introduction of some injectable vaccines. In 1885, an epidemic of jaundice followed a smallpox vaccination campaign among ship workers in Bremen, Germany which led to what seems like an early indication that hepatitis outbreaks could be caused by the reuse of needles or because this particular vaccine used human serum as a stabilizing agent through blood products.
Erin Allmann Updyke	Right.
Erin Welsh	But the link between the administration of this vaccine and the resulting hepatitis outbreak, it wasn't recognized for decades, possibly obscured by this long standing recognition that epidemics of hepatitis or jaundice were also known to frequently happen in overcrowded, unsanitary areas. So it was more difficult to pinpoint the vaccine itself as the cause rather than like oh well maybe they all went to the same-
Erin Allmann Updyke	Watering hole.
Erin Welsh	To the same watering hole where they all got hepatitis.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. But as blood transfusions increased and the practice of reusing needles persisted, there was this growing suspicion that an infectious hepatitis might also be carried in the blood or blood products. See our hepatitis C episode for more on the history of blood transfusions and the blood typing system and so on.
Erin Allmann Updyke	Yeah.
Erin Welsh	The differentiation of two different hepatitides, one called transfusion hepatitis and the other one being called infectious or food or waterborne hepatitis, this was finally made in the early 1940s. During WWII hundreds of thousands of US Army personnel received the yellow fever vaccine which like the 1885 smallpox vaccine had human serum as an ingredient. Obviously that's no longer done for safety reasons, needed to maybe clarify that. But after receiving this vaccine, 50,000 people came down with hepatitis.
Erin Allmann Updyke	Whoa.
Erin Welsh	Although those were just the clinically recognized cases. Later estimates put the total figure of hepatitis infections resulting from this vaccination campaign at around 330,000.
Erin Allmann Updyke	Oh dear. Okay. Oh gosh. Oh dear. Okay.

Erin Welsh	It's a lot. It's a lot. Yeah. And there was a british doctor named F. O. MacCallum who had been involved in the development and administration of this vaccine and he hypothesized that it might have been transmitted by reusing syringes or carried in the vaccine itself. And he thought that this hepatitis represented a bloodborne infection separate from the previously recognized food and waterborne hepatitis. He proposed that they be called hepatitis A and B and that they may represent different viruses.
Erin Allmann Updyke	So this is how it begins.
Erin Welsh	This is how it begins. Because at the time it was not known whether it was the same virus or different viruses and so it was more in the clinical picture of it in a way.
Erin Allmann Updyke	Yeah.
Erin Welsh	Because after this designation, after this recognition that like hey, this might be transmitted through blood products and not just through like food and water or whatever, other researchers began to describe differences in the way that these two hepatitides looked clinically and to kind of keep an eye out more on the different routes of transmission.
Erin Allmann Updyke	Right. Once you have it more like hey, there are two different things here, then you start to notice more of the differences.
Erin Welsh	Right. Once you once you create those columns then it becomes much easier to add to the list.
Erin Allmann Updyke	Yeah.
Erin Welsh	But just because people now knew that hepatitis could be transmitted by reusing needles or via blood products, that didn't mean they could stop it from happening. Like I talked about in our hepatitis C episode, blood transfusion or blood product technology vastly outpaced our ability to identify many bloodborne pathogens, especially viruses, which led to blood products that were unknowingly contaminated. And often it was seen as this kind of situation where it was like well we don't know whether or not this batch of blood has hepatitis virus in it but you can either receive the blood and possibly get hepatitis down the line or not take the blood and die of blood loss immediately. So there was no choice sometimes, there was no option.
	That's not to say that people weren't working on finding a way to test the blood supply and identify what was causing the hepatitis. If anything, it was that feeling of being powerless to protect people from this disease that created a sense of urgency in finding out what the hepatitis B agent was so that they could detect it in blood products. But despite a ton of people working on this, progress kind of stalled in the 1950s and early 1960s. And I think it stalled partially because this was a time when virology was kind of in its infancy as a field and the technology that would allow for genetic testing or sequencing was still decades away.
Erin Allmann Updyke	I'm sorry, I don't know how I didn't know that it was so recent.
Erin Welsh	I know!
Erin Allmann Updyke	Like 1950s, 1960s. That's not a long time ago.
Erin Welsh	All of the hepatitis viruses have very recent identification dates but have been recognized for decades before that.

Erin Allmann Updyke	Wow.
Erin Welsh	And it's just sort of this constantly unfolding tragedy where you see it and they know, like the people who were there at the time are like this might have hepatitis virus in it but I can't do anything about it.
Erin Allmann Updyke	Right. But I don't know it. Like I know it but I can't know it.
Erin Welsh	And we can also blame the virus itself because this isn't to say that virology research on all fields, on all viruses had stopped or stalled by the early 1950s or 60s because some were easier to work with in a lab setting than others.
Erin Allmann Updyke	Right, yeah.
Erin Welsh	And hepatitis B virus doesn't really lend itself very well to culturing in a lab setting. And so it was just more difficult especially if you don't know even what you're looking for, how do you know that you're on the right track at all?
Erin Allmann Updyke	Yeah. And it's a weird virus, we already said that.
Erin Welsh	Yeah, it's a weird one.
Erin Allmann Updyke	It's very weird.
Erin Welsh	And at the time people were using the term virus but it wasn't known for sure whether it was a virus or something else. It was known to be a virus in concept but without physical proof. But by the end of the 1960s that would change and the team that led to the breakthrough identification of the hepatitis B virus would not have been on anyone's short or even long list of people that were likely to have done the job.
Erin Allmann Updyke	Why? Who was it?
Erin Welsh	Okay, I'll get there. But before we get into the unlikely story of the discovery of the hep B virus, I want to quickly mention the Willowbrook State School hepatitis studies which were these unethical experiments that are sometimes referred to as the pediatric Tuskegee.
Erin Allmann Updyke	Oh dear.
Erin Welsh	Yeah. I'm going to be brief because these studies are mostly about hepatitis A and so when we do a hep A episode I'll go into more depth on them. But I wanted to bring them up here because these studies mark one of the major points in the history of medical ethics and also hepatitis B was a part of these studies. So Willowbrook State School was a state-funded institution established in 1947 on Staten Island, New York for children who were intellectually or developmentally disabled.
Erin Allmann Updyke	I hate this already, Erin.

Erin Welsh	I know, I know, I know. In 1958 infectious disease physician Dr Saul Krugman from New York University and Bellevue Hospital, he was asked to join Willowbrook to help figure out why there were such high rates of hepatitis among the children there. It was something like 30-50% admitted there would end up getting hepatitis. And they also asked him to help bring those rates down. And so he agreed and set out to not only bring down the rates of hepatitis but also to quote "describe the circumstances under which the disease occurred and the effect of gamma globulin and reducing its occurrence and an attempt to induce passive active immunity by feeding virus to persons protected by gamma globulin and to describe the excretion of virus during the incubation period of the disease."
Erin Allmann Updyke	Oh dear.
Erin Welsh	Your face tells me you've picked up on some of the problems with these studies intentionally infecting children.
Erin Allmann Updyke	Yeah.
Erin Welsh	So Krugman justified the research by saying that the children would inevitably get hepatitis anyway because it was so prevalent in the school and that this way with his experiments, the vaccine could be developed and tested. Parental consent was obtained but it's not clear the extent to which parents were told of the risks to their children and what exactly was involved. By his own estimation, Krugman's studies reduced the incidence of hepatitis by 85%. Again, it's not entirely clear which hepatitis but his study did demonstrate that there were two different types of hepatitis transmitted in different ways which like I said was already kind of known and also tested a prototype of a hep B vaccine which did seem to be somewhat effective. The legacy of the Willowbrook hepatitis studies is that the resulting outrage led to very strict regulations placed on including children in clinical trials and medical studies and more revamping of what could be considered medical consent. There's a lot more of course, like I said, to these studies and their place in the history of medical ethics. And so if you're interested in learning more and don't want to wait for our hepatitis A episode, I will list some sources for this on our website. And there's also a paper that Krugman wrote and published in 1986 in which he defends himself in the research. So that's kind of an interesting read.
Erin Allmann Updyke	Wow.
Erin Welsh	There's a lot of discussion about this and I didn't do it justice. So let me just say that.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. Okay.
Erin Allmann Updyke	Okay.
Erin Welsh	Back to strictly hepatitis B. So by the 1960s the hepatitis B virus had still not been identified despite the fact that tons of people were working on this problem. And when it was finally discovered, it wasn't by one of those researchers who had dedicated their lives to hepatitis but by a team who had not even been looking for hepatitis B or any other virus.
Erin Allmann Updyke	What were they looking for?
Erin Welsh	I feel like this story is such a good example of how science rarely proceeds in an orderly fashion, it's not A to B to C.

Erin Allmann Updyke	Yup.
Erin Welsh	Especially because B happens to be the first hepatitis virus discovered.
Erin Allmann Updyke	Yeah, okay. I saw that on a timeline and I was like, whoa, whoa, whoa, hold on, hold on, hold on. What?
Erin Welsh	I know. I was like, why is it called B then?
Erin Allmann Updyke	Yeah, it doesn't make any sense.
Erin Welsh	Yep, everything's just arbitrary.
Erin Allmann Updyke	Okay. Cool, cool, cool, cool.
Erin Welsh	But yeah it's like we often tell, I'm including myself in that, these stories of scientific discovery in a very linear way, in a very like, here's this nice little pretty narrative packaged. And that neat narrative does serve a purpose because it kind of is like well let's find the important things, let's find the compelling things.
Erin Allmann Updyke	Yeah.
Erin Welsh	But that's not the way things happen, it's just simply not. And so this I think really illustrates that. Sometimes you're looking for one thing and you end up stumbling upon something that never even crossed your mind. So let's meet Dr. Baruch Blumberg.
Erin Allmann Updyke	Okay. Hi.
Erin Welsh	Since early in his career Blumberg became interested in why some people get sick and others don't, how genetics interacts with human behavior and the environment to lead to disease basically. And he became interested specifically in polymorphisms. So these are genetic traits for which there are multiple forms. So things like tongue twisting, can you twist your tongue?
Erin Allmann Updyke	Yes, can you?
Erin Welsh	Me too.
Erin Allmann Updyke	Cool.
Erin Welsh	Blood types, what what blood type are you?
Erin Allmann Updyke	I'm O positive.
Erin Welsh	I'm AB positive.
Erin Allmann Updyke	I knew that about you.

Erin Welsh	(laughs) I knew that about you. So these are examples of polymorphisms, right? There are different forms of these and there are different distributions in human populations. And so he wanted to see whether there were any of these polymorphisms that were associated with susceptibility to certain diseases. So kind of asking the question do people with type A blood have a greater chance of developing heart disease and if they do why? But instead of blood types which at this point had already been pretty well established, Blumberg was interested in finding new blood plasma protein polymorphisms that could be associated with variation in disease susceptibility. So that's what he was looking for.
Erin Allmann Updyke	He wasn't even looking for virus.
Erin Welsh	No, he was looking for blood plasma protein polymorphisms.
Erin Allmann Updyke	Wow. I bet he found some proteins, all right.
Erin Welsh	He certainly did. But how did he find these proteins?
Erin Allmann Updyke	Yeah, I don't know.
Erin Welsh	Well he began his search by collecting blood samples from people all over the world and then testing them to see whether certain antigens appeared and in what frequency. Basically you use the blood of someone who had received multiple transfusions to find antibodies against a protein antigen that was new to them. And then you test those antibodies against other blood samples to see how frequently it reacts, meaning how often that protein antigen is present.
Erin Allmann Updyke	Yeah.
Erin Welsh	And this might seem like a very crude approach today in the days of super inexpensive genomic sequencing. But back then these were the early, early years of genetics.
Erin Allmann Updyke	I mean we still do that to do regular blood typing.
Erin Welsh	Yeah.
Erin Allmann Updyke	So it is still very useful.
Erin Welsh	It is super useful. But the approach, like the technology that he used which was agar gel diffusion, it was basically one of the only ones available at the time, immunology was in its infancy. And so with this approach Blumberg and his team identified a new protein that they called the AG protein, AG for antigen. This protein which they found to have an uneven global distribution turned out to be a serum lipoprotein. So serum protein combined with fats that may play a role in serum cholesterol and triglyceride levels. Maybe not a strong marker for disease susceptibility but it was an encouraging finding, it showed that their technique, even though it was maybe a little bit kind of rough handed could be used to find new serum proteins. So they kept looking. For the next hunt Blumberg teamed up with a blood researcher named Harvey Alter whose name you should recognize from our hepatitis C episode except when I looked through my notes for his name, I didn't mention that he was the person who identified the hepatitis C virus and I am so embarrassed. That's kind of a fundamental, important person for the history of hepatitis C.
Erin Allmann Updyke	I bet you talked about a lot of important things, Erin.

Erin Welsh	I'm ashamed. But I'm mentioning him here and I also want to shout out that in 2020 he was awarded the Nobel Prize for his role in hepatitis C research. Pretty cool.
Erin Allmann Updyke	Oh wow.
Erin Welsh	Yeah. So anyway Alter, who was in the beginning of his career in the early 1960s, he was interested in why some people developed an immune response like a fever, chills, rash, etc after receiving a transfusion. Yeah, interesting stuff. And it took a little bit of time, a little trial and error but Alter in Blumberg found another polymorphism and this they named Australia antigen because it was first found in the blood serum of a First Nations person from Australia. And we've talked about the problem with place names to describe a disease loads of times before. However I want to point out that at the time this Australia antigen was just thought to be a human protein, not necessarily an actual pathogen which surprise, spoilers, it turned out to be. But in any case the name Australia antigen didn't stick around for very long because it was soon shown that the Australia antigen was actually the hepatitis B virus.
Erin Allmann Updyke	I love this story.
Erin Welsh	I know, I know. I just think it's so amazing. It's just such a fun story. So how did they make this connection? Well first after finding this new protein, they decided to look at its geographic patterns of prevalence just like they had for their earlier AG protein, was it more common in some areas or in some populations than others? And they did find variation in the global distribution. They found that the Australia antigen seemed to be somewhat rare in the US blood samples that they had but it was a little bit more common in parts of Asia, in the Pacific, Africa, and Eastern and Southern Europe. They also showed that the antigen seemed to cluster in families which at first glance suggested that it was an inherited trait. But as more data came in, that assumption kind of broke down.
Erin Allmann Updyke	Yeah.
Erin Welsh	Blumberg and his team began getting suspicious that it might not be a human protein after all but rather an infectious agent, one that was possibly bloodborne as they had found it in several people who had at first tested negative for the antigen but later tested positive shortly after receiving a blood transfusion.
Erin Allmann Updyke	Oh no.
Erin Welsh	And then the connection to hepatitis B fell into place when they began to find the antigen at high rates and people who had hepatitis.
Erin Allmann Updyke	Okay.
Erin Welsh	Especially those with a history of transfusion. By 1965 or so they had become convinced that they had finally found the long sought after hepatitis B virus almost by accident.
Erin Allmann Updyke	Wow.
Erin Welsh	I mean truly by accident really.
Erin Allmann Updyke	Yeah.

Erin Welsh	And they sent off a couple of papers to be published. One was outright rejected with a reviewer commenting that there simply wasn't enough evidence in support of their hypothesis. And now we look back on this and go that's absurd, how could this monumental finding be rejected? But if you consider this in the larger context of the time, it does seem like it was kind of like a boy who cried wolf scenario, people were always submitting articles saying, 'I found the hepatitis B virus. I found it, it's this, it's this.' Kind of like how I feel like every few months nowadays there's an article saying the Zodiac Killer has finally been identified. Okay, if we dig a little deeper, is it true or is it not so close to the truth? But another reason for the rejection, and this one is much more unfair, is that Blumberg and his group were in no way part of the hepatitis B scene. They had no background in studying hepatitis, none of them had been trained as epidemiologists let alone virologists. So what did they know about hepatitis?
Erin Allmann Updyke	Yeah.
Erin Welsh	But despite this initial rejection and the resentment from some prominent hepatitis researchers, they managed to get a paper published in 1967 that awakened the world to the possibility that the virus causing transfusion hepatitis, the hepatitis B virus, had finally been found.
Erin Allmann Updyke	1967. Wow.
Erin Welsh	Yeah. And this seems like an understatement but this was huge news. At the time, post-transfusion hepatitis rates reached 30%.
Erin Allmann Updyke	Oh my.
Erin Welsh	The beginnings of the incredible prevalence of global hepatitis that we have today really does have its roots during this time when there was a lot of blood transfusion happening, a lot of blood products being used, a lot of needles being reused without knowing what the virus was, how to test for it, how to prevent it.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. But there was still another step and that was confirmation from other researchers. Boom, easily done. Check. Here's Hepatitis B.
Erin Allmann Updyke	The end. (laughs)
Erin Welsh	Almost the end actually. The discovery of the hepatitis B virus, this allowed not only for the testing of hepatitis B virus and blood products but also the identification of carriers of the virus and the eventual development of a vaccine. This isn't to say that it was all smooth sailing after the link between the Australia antigen and the hepatitis B virus was made. For instance the virus was still not able to be maintained in conventional tissue cultures which made fulfilling Koch's postulates difficult and the test for determining whether or not the virus was present were pretty insensitive at the time. I've seen estimates of 15-20% of the time it would detect hepatitis B virus.
Erin Allmann Updyke	Oh jeez.
Erin Welsh	Yeah.
Erin Allmann Updyke	That's pretty bad.

Erin Welsh	It's gotten a lot better, we should point out. A lot better.
Erin Allmann Updyke	Yes.
Erin Welsh	Very good. Excellent. And as I always talk about there's typically this delay from when something new is discovered to when there is wide enough acceptance for that knowledge to be applied, especially in a medical setting. So screening the blood supply for hepatitis B even with this pretty poor test didn't start for a few years after the virus was discovered. So in 1970 the hepatitis B virus test became official in the US and in 1972 the American Association of Blood Banks had begun to require the testing of donors. And even though the test desperately needed to be improved, that was a good start.
	But being able to test for hepatitis B virus also meant that it could identify people who were carriers or infected with hepatitis B which then led to widespread discrimination and ostracization for people who were positive for hepatitis B. People were fired from jobs, they were not allowed in classrooms, children were taken off adoption lists, people were being denied healthcare from shared machines like dialysis machines, they were being denied admittance to medical school or kicked out of their jobs as doctors or dentists. I mean the list goes on and on. It was just like oh great we have this test, we can help prevent hepatitis and also we can put the scarlet letter of hepatitis on every single person that we test.
Erin Allmann Updyke	I feel like that part of hepatitis B especially is so overlooked today.
Erin Welsh	Yeah. A lot of these, many or most of these restrictions or regulations have been overturned but the stigma and isolation faced by many people with hepatitis B continues today and has a huge detrimental impact on their quality of life. Right after the hepatitis B virus was identified, many people began working on a hepatitis B vaccine including Blumberg and his colleague Dr. Irving Millman who came out with one in 1969. And over the next decade people would work on refining the vaccine and incorporating it into routine vaccine schedules. And I think since then it's kind of faced continuous tweaking and we've gotten a pretty solid, from my understanding, hepatitis B vaccine.
Erin Allmann Updyke	Yes. 1981 was when the hepatitis B vaccine was licensed like in the US widespread by the FDA and then 1986 it was updated to not have any human parts in it essentially. It's made in a yeast and it's a recombinant vaccine. And as far as I know it's the same vaccine since 1986.
Erin Welsh	Right. Do you know who helped work on the yeast aspect of it?
Erin Allmann Updyke	Tell me who, Erin.
Erin Welsh	Maurice Hilleman, our friend.
Erin Allmann Updyke	Oh let's hear it for Maurice!
Erin Welsh	Let's hear it for Maurice. And I already mentioned one person in this story who was the recipient of a Nobel Prize for their work on hepatitis viruses and that was in 2020. But in 1976 Dr. Baruch Blumberg was awarded the Nobel Prize in physiology or medicine for his work in identifying the hepatitis B virus.
Erin Allmann Updyke	Love it.

Erin Welsh	Also that same year it was co-awarded to two different people that didn't have any work together. The other person awarded was Carleton Gajdusek. Do you remember him from prions, the bad guy?
Erin Allmann Updyke	Oh yes, I do. Ugh.
Erin Welsh	Over the decades since the discovery of the hepatitis B virus there's been a great deal of research on understanding transmission dynamics, genotype differences, the cancer-causing potential of the hepatitis B virus, new hepatitis viruses like hepatitis D, like hepatitis C, like hepatitis E, better blood tests, improved vaccines, harm reduction programs, and a growing recognition of the tremendous global burden that this virus has in a physical, economic, and emotional sense. And despite all of the advancements made in the field of hepatitis B research, the virus is still extraordinarily prevalent and transmission continues today. So Erin, that was kind of a quick wrap up to the future. But I want to hear where we stand with hepatitis B today. So can you fill me in?
Erin Allmann Updyke	Oh I can't wait to. Right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	Unlike our first three episodes, I have a lot of statistics for this section, Erin. First three episodes of this season, I mean. But they're pretty sobering.
Erin Welsh	Okay.
Erin Allmann Updyke	Globally it is estimated that close to 4% of the entire world's population is living with chronic hepatitis B infection. That is close to 300 million human beings. And believe it or not, that's an improvement because the very first paper I read was a bit older, from 2004. And that started off by saying over 400 million people. So we're down.
Erin Welsh	So those are people chronically infected.
Erin Allmann Updyke	Right, living with chronic hepatitis B.
Erin Welsh	And how many people are infected newly every year? What's the incidence?
Erin Allmann Updyke	The World Health Organization estimates 1.5 million people are newly infected every year.
Erin Welsh	Wow.
Erin Allmann Updyke	Yeah. It's horrific. If we look at the entire spectrum or the whole alphabet of hepatiti or viral hepatitides, viral hepatitis caused an estimated 1.34 million deaths in 2015 alone which is more than HIV, it is substantially more than malaria, and it's nearly as much as tuberculosis.
Erin Welsh	So why does it feel like it's not talked about?
Erin Allmann Updyke	Why, Erin? I don't know. Okay. And that's all of the viral hepatiti.
Erin Welsh	Okay.

Erin Allmann Updyke	Of all of those deaths, 96% are estimated to be from chronic hepatitis and of that 96%, 66% of those are from hepatitis B. So if we do some Erin math, just kidding, the World Health Organization did this math, that is 820,000 humans that are dying from chronic hepatitis B infection every single year.
Erin Welsh	Wow.
Erin Allmann Updyke	Now you asked why we're not talking about it. Here's probably a large part of it. That burden is not borne equally across the globe.
Erin Welsh	Of course not.
Erin Allmann Updyke	The World Health Organization divides the globe into different regions. The Western Pacific region by far has the highest incidence and prevalence of hepatitis B followed by the World Health Organization African region. And in these areas the prevalence can be as high as 6% or greater in some cases.
Erin Welsh	Wow, oh my gosh.
Erin Allmann Updyke	Whereas in some parts of the world like in Europe or in North America, the prevalence maybe less than 1%. And so I think that huge global discrepancy can lead for some countries to not think a lot or talk a lot about hepatitis B.
Erin Welsh	Yeah. It's, 'Oh well, it's not a problem here, so...'
Erin Allmann Updyke	Exactly, Erin. I think I wrote those exact words later on. Yeah. And it gets more sobering because it's also estimated that only 10.5% of people that are living with hepatitis B know their status. And it's also estimated that only 22% of those that are diagnosed that know their status are on treatment for chronic hepatitis B. That statistic I want you to take with a grain of salt because not everyone who was diagnosed with chronic hepatitis B necessarily needs treatment, at least not right away. So that statistic at least might not be quite as bad as it sounds. But 10% of people knowing their status is pretty bad.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. I have more numbers, this is the number-heavy one. And these numbers are from a modeling study from 2016 data but of this almost 4% of the global population that is infected with chronic hepatitis B, between 1.6-2.2 million are children under the age of 5. And the World Health Organization's most recent data does suggest that it's now finally just under 1% of all children worldwide under age 5 that are chronically infected, that's down from around 5% of all children in the pre-vaccine era.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	I know. And still just under 1%, essentially 1% of all kids under age 5 globally living with this chronic infection that I can't emphasize enough is entirely preventable at this point. We have had a vaccine for hepatitis B that is 98-100% effective for 17-30 years. Like not a lot of waning immunity, incredibly effective vaccine for 40 years.
Erin Welsh	So I have a question about that. So is it part of every single routine vaccine schedule?

Erin Allmann Updyke	Over 180 countries have hepatitis B as part of their universal vaccine program and it's estimated that 87% of infants worldwide received the three dose hep B vaccine series in their first year of life which is great. But only 46% likely had a timely birth vaccination, that critical 12-24 hour window and even less, the study estimated about 13% got both the hepatitis B vaccine and if needed that IVIG to actually treat and provide more passive immunity.
Erin Welsh	Right.
Erin Allmann Updyke	But with IVIG and the vaccine within 12-24 hours of birth, it's still about 91% effective to prevent hep B infection in those babies. But it's even more effective if you can treat the pregnant person to lower their viral load.
Erin Welsh	Okay.
Erin Allmann Updyke	And it's estimated that only about 1% of pregnant people are actually getting that testing and then treatment.
Erin Welsh	1%?
Erin Allmann Updyke	Yeah, 1% or less. And so that contributes a lot to the overall burden and why we still have such high infection rates.
Erin Welsh	We have the tools just not the delivery.
Erin Allmann Updyke	Yeah. So we have a lot of improvements to still be made.
Erin Welsh	Yeah.
Erin Allmann Updyke	Overall this is a massive, massive disease. I honestly didn't even realize how massive it was before researching for this episode. And because it's such an enormous global problem, I'm glad that we were able to highlight so many different parts of this really important disease. But there are still several aspects that we didn't fully cover in this episode, especially the substantial stigma and discrimination faced by so many people living with hepatitis B around the world.
Erin Welsh	Right. And because this is such an important part of the hepatitis B story, I am so excited to be able to take a deeper dive into it in a bonus episode coming out next week.
Erin Allmann Updyke	Woo woo! You heard that right. Bonus episode!
Erin Welsh	So I enlisted the help of the amazing Dr. Chari Cohen who is Senior Vice President of the Hepatitis B Foundation to discuss some of the drivers of stigma and discrimination in hepatitis B and what's being done about it. I also got to pick Dr. Cohen's brain about what it's like to work in the public health nonprofit world, what the difference between a doctor of public health and a PhD is, and some fantastic advice for people who might be interested in pursuing a career in public health.
Erin Allmann Updyke	And we know there's a lot of you out there.

Erin Welsh	There's a lot of you out there, yes. It was so much fun chatting with Dr. Cohen and you should definitely mark your calendar so you don't miss the ep. It comes out next Tuesday, February 1st. Okay but should we maybe wrap up this episode for now?
Erin Allmann Updyke	I think we should. Time for sources?
Erin Welsh	It is. All right. So I have a lot of papers for this and I'll post them all on our website but I do want to shout out one book in particular and that is of course 'Hepatitis B: The Hunt for a Killer Virus' by Dr. Baruch Blumberg.
Erin Allmann Updyke	I have a few papers, not as many for this as some episodes but a few really nice review papers. Most of them are from The Lancet and they've just been updates on each other. So the most recent one that I read was published in 2018 and called 'Chronic hepatitis B virus infection', has a lot more detail about the different phases of chronic infection. And we'll post the sources for this episode and every one of our episodes on our website thispodcastwillkillyou.com.
Erin Welsh	We sure will. A big thank you again to Dr. Wang for taking the time to chat with us and being willing to share your experiences with hepatitis B and also thanks for all the awesome work you do.
Erin Allmann Updyke	Yeah, thank you so much. Thank you also to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	And thank you to Exactly Right of whom we are a very proud member.
Erin Allmann Updyke	And thank you of course to you, listeners. We love making this podcast and we couldn't do it if you didn't listen to it.
Erin Welsh	That's that's very true. And also an extra big thank you as always to our wonderful patrons. We love you. You're amazing.
Erin Allmann Updyke	We love it.
Erin Welsh	Okay well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.