

Erin Welsh

"I come to the fatal hour when we were about to be seized by the terrible influence of the atmospheric decompression. At 7000 meters, we were all standing in the basket. Sivel, numbered for a moment, has revived. Croce-Spinelli is motionless in front of me. Look, he says to me, how beautiful those cirrus clouds are. The sublime spectacle before our eyes was indeed beautiful. Towards 7500 meters, the numbness one experiences is extraordinary. The body and the mind weaken little by little, gradually, unconsciously, without one's knowledge. One does not suffer at all. On the contrary, one experiences inner joy as if it were an effect of the inundating flood of light. One becomes indifferent. One no longer thinks of the perilous situation or of the danger. One rises and is happy to rise.

Vertigo of lofty regions is not a vain word. But as far as I can judge by my personal impressions, this vertigo appears at the last moment. It immediately precedes annihilation, sudden, unexpected, irresistible. Soon I wanted to seize the oxygen tube but could not raise my arm. My mind however was still very lucid. I was still looking at the barometer. My eyes were fixed on the needle which soon reached the pressure number of 290, then 280, beyond which it passed. I wanted to cry out we are at 8000 meters! But my tongue was paralyzed. Suddenly I closed my eyes and fell inert, entirely losing consciousness. It was about 130.

At about 330 I opened my eyes again. I felt numb, weak, but my mind was active. The balloon was descending with terrifying speed. Sivel's face was black, his eyes dull, his mouth open and full of blood. Croce's eyes were half shut and his mouth bloody. The shock as we struck the ground was extremely violent. It was four o'clock. As I set foot on the ground, I was seized by a feverish excitement and fainted, growing livid. I thought I was going to join my friends in the other world. However I recovered little by little. I went to my unhappy companions who were already cold and rigid. I had their bodies sheltered in a neighboring barn. Sobs choked me."

TPWKY

(This Podcast Will Kill You intro theme)

Erin Allmann Updyke

What?

Erin Welsh

Yeah. A fatal balloon flight.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah.

Erin Allmann Updyke

Erin, well you have to tell me what that's from.

Erin Welsh

Okay. So that was an account by Tissandier of the fatal balloon ride of 1875. He and his two companions went up to past 8000 meters, which by the way is like over 26,000 ft, and they all lost consciousness and then their balloon went out, they crashed, and two of the three died.

Erin Allmann Updyke

That is horrific and also makes me so intrigued in what the history of today's episode is going to be because it is nothing like what I expected. And wow.

Erin Welsh

Yeah. I didn't even realize that the balloon thing would be kind of a left turn or seem like a left turn. But it is surprisingly relevant.

Erin Allmann Updyke

I cannot wait to hear all about it.

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: And today we're taking a few left turns or ascents and descents. I don't know, I tried.

Erin Welsh: I appreciate the effort.

Erin Allmann Updyke: To talk about altitude and altitude sickness.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah.

Erin Welsh: I am really excited for this, especially because before starting this I had no idea what the history was going to be and it turned out to be I think one of my favorite episodes to put together.

Erin Allmann Updyke: Ooh.

Erin Welsh: Also do you remember our very first episode this season, RSV, and I told the history of ventilators?

Erin Allmann Updyke: Yeah.

Erin Welsh: And I said at some point in that episode, gosh, I would love to tell the story of oxygen someday.

Erin Allmann Updyke: Do we get to?

Erin Welsh: A little teaser. Maybe.

Erin Allmann Updyke: Can't wait.

Erin Welsh: So I'm very excited.

Erin Allmann Updyke: Yeah, it's gonna be really fun. I know nothing about the history of this and only really knew prior to this what I learned in various physiology classes, so it was really fun to research. And it's just going to be a fun episode.

Erin Welsh: It is. And it's going to be made extra fun by the presence of a very special guest who is near and dear to our hearts.

Erin Allmann Updyke: Especially yours.

Erin Welsh: Especially mine. And that's just another little teaser. And you'll hear more about this very special guest later in the episode when they will come on to discuss some of the evolutionary aspects and current research going into altitude sickness and high altitude adaptation.

Erin Allmann Updyke: I can't wait, I'm really excited about it.

Erin Welsh: Me too.

Erin Allmann Updyke: Okay but before that, it is definitely quarantini time.

Erin Welsh: It is. What are we drinking this week?

Erin Allmann Updyke: We're drinking High & Dry.

Erin Welsh: We are. It was really difficult to come up with a quarantini recipe, everyone.

Erin Allmann Updyke: It really was.

Erin Welsh: We are struggling.

Erin Allmann Updyke: This is one of the hardest parts of this job at this point.

Erin Welsh: Honestly, it is. It used to be one of the easiest and now it's like just scrolling through pages and pages of our past quarantinis.

Erin Allmann Updyke: Right. Like how many different times can we use this one item? A lot.

Erin Welsh: Yeah, yeah. So we wanted to make this as dry a cocktail as possible, so that means as little sugar as possible. And so in this, which is essentially a modified Paloma, we have tequila, we have grapefruit juice, we have a little bit of blood orange juice, and we're topping it with an egg white foam.

Erin Allmann Updyke: For that aeration. Get it? We're so funny.

Erin Welsh: We will post the full recipe for the quarantini as well as the nonalcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels.

Erin Allmann Updyke: Our website, thispodcastwillkillyou.com, it's a really great website that has a lot of stuff on it. So you should go there and check it out.

Erin Welsh: You should, you should.

Erin Allmann Updyke: The end.

Erin Welsh: That's all that needs to be said.

Erin Allmann Updyke: Any other business, Erin?

Erin Welsh: I don't think so.

Erin Allmann Updyke: Okay. Well I have lots of questions about the history of this. So let's start with the biology.

Erin Welsh: Come on, I want to hear about the biology. Yeah. We'll take a quick break and then you can answer all my thousands of questions about the biology of altitude sickness.

Erin Allmann Updyke

We'll try, we'll try.

TPWKY

(transition theme)

Erin Allmann Updyke

So to understand the kind of disordered states that can result from ascending to or existing at high altitudes, we first have to understand what the heck actually changes at high altitude and what our normal physiologic response is to these changes. So that's how we're gonna kind of divide up this section of the episode. First we're gonna talk about the environmental variables that actually change when we go to altitude and then we'll talk about what our typical physiologic response is to those environmental changes, both in the short term and the medium to long term. And then we'll talk about what happens when these changes maybe don't work that well or don't go as planned or something along those lines. And that's when we'll get into both acute as well as a little bit of detail on chronic mountain sickness in their various forms.

Erin Welsh

Sounds excellent.

Erin Allmann Updyke

And one thing I will say for those who are really into the physiology part of this is I am going to do this with like a minimum of math. Okay. Math formulas, turns out, don't really translate well to like podcast audio format, okay.

Erin Welsh

Oh really?

Erin Allmann Updyke

Yeah. P1s and Bs. Okay, let's get into it. By far the single greatest environmental change that we see with respect to increasing altitude is a decrease in the partial pressure of oxygen. What does this actually mean? So when we ascend, either up a mountain or perhaps a balloon, the barometric pressure, that is the pressure that the atmosphere exerts on our bodies, declines because the mass of atmosphere above us is literally less mass.

Erin Welsh

Right.

Erin Allmann Updyke

And this decline in barometric pressure leads to a decline in the partial pressure that oxygen exerts. So the air at high altitudes is the same percentage of oxygen, 21% oxygen as we talked about in our bends episode last season.

Erin Welsh

That's right.

Erin Allmann Updyke

But what you can think of it as is the density of those oxygen molecules is less. So per breath, you're getting less dense oxygen molecules. And as we talked about in our bends episode, when we inhale air, which is 21% oxygen, some amount of that oxygen in that breath travels down our lungs into our alveoli and has to diffuse across our alveoli into our bloodstream, into our capillaries. And the transfer of this oxygen into our bloodstream is determined in part by its partial pressure gradient, by how much pressure it's exerting in our alveoli relative to our capillaries. So if this partial pressure declines, which we know it does as we ascend in altitude, that means that we are transferring less oxygen into our bloodstream.

So in short, what we see is less density, less pressure of oxygen in the air, which leads directly to less oxygen making it into our bloodstream which is called hypoxemia. Then what we see is less oxygen in our tissues which is called hypoxia. Sometimes people use the terms hypoxemia and hypoxia interchangeably, they're technically different things. But anyways. ICU nerds will love that little tidbit. Okay. But obviously in any case this is not great because our cells and our tissues do rely on oxygen to make energy and to function. So luckily our body has a lot of compensatory mechanisms that it uses when we ascend to altitude. Or in other words, when we are faced with what's often called hypobaric hypoxemic or hypobaric hypoxic situations, that means low pressure, low oxygen situations.

This process is known as acclimatization and it has several steps that occur both in like a very short term and a longer period, like days to weeks timeframe. Let's get into it. So first, involuntarily, all of these are involuntary, we're not conscious of these things happening. But most quickly, the change that we see as we ascend in altitude is that we see an increase in ventilation. So basically because of this drop in partial pressure, you have less oxygen diffusing into our capillaries and arteries. What happens then is that this decrease in oxygen leads to the stimulation of chemoreceptors in our aorta which comes off of our heart, as well as our carotid arteries that go up to our brain. There are receptors in these vessels whose job it is to sense how much oxygen there is in our blood and then stimulate our brain to fluctuate the depth and the rate of our breathing.

Erin Welsh

That is so cool.

Erin Allmann Updyke

It's so cool because it is entirely involuntary. It's not like if you go up to altitude, you'll sit there feeling like you need to take deep breaths. This is an involuntary response that's just happening.

Erin Welsh

Yeah.

Erin Allmann Updyke

It's called the hypoxic ventilatory response. And we'll get into that a little bit more later. But let's keep going because that's just the first of like a cascade of changes. So first we start breathing deeper and faster. What that does is it ends up lowering the amount of carbon dioxide in our alveoli. You can essentially think of it as we're breathing off extra carbon dioxide as we breathe like this. And that helps to increase the partial pressure of oxygen because they are inversely related in our alveoli.

Erin Welsh

How are we doing that?

Erin Allmann Updyke

That's just like a matter again of mathematics.

Erin Welsh

Okay. Just like properties of gasses and behaviors of gasses.

Erin Allmann Updyke

Exactly, yeah.

Erin Welsh

Okay.

Erin Allmann Updyke

So it's not changing the concentrations, it's just changing the partial pressures by blowing off more CO₂, you have an increased pressure of oxygen.

Erin Welsh

Right, right.

Erin Allmann Updyke

So what that does is allow our capillaries to continue extracting, to maintain a steeper gradient for the diffusion of oxygen into our capillaries, which is what we need because there's less pressure of oxygen from the atmosphere itself.

Erin Welsh

It's so cool.

Erin Allmann Updyke

I know, I know. It keeps going.

Erin Welsh

It keeps going.

Erin Allmann Updyke

At the same time, this reduction in carbon dioxide that we see also leads to what we know of as a respiratory alkalosis because carbon dioxide, as I'm pretty sure we talked a lot about in our bends episode, in our bloodstream results in acidification. So you can think of it as an acid. So if we're blowing off carbon dioxide, now we have an increase in the pH of our blood which is alkalosis. If this happens at sea level, like when we hyperventilate at sea level, our brain would try to compensate for this change in pH that we see to actually inhibit our respiration. But at altitude this process is maintained by this hypoxic ventilatory response, by those chemoreceptors we already mentioned and additional chemoreceptors in our brain to continue these high levels of ventilation because we're specifically facing lower partial pressure of oxygen in this setting.

Erin Welsh

So hyperventilation at sea level is different than the hypoxic ventilatory response?

Erin Allmann Updyke

It sure is, Erin.

Erin Welsh

What? How? So is this those specific chemoreceptors that are only activated at altitude?

Erin Allmann Updyke

So no, it's not that they're only activated at altitude but they're being activated in part by this lowered partial pressure of oxygen. And then in combination with this response, the changes in alkalosis. So it's more like a combination of all of these factors rather than a pure hyperventilation that you see at sea level without all of the additional factors. If that makes sense.

Erin Welsh

Yes, okay.

Erin Allmann Updyke

Altitude is not necessarily the only place that you would see this happen but this is what happens at altitude.

Erin Welsh

So Erin, where else would we see this happen?

Erin Allmann Updyke

So there have been other studies that look, we'll get into it a little bit more later, but at is it the pressure changes or is it just the hypoxia? But so really it seems that a lot of it is driven by the hypoxia initially.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. So the next part of what we see because of this respiratory alkalosis is that this naturally triggers our kidneys to try and compensate by peeing off more base in the form of bicarbonate. So we absorb less by carbonate and that is actually just a normal physiologic response to a respiratory alkalosis. That's how we compensate.

Erin Welsh

Okay.

Erin Allmann Updyke

And that happens kind of in a slightly longer timeframe than the respiration part of it. So that I know was like a lot of different...

Erin Welsh

I loved it. I'm thrilled.

Erin Allmann Updyke

But basically to sum it up in short, we have a decrease in the partial pressure of oxygen, which is less oxygen in our arteries, that triggers our brain to breathe deeper and faster to then breathe off more carbon dioxide and allow more oxygen to diffuse into our arteries so that we maintain good oxygen concentration. But that's not all.

Erin Welsh

Of course not.

Erin Allmann Updyke

Because oxygen in our bloodstream is not just dissolved in our bloodstream like a gas. In fact, nearly all of the oxygen in our bloodstream is bound to a pretty important protein that everyone's probably heard of on our red blood cells, aka hemoglobin. So the next bit of the acclimatization process involves hemoglobin and this part takes a little bit more time. So the respiratory response is starting immediately as we ascend. But within 1-2 days of ascent to altitude, what we see is a rise in the concentration of hemoglobin. Hemoglobin is the protein that's binding and carrying oxygen and then delivering it to our tissues. And that's important. Binding oxygen and then releasing it and delivering it.

Erin Welsh

Okay. I could tell that's like sort of remember this because it's going to come back later.

Erin Allmann Updyke

Is that like this is on the test?

Erin Welsh

That's exactly how I felt.

Erin Allmann Updyke

This is on the test, kids. So within 1-2 days, we see a rise in the concentration of hemoglobin. And this happens because the volume of our plasma in our blood actually falls up to 15-25%, which is a phenomenal amount.

Erin Welsh

Yeah.

Erin Allmann Updyke

And this happens primarily via a gentle diuresis. We start peeing off more fluid to decrease the plasma volume and then increase the concentration of hemoglobin.

Erin Welsh

Okay. Question here about altitude.

Erin Allmann Updyke

Yeah?

Erin Welsh

At what point do these things happen?

Erin Allmann Updyke

This is such a good question. There's no threshold, there's gradients. Because as you ascend, the partial pressure falls, right, just no matter what. But when we look at, for example, dysfunction in this process, we don't tend to see altitude sickness until we're getting pretty high, like 2500 meters or about 8,000 ft. Sometimes we can see it at slightly lower altitudes. But I don't think from what I have read, there's not like an altitude at which you see respiratory compensation starts vs stops. It's just a kind of gradual process.

Erin Welsh

But is there a proportional response to altitude? Like do you lose less plasma if you go up only 2500 meters compared to 5000 meters?

Erin Allmann Updyke

Yeah, that's a good question. I don't know, I didn't see that in the studies that I read. We can ask our guest.

Erin Welsh

Okay, I'll note it down.

Erin Allmann Updyke

Yeah. Because I think that would be really interesting, especially I think we'd have more data on that in animals than we do in humans. Because what I will say about this whole process that we've learned about, the acclimatization process, is that it tends to be studied once we get to an altitude at which you're at risk for acute mountain sickness, so above that 2500 meters usually, and then studied in people depending on how quickly they go up vs how slowly they continue to ascend, if that makes sense.

Erin Welsh

Yeah.

Erin Allmann Updyke

Okay. But that's the first step of this next process, reduction in plasma volume, increase in concentration of hemoglobin. This is actually a relatively short lived phenomenon that we see because then what happens over the next period of days to weeks is that this triggers erythropoietin, which is one of the major things that we make to stimulate red blood cell production. So what we see is an increase in red blood cell production. And then over the course of days to weeks to a month or two, our total red blood cell mass will actually increase overall. So if you're at altitude for less than a week, you're not going to see all of this play out. This is something that happens over the course of time.

But here's why this gets to be so important because there's also this thing in physiology called the oxygen dissociation curve that people might have heard of. This is a measure of both how tightly our hemoglobin binds this oxygen, like how much of an affinity it has for grabbing and becoming fully saturated with oxygen which it has to do in our lungs, and also how readily it gives up its oxygen at the level of our tissues. Because both of these parts of hemoglobin are really important, there has to be a balance between grabbing and holding all that oxygen and then letting it go when we need to let it go.

So what's really cool about this acclimatization process is that we see effects on both levels of this oxygen dissociation curve. What we see is that the increase in blood pH that I mentioned from that respiratory alkalosis shifts this oxygen curve such that hemoglobin has a greater affinity for oxygen. So under alkalotic conditions, a greater pH, hemoglobin is like ah, I need that oxygen, give it to me, I'm gonna grab it and hold it! And it gets really efficient at that. But in addition to what I mentioned about just increasing overall hemoglobin mass, the other thing that we see are red blood cells making more of as we acclimatize is a substance called 2,3-BPG.

Erin Welsh

Okay.

Erin Allmann Updyke

Or 2,3-bisphosphoglyceric acid. No one cares. This is something that helps our hemoglobin actually have a decreased affinity for oxygen or an increase in the ability of our hemoglobin to offload oxygen at the level of our tissues. And these two processes work together rather than canceling each other out, right. So that we have hemoglobin that becomes more efficient at grabbing oxygen under conditions which it needs to which is in our lungs when that partial pressure dictates that it needs to grab oxygen, and better at offloading it at the level of our tissues when the gradients are dictating we need to offload this oxygen.

Erin Welsh

Very cool.

Erin Allmann Updyke

Those are the major processes of acclimatization. We see them in the short term mostly with respiration, we see them in the long term with these changes in hemoglobin. We do also see especially in the very short term, like within 24 hours of ascending to altitudes, above 2500 meters is most of our data, we see an increase in cardiac output and heart rate which is thought to be related to increases in our sympathetic nervous system activity because of this initial hypoxia. This part, the increase in cardiac output, tends to normalize over a period of days. And then what we actually can see is a decrease in stroke volume or the amount of blood that each heartbeat pushes out because of that decrease in plasma volume, which is really interesting.

And then we also see changes that happen at the level of our vasculature, so our blood vessels in some cases might vasodilate to allow blood to push more oxygen to our tissues. But in our pulmonary vasculature, so the blood vessels in our lungs, we often can see a vasoconstriction that happens because of the decrease in the concentration of oxygen. And so this is kind of a balance that our body has to do and we'll get into what can happen when maybe that doesn't go so well. Shall we? So I know that that's a lot. And that's just what's happening in our bodies in general when we go up a mountain or a balloon.

Erin Welsh

Yeah.

Erin Allmann Updyke

That is physiologic acclimatization. You can think of it really as our body doing the best that it possibly can to try and deal with the fact that we just rapidly decreased the amount of oxygen surrounding us. But as I described, that process itself is not instant, it takes time, it takes hours to days to weeks. Parts of it are relatively rapid but that full process of acclimatization really can take quite a long time. So what we can see is that in the time period between ascent to altitude and full acclimatization, we are at risk for illness if this process doesn't go according to plan, I guess. And this illness can take three major forms. Acute mountain sickness or AMS, high altitude cerebral edema or HACE, and high altitude pulmonary edema or HAPE. And these are the three major forms that are often lumped under altitude sickness for example.

Erin Welsh

Question about acclimatization when it comes to humans. Because there are elevations or altitudes at which we simply can't acclimatize enough, where symptoms of acute mountain sickness could occur or probably will occur. There's a limit, right?

Erin Allmann Updyke

Absolutely there is a limit to this process. Acclimatization can only do so much. And just for reference so that people can understand like when we say the partial pressure decreases, how much are we actually talking? Everest base camp is at 5300 meters and at that point the partial pressure of oxygen is about half what it is at sea level. So already you've reduced it by half. And then at the summit which is over 8,000 meters, the partial pressure of oxygen is a third of what we see at sea level. So these are extreme conditions that we're talking about. We cannot acclimatize to that point for the long term.

Erin Welsh

Right. I mean obviously people have climbed it without supplemental oxygen but yeah.

Erin Allmann Updyke

Right. We can't hang out up there.

Erin Welsh

No.

Erin Allmann Updyke

Let's get into these three forms of altitude sickness, acute mountain sickness, HACE or high altitude cerebral edema, and then we'll talk about high altitude pulmonary edema or HAPE. So acute mountain sickness, this is the most benign, the most common, and the most rapid onset. Usually we see the symptoms of acute mountain sickness within 4-12 hours though it could be within a day or so of ascent to altitude. And again at this we're usually talking about altitudes greater than 2500 meters or about 8000 ft, although it can happen in some instances at lower than 2500 meters, at lower altitudes. And there are a few different scoring systems that you can use to diagnose this.

But in general, we look at a constellation of symptoms that include a headache. And in a lot of scoring systems, a headache actually has to be present to diagnose acute mountain sickness, so headache is a defining feature. And simultaneously you might see GI symptoms like a loss of appetite, maybe some nausea, vomiting. You might have some dizziness, fatigue is a really common symptom that progresses to lassitude, which I love as a word. But that is just a complete lack of energy, lack of motivation to do anything, like you can't even kind of get up. And very, very commonly we also see insomnia or sleep disturbances despite the fatigue.

Erin Welsh

Yeah.

Erin Allmann Updyke

And then we also can often see a decrease in urine output. Those are the constellation of symptoms that encompass acute mountain sickness. In terms of if we look at labs or imaging findings which become important in some of the other forms of altitude sickness, lab values tend to actually be pretty normal. You can see a slightly lower than average blood oxygen level if you're testing people's blood oxygen. But there's a large amount of variation in that number when it comes to just acute mountain sickness itself. Most of the time this can be self-limited and can resolve even without necessarily descending to a lower altitude. This can resolve with just time or sometimes with the assistance of various medications that I'll talk about a little bit later on. But then there is HACE.

Erin Welsh

Quick question though.

Erin Allmann Updyke

Yeah, I know you're gonna ask a question. What is it?

Erin Welsh

Before we go on to HACE and HAPE, why do we see those symptoms of acute mountain sickness?

Erin Allmann Updyke

So I'm not going to answer that question right now.

Erin Welsh

Okay.

Erin Allmann Updyke

Because there's still a lot of debate on this but a lot of papers consider acute mountain sickness and HACE or high altitude cerebral edema as ends of a spectrum.

Erin Welsh

Okay.

Erin Allmann Updyke

So that's why I want to talk about that before I let you ask those questions, Erin.

Erin Welsh

Sorry, sorry, sorry.

Erin Allmann Updyke

Because I knew that was your question.

Erin Welsh

I'm always getting ahead of things.

Erin Allmann Updyke

You're like no, but I have to ask it!

Erin Welsh

I have to know right now, right now.

Erin Allmann Updyke

I know.

Erin Welsh

I demand it.

Erin Allmann Updyke

But let's talk about HACE first and then we can try and understand acute mountain sickness and HACE simultaneously. HACE is characterized predominantly by exactly what the name says, swelling or edema of the brain itself. HACE is terrifying. It is extremely life threatening and the symptoms that we see in many cases are considered a progression of what we saw in acute mountain sickness. So if you think of lassitude and fatigue, this then progresses to altered consciousness, to mental status changes. One big thing that we see is what's called truncal ataxia. So Ataxia is not being able to walk in a typical fashion, like having a lot of instability and irregular gait all of a sudden. You can still see the headache but a lot of it really is this altered consciousness. And it's terrifying because HACE can progress to coma and death in as little as 24 hours.

Erin Welsh

Okay. And it's scary because if you are having mental status changes and that may make you less likely to recognize that you need help.

Erin Allmann Updyke

Absolutely, yeah. And again, just the rapidity of this progression, right.

Erin Welsh

Yeah.

Erin Allmann Updyke

The need for very, very urgent treatment. So even if you have people that are there with you that recognize that something is not right, being able to access treatment really quickly is important. And you asked Erin, why, like why do we see this? What's happening here? The truth is, and I found this really fascinating given how much we know about the physiology of the acclimatization process, is that when it comes to the pathophysiology of these disorders, we don't understand them.

Erin Welsh

Like at all?

Erin Allmann Updyke

Very little, like very little. So first of all, there's still some debate as to whether AMS and HACE are really these ends of a spectrum or not. There's a lot of thought that it is purely this hypoxia that is driving this process. But why are we seeing this hypoxia? What parts of this acclimatization process are failing us? Is it poor ventilatory response that we're just not seeing and that leads to hypoxia that leads to all these other things? We don't necessarily have super strong data to say that yes, that's true. There is some data that suggests that this is driven by fluid shifts. So I mentioned that we have this sympathetic stimulation which can cause vasoconstriction. We also are having vasodilation and we can see increases in cerebral blood flow.

There's also suggestion that we have an increase in vascular permeability because of oxidative stressors that are happening at the level of our blood vessels. So there might be low grade inflammation that is going on in the process of AMS and progression to cerebral edema. But truly, that is kind of the extent of what we really know about AMS and HACE, which is really interesting to me.

Erin Welsh	Okay, two questions. Number one, I know you can get HAPE without AMS. Can you get HACE without AMS?
Erin Allmann Updyke	It's a really good question. Like I said, one of the defining features of AMS is a headache and by some scoring systems you can't call it AMS unless there's a headache. You can have HACE without a headache. But does that really mean that someone didn't have AMS previously or not? I don't know. So to answer your question, I don't know.
Erin Welsh	Okay.
Erin Allmann Updyke	And I think that that's kind of part of this debate. And there is a lot of study to try and look at do we see any signs of a little bit of cerebral edema? A little bit of increased cerebral blood flow? A little bit of the things that make us so worried about HACE? Do we see those signs starting in AMS? And we just don't have a ton of answers.
Erin Welsh	And we really don't know why things like nausea or a lack of appetite or a headache are all somehow connected.
Erin Allmann Updyke	So we have some data on that.
Erin Welsh	Okay.
Erin Allmann Updyke	So with AMS, there are some studies that suggest we do have a little bit of intracellular edema if not full on cerebral edema, like our cells are at least getting a little swollen.
Erin Welsh	Okay.
Erin Allmann Updyke	And while we think that this likely doesn't irritate our cerebral pain receptors, what does make sense is the nausea, vomiting because there's nerve fibers that connect to certain centers in our brain that our sensory nerves travel through that if these areas are a little bit swollen and irritated, that might result in nausea and vomiting.
Erin Welsh	Okay.
Erin Allmann Updyke	But yeah, that's kind of the most specific thing that I found.
Erin Welsh	Wow. Okay.
Erin Allmann Updyke	I know.
Erin Welsh	I'm so surprised.
Erin Allmann Updyke	I'm so surprised too honestly. But it's really, really interesting. And it's not the end because we still have high altitude pulmonary edema or HAPE. This is different because it's our lungs and not our brain but otherwise I think of it as kind of similar. The onset of this is slower and tends to happen 1-5 days after ascent and is rare after a week or so. We often, like you mentioned Erin, we often can see acute mountain sickness, AMS, first but not always in the case of HAPE. And the symptoms here are again what you'd expect based on the name. We have edema in our lungs, fluid shifting into our lungs. So the symptoms that we see are dyspnea, difficulty breathing, shortness of breath. And a lot of it starts as severe exertional dyspnea or exertional shortness of breath.

Now everyone who exercises is going to get breathless or feel short of breath but what this is characterized as is excessive shortness of breath compared to everyone else that you came up the mountain with or other people around you on the mountain. So an excessive amount of shortness of breath along with cough, a feeling of chest tightness. And then this can progress to a more severe cough, shortness of breath that makes it difficult to even lie down flat. If you listened to someone's chest, you would hear crackles or maybe even gurgling sounds. And eventually this can progress to the production of a pink frothy sputum, which would mean that things are getting pretty severe. And when we look at things like labs, we would see pretty severe hypoxia, so we have pretty low levels of blood oxygen in these people which then is going to result in really fast breathing, that tachypnea, breathing really fast, and a faster heart rate. And on X-rays we see a lot of evidence of fluid throughout the lungs in this very patchy distribution usually.

And again here, Erin, we do not fully understand this pathophysiology but what we do know is that there's at least some component driven by this hypoxic pulmonary vasoconstriction that we see as part of this acclimatization process. So what this then can lead to is an increase in pressure in the pulmonary arteries. And then there's a few different thoughts on how this then leads to the edema that we see. It could be that then these arteries become a little bit leaky because of this increased pressure. It could be that this vasoconstriction is happening just in certain places, like in patchy distribution, both in our arteries and/or maybe in our veins even, in our lungs, which can then lead to increases in pressure just in small areas that then might lead to fluid being able to leak out of just those small areas, which would explain the patchiness that we tend to see on X-ray. Honestly it didn't seem very well fleshed out in terms of like the real drivers.

Erin Welsh

Yeah.

Erin Allmann Updyke

It used to be thought that it was really more heart failure that was driving it but now it's really thought that it's probably more a pulmonary process that then can lead to dysfunction in the heart as well rather than heart failure that's the initial driver of this process.

Erin Welsh

Okay. That's interesting.

Erin Allmann Updyke

Yeah, yeah.

Erin Welsh

Because that is in contradiction with some of the historical texts that I read. But that makes sense that we've learned more.

Erin Allmann Updyke

Right, yeah. Because historically this looks like a heart failure response.

Erin Welsh

Yeah, yeah.

Erin Allmann Updyke

Absolutely. Then there's also a big thought that inflammation plays a role because in some people with HAPE, if you look at the fluid that you collect from this edema, it has a lot of inflammatory markers. But not all of them and usually not until later in the disease process. So it's really unclear how big of a role inflammation really plays in this disease.

Erin Welsh

So I really want to talk about treatment. But first, I want to ask about risk factors. So these things can happen to anyone who goes up to altitude. Are there certain risk factors associated with either HACE or HAPE or even AMS?

Erin Allmann Updyke

Honestly no.

Erin Welsh: Okay.

Erin Allmann Updyke: Which is fascinating.

Erin Welsh: Yeah.

Erin Allmann Updyke: The major determinants of risk are altitude, how high are you actually going, the rate of ascent, the degree to which someone is pre acclimatized, like have you ever been to altitude? Have you been going to altitude over the course of the last few weeks and now you're going a little higher than before? And that kind of a thing. And then the rest of it is literally individual susceptibility.

Erin Welsh: Weird.

Erin Allmann Updyke: And that we just don't know.

Erin Welsh: Okay.

Erin Allmann Updyke: There's no differences in terms of other disease states, even when it comes to like lung disease. With HAPE, the one exception is that someone with a history of HAPE has an over 60% chance of getting HAPE again if they go to that same altitude.

Erin Welsh: But not things like chronic lung conditions or age?

Erin Allmann Updyke: Not even age. Older individuals seem slightly more susceptible than younger adults and children but not even dramatically so. Things like smoking and alcohol use do not increase the risk of AMS. Erin, I can see your face.

Erin Welsh: This is wild. Yeah, this is not what I expected.

Erin Allmann Updyke: I know. It's really, really interesting. Having a history of migraines may be a very minor risk factor, very minor. That's it, that's it. That's the only thing.

Erin Welsh: Wow. Okay.

Erin Allmann Updyke: I know. Treatment, which you asked about-

Erin Welsh: Yes.

Erin Allmann Updyke: (old-timey voice) An ounce of prevention is worth a pound of cure!

Erin Welsh: Love the accent.

Erin Allmann Updyke: Thank you.

Erin Welsh: That was magnificent.

Erin Allmann Updyke

1940s? I don't know. So really the major way to prevent this is to ascend slowly, that's it, that's the number one thing. And I'm not going to tell you exact numbers on this because even all of the recommendations on the slowness or quickness of your ascent and how many rest days are based purely on observational studies, there's no randomized control trials, it's not like real data that we can base it on.

Erin Welsh

Right.

Erin Allmann Updyke

And every individual has different tolerances, etc. So anyways. But there are also medicines that we can use to reduce the risk of AMS and/or help treat AMS. And because HACE and to a lesser extent HAPE are thought to be all reflective of this impaired acclimatization process, in theory these medicines might also reduce your risk of those as well rather than just AMS.

Erin Welsh

Okay.

Erin Allmann Updyke

So there's a couple of different things that we can use. The main one that's often used is acetazolamide which acts both to stimulate respiration at least a little bit and then is also a mild diuretic. So this helps to increase our plasma volume and increase hemoglobin concentration to basically just jumpstart or boost our normal acclimatization process. Dexamethasone or steroids is the other thing that we use to do similarly.

Erin Welsh

Okay.

Erin Allmann Updyke

There's some limited evidence for things like ibuprofen but I don't know that there's super great evidence for any of those other things. And beyond that, for anything severe, it's access to increased oxygen, so pure oxygen on the face, and descent immediately to lower altitudes.

Erin Welsh

Right. It is I guess maybe not easy but straightforward.

Erin Allmann Updyke

Straightforward and logical, just like in our bends episode.

Erin Welsh

Yep, precisely.

Erin Allmann Updyke

Yeah. AMS, which is by far the most common form that we see, can often be treated conservatively, so without having to descend to a lower altitude, with just rest, rehydration, treating the headache, and then just waiting it out before ascending to further altitudes. But again, we worry about progression to HACE. So that's terrifying.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. A quick side note. When I said that alcohol use, for example, doesn't increase your risk of AMS or HACE, this is true but alcohol and other medications like sleeping medications, etc, can depress the hypoxic drive to breathe so might worsen hypoxemia, might worsen any hypoxemia that does exist. But there have been no trials that show that conclusively. Just so you know. So that is all acute mountain sickness, altitude sickness. But that's not the end quite, Erin. There's also chronic mountain sickness. And this is what can happen when someone lives at altitude for, we're talking like their whole entire life and continues to grow in age at altitude.

What we see in chronic mountain sickness is what's called a polycythemia or an increased overall red blood cell mass to an extent that is problematic, coupled with a decreased ventilatory drive which we think maybe in part just happens with age. But this leads essentially to chronic hypoxia. So what we see is very, very high hemoglobin levels, very high hematocrits, along with chronic hypoxia, which the symptoms of that might mean dilated blood vessels because again your blood vessels are trying to get this oxygen to our tissues. We can see cyanosis, so skin turning blue. And then a host of complications that can arise from just how high these hemoglobin levels can get. And again here we don't fully understand this process. But what I really didn't realize is that it's estimated to affect like 5-10% of people potentially that live at very high altitudes for the entirety of their lives.

Erin Welsh

It's really interesting. Yeah.

Erin Allmann Updyke

Yeah, it's really interesting. There's a lot. Erin, I don't even know how to ask. How did we get here I guess?

Erin Welsh

Well I'll take us on some kind of journey. And I'll get started right after this break.

TPWKY

(transition theme)

Erin Welsh

The history of altitude sickness can be framed around a single word, hypoxia.

Erin Allmann Updyke

Oh yeah.

Erin Welsh

We learned in the biology section that hypoxia means that there are low levels of oxygen in your tissues. Now let's take a step back and consider all of the layers of knowledge that go into that word. What are all the things we have to know in order to understand hypoxia in the context of altitude sickness? Well we have to know what are considered normal levels of oxygen in our tissues and how a decrease can be detrimental to our health, which means we have to know how to measure oxygen concentration in tissues. We have to know how oxygen gets into our tissues and the role that it plays in our bodies, which means understanding cellular respiration as well as how our lungs function with our circulatory system. We have to know what things can cause oxygen levels to drop and why.

In the context of altitude sickness, this means that we have to know the relationship between altitude and oxygen, which requires knowing about how atmospheric pressure behaves under certain conditions and the composition of air, which means we have to know what oxygen is. So in this one word, hypoxia, there are crammed hundreds of years of scientific investigations and observations, integrating knowledge from disparate fields from anatomy and physiology to chemistry and the properties of gasses.

Erin Allmann Updyke

I love this already, Erin. You've hooked me.

Erin Welsh

Good, that was my goal. But I just felt like it's so easy for us today to take this word for granted along with the knowledge that goes into it. Which is why my goal for this history section is to take us through how we fit those puzzle pieces together to gain a big picture understanding of why high altitudes affect us the way they do. Kind of like with our bends or decompression sickness episode where I barely talked about scuba, the history of altitude sickness, as I am choosing to tell it, you could tell it a number of different ways, is not one filled with the daring exploits of a bunch of dudes attempting to climb the world's tallest mountain and learning that life at altitude is very dangerous.

Erin Allmann Updyke

Honestly, thank goodness.

Erin Welsh

There are many books out there if that's what you're interested in. But instead this is going to be a history of scientific discovery, of the big moments in physiology and chemistry that brought us from not knowing that air exerts pressure or that oxygen existed, having no idea what the lungs actually do or why high altitude makes you sick, all the way to breezily using the word hypoxia, dropping it in a sentence.

Erin Allmann Updyke

I love it. Thrilled.

Erin Welsh

Now that I've said what this history does include, let me tell you what it doesn't. Namely the evolutionary aspects of life at high altitude. For that piece of the puzzle we're going to be chatting with, as we mentioned, a very special guest later in this episode who is going to share some fascinating information on how certain animal and human populations have adapted to living at high altitudes, how varied those adaptations can be, and what high altitude adaptation can tell us about human health.

Erin Allmann Updyke

I cannot wait.

Erin Welsh

I know, I'm really excited. But first we've got a whole history to get through. As we'll learn more about, humans have been living at high altitudes for tens or even hundreds of thousands of years as well as just traveling through certain areas that are at high altitude. So we as humans have likely noticed the effects of high altitude on our health for a very long time. Observations of high altitude are scarce or close to nonexistent in Ancient Greek and Roman medical texts, although scientists in the 17th century believed that Greek and Roman physicians were well aware of the dangers of high altitude. From an English translation of Francis Bacon, quote: "The ancients also observed that the rarity of the air on the summit of Olympus was such that those who ascended it were obliged to carry sponges moistened with vinegar and water and to apply them now and then to their nostrils as the air was not dense enough for their respiration."

Erin Allmann Updyke

Ooh.

Erin Welsh

And so the sponge part shows that people believed that it was the lack of water vapor in the air at high altitude that made it difficult to breathe.

Erin Allmann Updyke

Interesting.

Erin Welsh

Because they didn't know what oxygen was yet. Okay. It's possible that we simply haven't found the Ancient Greek and Roman references to altitude sickness but there are certainly descriptions of the negative effects of high altitude in Ancient Chinese texts. In a classical history text from the 1st century CE, there is a description of an envoy traveling over mountainous terrain around 37-32 BCE. And this envoy was warned of the danger along the route. Not just in terms of the robbers known to frequent the area but also because of the terrain. Quote: "Again on passing the Great Headache Mountain, the Little Headache Mountain, the Red Land, and the Fever Slope, men's bodies became feverish, they lose color, and are attacked with headache and vomiting. The asses and cattle being all in light condition."

Erin Allmann Updyke

Ooh. Great Headache Mountain and Little Headache Mountain.

Erin Welsh

And 400 years later, also from Ancient Chinese texts, is where we find what is likely the first description of high altitude pulmonary edema, HAPE. Quote: "Having stayed there till the third month of winter, Fa-hien and the two others proceeding southwards crossed the little snowy mountains. On them the snow lies accumulated both winter and summer. On the north side of the mountains in the shade, they suddenly encountered a cold wind which made them shiver and become unable to speak. Hwuy-king could not go any farther. A white froth came from his mouth and he said to Fa-hien, I cannot live any longer. Do you immediately go away that we do not all die here. And with these words, he died." Endquote.

Erin Allmann Updyke

Gosh.

Erin Welsh

Yeah. But the frothy mouth could be-

Erin Allmann Updyke

Frothy sputum, can't breathe.

Erin Welsh

Yeah. We have to jump ahead quite a bit in time to about the 1500s before we find more mentions of altitude sickness, beginning with those given by the Jesuit priest Father José de, Acosta who described the headache, nausea and difficulty breathing that appeared when he was at high altitudes in the Peruvian Andes. And he wasn't the only Jesuit priest who noticed these effects. Shortly after Father Alonso de Ovalle wrote in the early 1600s that quote "when we come to ascend the highest point of the mountain, we feel an air so piercing and subtle that it is with much difficulty we can breathe, which obliges us to fetch our breath quick and strong and to open our mouths wider than necessary." I mean yeah.

Erin Allmann Updyke

Love it.

Erin Welsh

These various descriptions of altitude sickness clearly demonstrate that yes, people noticed the effects of altitude and some even went as far as to explain, in vague terms anyway, why this thin air or subtle air made you feel this way. But to them, the air was thin because it didn't have much moisture, it was dry. When did thin air come to mean what it does today? In other words, when did people discover atmospheric pressure and oxygen? As it turns out, at very different times. Let's start with the discovery of atmospheric pressure because if you want to know what's in the atmosphere, like oxygen, you first have to know that the atmosphere exists and you have to understand how it behaves.

Like today, if you tune into a weather forecast you may hear something about a low pressure or a high pressure system, like a low pressure system is moving into the Four Corners region today, bringing with it gusty winds, hail, frequent lightning, and heavy rainfall. And that forecast probably wouldn't even register or make you do a double take unless your car was out in the open and you're like oh my god, hail, what am I gonna do? But it would make Galileo for instance do a double take as well as many other scientists of the early 17th century because they did not believe that air weighed anything or exerted any pressure.

We know today of course that it does, that atmospheric pressure can be thought of as how much the air weighs or is pressing down on you and that things like temperature and weather and altitude can affect this pressure. For instance, when you go closer to sea level, that air presses down on you more and more and as you ascend, it presses down less and less. And we know these things today about atmospheric pressure in large part thanks to one of Galileo's students, Evangelista Torricelli, who invented the first barometer which is a tool of course to measure the level of atmospheric pressure.

Erin Allmann Updyke

I love this.

Erin Welsh: I am going to attempt to explain what Torricelli's barometer looked like and how it worked so that we can picture how air pressure changes, like how you can see that happening.

Erin Allmann Updyke: Okay.

Erin Welsh: Okay. Imagine a test tube, right, a long test tube. One end is open. Fill it with a liquid, let's go with mercury.

Erin Allmann Updyke: Okay.

Erin Welsh: And then imagine a little dish that you also fill with mercury. You're gonna plug the open end of that test tube with your thumb, right.

Erin Allmann Updyke: Okay.

Erin Welsh: And then you're gonna flip it over so that the plugged end is in the dish of mercury. By the way, don't try this at home.

Erin Allmann Updyke: Okay.

Erin Welsh: Don't do this. And it's standing upright.

Erin Allmann Updyke: Okay.

Erin Welsh: Then you're gonna quickly remove your thumb plug, trying to let no air in, right, so it's already under the mercury level.

Erin Allmann Updyke: Right.

Erin Welsh: And when that happens, a little head space will appear at the top of the test tube as the atmospheric pressure outside of the tube equalizes with the pressure inside, right. So now you have this upside down test tube that contains mercury with a little bit of head space in this dish that also has mercury level, right.

Erin Allmann Updyke: Sorry, did I fill the test tube completely or was it half full?

Erin Welsh: Completely.

Erin Allmann Updyke: Completely full. Okay, okay. Cool, cool, cool.

Erin Welsh: And so right now everything, all the pressures have equalized. The air is pressing down on the mercury in that dish to keep it at that level. If the air pressure increases, like let's say you go below sea level, the air will press down more on the mercury in the dish, forcing the level in the tube to climb a bit higher. And if air pressure decreases, maybe because you went up in altitude, then air will press down on the mercury in the dish less, allowing the outside level of mercury to rise and the level of mercury in the test tube to drop. So there's more head space.

Erin Allmann Updyke: Okay, I think I'm there.

Erin Welsh: Okay, okay.

Erin Allmann Updyke: Because you're pushing down on the dish if your pressure is increasing, you're pushing more on that. So that's going to push up on the mercury in the tube because they're connected in there. And then the opposite is going to happen if you release that pressure, then that's going to drop. Yeah, I got it.

Erin Welsh: Yeah, isn't that cool?

Erin Allmann Updyke: Yeah, yeah.

Erin Welsh: So that was Torricelli's barometer.

Erin Allmann Updyke: Okay.

Erin Welsh: And this is a really remarkable device because with it he showed that the air around us does exert pressure and that pressure can change.

Erin Allmann Updyke: The part that gets me is I can follow your logic of how he got there but why did he do that?

Erin Welsh: Why did he do it in the first place?

Erin Allmann Updyke: What made him think of doing that thing in the first place? And was that what he was trying to show?

Erin Welsh: Yes.

Erin Allmann Updyke: Okay.

Erin Welsh: Yeah. So he was trying to show that, I think it was sort of like Galileo and others believed that the air exerted no pressure, but I think it was kind of beginning to be more of a contentious issue.

Erin Allmann Updyke: Okay.

Erin Welsh: And I can't remember the exact sequence of events or how I read it but yeah, he just decided to test this out.

Erin Allmann Updyke: How does your brain think of that before it's ever been done? I just love that.

Erin Welsh: This is why I loved this history so much because there's so much more of that in here.

Erin Allmann Updyke: Yeah.

Erin Welsh: Torricelli also went so far as to suggest that the air on top of a mountain weighed less and thus exerted less pressure than air at sea level. But he didn't demonstrate it with his barometer. That honor would fall to Blaise Pascal, child prodigy, philosopher, mathematician, all around pretty famous dude, you've probably heard his name before.

Erin Allmann Updyke: He's a unit of measure.

Erin Welsh

There you go. So is Torricelli, torr.

Erin Allmann Updyke

Oh torr! Cool.

Erin Welsh

But it wasn't actually Blaise Pascal that would do it, it was his brother-in-law that would physically carry the barometer up the hill because Pascal was not in great health and he asked him to do it and report back.

Erin Allmann Updyke

Cute.

Erin Welsh

Well when brother-in-law came back down the hill he was super pumped to tell Pascal that yes indeed, the liquid dropped. And while this result was somewhat expected, this ground truthing of the concept was a really exciting development and it allowed Pascal to extend the logic about altitude and atmospheric pressure to suggest that the human body and pressure throughout the body in blood, tissues, etc, is also subject to atmospheric pressure changes such as those you may experience if you go up in altitude.

Erin Allmann Updyke

I love it.

Erin Welsh

But just like Torricelli, Pascal left the experimental demonstration of this concept to others.

Erin Allmann Updyke

Okay.

Erin Welsh

At this point in the story, the mid 1600s or so, we're slowly building our understanding of how the atmosphere works, how it exerts pressure, and how that pressure changes based on things like temperature or altitude. But how do we relate this to the human body in like a demonstrable way or any vertebrate's body really? For that we'll need a couple of Roberts, Boyle and Hooke. You may remember me mentioning some of Robert Boyle's experiments with air pressure and vacuums on animals in the 1670-1680s during our bends episode. Like remember the bubble in the viper's eye as the first observation of decompression sickness? Well it turns out that Boyle and Hooke, they worked together a lot, so a belated apology to Hooke for leaving him out of the bends episode.

This pair did many more experiments using an air pump to investigate animals' responses to air pressure, such as testing how long animals could survive at different pressures, clearly demonstrating that at lower pressure survival was shortened. Hooke didn't stop with animal experimentation however, he also devised a decompression chamber that humans could sit in to experience the effects of low pressure, testing it out of course on himself. He sat in his chamber for about 15 minutes at a pressure of about 570 torr or the equivalent of 2400 meters, 7800 ft, experienced a little bit of hearing loss and the candle he brought in with him extinguished long before time was up. No fresh air was being pumped in by the way. The why of this, why survival was shorter at lower air pressures, why a candle would extinguish, why low air pressure led to certain symptoms, this why was still a big unanswered question, one that Hooke and Boyle would begin to scratch the surface of with their experiments on animal respiration. Because remember at this point, no one knew what precisely the lungs did or what oxygen was.

Erin Allmann Updyke

Right, right.

Erin Welsh

And I just want to pause and say how amazing it is that so many things are fitting together in terms of other topics we've talked about on the podcast before. Like I also mentioned Hooke during our RSV episode when I talked about the development of artificial respiration.

Erin Allmann Updyke

Ooh yeah.

Erin Welsh

And his experiments on this subject would prove to be key to getting at this question of why. This period during which Hooke and Boyle were active in their research followed close on the heels of a time when anatomical dissections of both animals and humans had greatly increased in popularity, being seen as not as sacrilegious as they had been in the past. These dissections and the beautifully illustrated anatomy books that were created by people like Andreas Vesalius encouraged physicians and scientists to link form with function. We can draw the circulatory system, the major arteries and veins, the ventricles of the heart. But how did the heart pump blood? What role did the lungs play in the circulation of blood? Obviously animals needed to breathe air using their lungs to stay alive, which Hooke demonstrated with his dog experiment that I mentioned in the RSV episode where he uses bellows through a cut in the dog's lungs.

Erin Allmann Updyke

Right.

Erin Welsh

Yeah. But how did the lungs do this?

Erin Allmann Updyke

Right.

Erin Welsh

And why did all the blood pass through the lungs? Was it to cool the blood down, which was Galen's thought that still predominated during this time, or was it something else in the air that was essential for survival? Clearly the lungs did something. Hooke's colleague Richard Lower performed an experiment in 1669 where he compared the blood that had passed through the lungs with fresh air, like the lungs had just had fresh air-

Erin Allmann Updyke

Okay.

Erin Welsh

With venous blood. And noticed a stark difference in color, with the freshly ventilated blood being bright red and the venous blood a much darker red. What this color difference meant wasn't clear but it did show that when blood came into contact with fresh air in the lungs, something changed. And around the same time, Malpighi shed light on that lung-blood interface through his descriptions, the first of the alveoli and the pulmonary capillaries that linked the arteries and veins, descriptions that were made possible due to the increasing popularity, availability, and technological advancements of the microscope.

Erin Allmann Updyke

Oh my gosh, it all comes full circle.

Erin Welsh

It all comes full circle. So now people were able to make the connection that fresh air inhaled through the lungs changes the blood through these structures that Malpighi described.

Erin Allmann Updyke

Wow.

Erin Welsh

But what about that fresh air was so important? Was it the air as a whole or was it a particular component of that fresh air? Jon Mayow, a contemporary of Hooke and Boyle, began to suspect that it was the latter, that air was not uniform but made up of at least two distinct substances. One that was involved in combustion and respiration, and one that was not. He set out to test his hypothesis with a pretty cool experiment in my opinion, so I want to describe it here. First he filled a shallow dish with water.

Erin Allmann Updyke

Okay.

Erin Welsh: Think of like a dog water bowl.

Erin Allmann Updyke: Okay.

Erin Welsh: Then he put a taper candle standing upright in that water, lit it, and then put a glass bell over it.

Erin Allmann Updyke: Okay, yeah.

Erin Welsh: With the open end extending down into the water and resting on the bottom of the dish, effectively sealing the bell off along with the candle inside of it.

Erin Allmann Updyke: Right.

Erin Welsh: He observed that as the candle burned, the water level inside the bell rose, which suggested to him that the flame was consuming some part of the air which the water came in to fill. And when that portion of air was used up, the flame went out, which it did.

Erin Allmann Updyke: Oh my goodness.

Erin Welsh: Very cool. He then replicated this experiment but instead of a candle, he put a little mouse alive on a stool and covered it with a glass bell. Again he saw that the water level inside the bell rose as the animal breathed.

Erin Allmann Updyke: Stop it.

Erin Welsh: And at a certain point, all of the respiration air component was used up and the animal died.

Erin Allmann Updyke: This is very cool. I mean not for the mouse.

Erin Welsh: No, I know, I know. But just to think of the these things, these are like principles, major principles.

Erin Allmann Updyke: Right.

Erin Welsh: That are being uncovered through beautiful experiments that...

Erin Allmann Updyke: I feel like this is something that maybe they offhandedly mentioned during like a chemistry or a physics class at some point. But it was like in the middle of 16 different equations And I was like why do I have to learn this? But now it's like without the equations, it's so cool.

Erin Welsh: And that's a lesson for life, everyone. These simple experiments by Mayow were groundbreaking for a couple of reasons. One was that they showed that air was made up of at least two different components and that the second was that one of those components was crucial for both combustion as well as animal respiration.

Erin Allmann Updyke: And did he assume that this must be the same component?

Erin Welsh: Yes.

Erin Allmann Updyke: Because that's also an interesting conclusion, right?

Erin Welsh	Yes.
Erin Allmann Updyke	Why combustion and respiration?
Erin Welsh	Right. So he thought that there were two components of air.
Erin Allmann Updyke	Okay.
Erin Welsh	Like only two components. One that was usable and one that was more inert, I guess.
Erin Allmann Updyke	Okay, yeah.
Erin Welsh	And that was something that Hooke and Boyle hadn't picked up on. But I want to read this quote from Lavoisier from about 100 years later.
Erin Allmann Updyke	Okay.
Erin Welsh	Quote: "Respiration is nothing but a slow combustion of carbon and hydrogen, similar in all respects to that of a lamp or a lighted candle. And from this point of view, animals which breathe are really combustible substances, burning and consuming themselves."
Erin Allmann Updyke	I love it, it's beautiful.
Erin Welsh	Yeah. Okay. And we'll get back to Lavoisier in a second. But also Mayow didn't stop there with these experiments. He went on to suggest that this component of air, the one that's involved in respiration and combustion, is taken up by the lungs and passed into blood where it is involved in heat production and muscle movement, which he pointed out was why breathing increases during exercise since you need more of this substance in the air to move. Amazing. All right, so we've covered a lot of ground. So let's take stock briefly of what we've learned so far.
Erin Allmann Updyke	Yeah.
Erin Welsh	We learned that the atmosphere exerts pressure, pressure that can be measured and that can change based on several different factors including altitude.
Erin Allmann Updyke	Okay.
Erin Welsh	We've learned that air is not just one homogeneous substance, that it is actually made up of several different components, at least one of which is necessary to sustain life and a candle flame.
Erin Allmann Updyke	Okay.
Erin Welsh	Through some process involving respiration via lungs and the exchange of venous and arterial blood in the lungs.
Erin Allmann Updyke	Okay.
Erin Welsh	And we learned all of that over the course of just a few decades in the 17th century.

Erin Allmann Updyke

So now we're still in the late 1600s still.

Erin Welsh

Roughly. Now we're probably going mostly into the early to mid 18th century, 1700s, yeah.

Erin Allmann Updyke

Okay. 1700s. Okay. Cool, cool, cool.

Erin Welsh

And I really kind of feel that at this point the discovery of oxygen itself as one of those components or the naming of it seems almost anticlimactic. What doesn't help is that there seems to be a good deal of contention over who gets priority for the discovery. As far as I could gather, there are four contenders for the title. Joseph Priestley, Carl Scheele, Henry Cavendish, and Antoine Lavoisier. And I'm not going to go into how each of them quote unquote "discovered" oxygen or the contribution they made. But in general, all of these discoveries involved the burning of an oxide of some sort in a sealed chamber and the realization that the released gas from that burning oxide could sustain life longer than ordinary air in the same type of chamber.

Erin Allmann Updyke

Okay.

Erin Welsh

Yeah. These experiments also helped to lay the groundwork for describing the properties of other components of air besides oxygen, including carbon dioxide and nitrogen. So Lavoisier, the person who gets credit not so much for the priority but the most impactful early research done on oxygen, in 1771 described these gasses role in respiration as such. Quote: "Eminently respirable air," which he later called oxygen, "that enters the lungs, leaves it in the form of chalky aeroform acids," carbon dioxide, "in almost equal volume. Respiration acts only on the portion of pure air that is eminently respirable. The excess, that is its mephitic portion," nitrogen, "is a purely passive medium which enters and leaves the lung without change or alteration. The respirable portion of air has the property to combine with blood and its combination results in its red color." At this point in the story, I wouldn't blame you if you asked but what about altitude sickness? Isn't that what the episode is about?

Erin Allmann Updyke

Honestly I'm enjoying this so much that like...

Erin Welsh

Good. Well if you listeners out there have been waiting for some mention of altitude sickness in the history section, your long wait is almost over. And I appreciate your patience. I wanted to go into how these connections were made between the atmosphere and altitude and respiration and oxygen because they are fundamental to understanding so many things, including the effects that altitude has on our bodies, something that people were about to experience in ways they never had before.

Erin Allmann Updyke

Ooh, because?

Erin Welsh

Because balloons.

Erin Allmann Updyke

Balloons though.

Erin Welsh

I know. Well think about it.

Erin Allmann Updyke

I would never have guessed balloons even if I thought about it, Erin. I don't often think about balloons.

Erin Welsh

Well you're going up super high, super fast.

Erin Allmann Updyke

I know. But I forget that balloons are a thing that people decided to jump in at some point. Who, why, what?

Erin Welsh

They still do. There are many people that still do hot air ballooning.

Erin Allmann Updyke

I would love actually to go and a hot air balloon is on my list. But still.

Erin Welsh

I know, I know. I did not expect it either but I was pleasantly surprised. So as Lavoisier was characterizing these gasses that are involved in respiration, other scientists were seeing how they could turn this new information about these and other gasses into application, especially in the context of controlled combustion. Perhaps using combustion to power some sort of vehicle, say a balloon that could travel long distances both across the landscape as well as vertically.

Erin Allmann Updyke

Say a balloon.

Erin Welsh

Say a balloon. People had for hundreds of years, like I've said now 1000 times, climbed mountains or crossed mountain passes or lived at high altitudes. And many people, most people who experienced those things or lived at altitude recognized and noted the signs and symptoms of being at high altitude. But these at least in the written literature often tended to be isolated descriptions and didn't necessarily lend themselves to systematic study, which was the opportunity that hot air balloons provided. Along with being able to see the effects of high altitude, namely acute and extreme hypoxia, separate from the physical exertion of climbing a mountain with no time for acclimation.

Erin Allmann Updyke

Yeah, that's really interesting.

Erin Welsh

Yeah. These early hot air balloonists were reaching heights of 6000, 7000, even 9000 meters.

Erin Allmann Updyke

Oh my.

Erin Welsh

So 9000 meters is 29,500 ft, which is taller than Everest.

Erin Allmann Updyke

Don't go there.

Erin Welsh

Don't, no.

Erin Allmann Updyke

Don't. Don't do it.

Erin Welsh

Yeah. And they were doing this within a matter of minutes.

Erin Allmann Updyke

Yeah.

Erin Welsh

And so of course they noticed that as they ascended, breathing became more and more difficult, their heart beat faster and faster, and they became confused and tired, often hit with this massive headache. And even though they could recognize that altitude had this effect, they weren't sure how and had yet to make the link that as air pressure changed, so did pressure in blood and tissues. Experiments in decompression chambers, mainly by Paul Bert who we'll meet in a bit, had shown that supplemental oxygen could be helpful for keeping symptoms at bay at higher altitudes, but only if you use it. So in the firsthand account that I read, the people in that balloon were carrying oxygen but not enough of it and they didn't use it until it was too late. So he talked about how he was grabbing for the oxygen but couldn't do it.

Erin Allmann Updyke

Right.

Erin Welsh

But while these balloon excursions demonstrated the potentially deadly effects of rapid ascent to extreme altitude, they're not quite the same as altitude sickness or acute mountain sickness. But don't fret because as balloons were getting more popular, so was mountaineering, which had been popular for hundreds of years but the sport underwent a big boom during the period of widespread colonization by European nations, often pleasantly called something like the Golden Age of Exploration, particularly during the mid 1700s and into the 1800s. Naturalists with an interest in mountaineering like Alexander Von Humboldt or mountaineers with an interest in science like Edward Whymper, set their sights on various mountain peaks. The Matterhorn, Chimborazo, Mont Blanc, etc. And as they learned how to set a route or which gear was best, they also learned to recognize the signs and symptoms of mountain sickness and they wrote about their experiences.

And so at this point in the story, I should probably introduce the quote unquote "father of modern high altitude physiology and medicine", Paul Bert. When Bert enters the picture around the 1860s/1870s or so, what we get is a switch from the largely anecdotal reports of the effects of altitude from mountaineers and balloonists to a systematic study analyzing what was happening to your body physiologically when you go up in altitude. And with the patronage of a Parisian physician, Denis Jourdanet, who also had an interest in high altitude medicine, Bert conducted a series of experiments where he put animals in hypobaric chambers which simulated the low pressure of high altitude. He then played around with pressure levels until the animals became sick or died. And then he measured the amount of oxygen in their blood.

What he found was that illness or death always occurred at a certain level of blood oxygen. But even more than that, he repeated this experiment where he kept the air pressure at sea level but he lowered the overall oxygen concentration in the air. Again he played around with oxygen concentrations in the air and watched for when the animals got sick or died and then measured their blood oxygen. He found that regardless of whether he lowered the pressure or lowered the oxygen concentration, the animals got sick or died when their blood oxygen hit a certain point. Basically he showed that it mostly came down to oxygen.

Erin Allmann Updyke

Yeah.

Erin Welsh

He also plotted the first oxygen dissociation curves.

Erin Allmann Updyke

Oh that's cool.

Erin Welsh

Yeah.

Erin Allmann Updyke

I love those.

Erin Welsh

This finding was important both because it filled in a piece of the conceptual puzzle of high altitude physiology and also because it provided a relatively straightforward way to treat the negative health effects of high altitude. More oxygen whether by descending or through use of supplemental oxygen. Although whether supplemental oxygen was actually helpful was under debate for a surprising number of decades after this. This also raised the question of whether humans could get used to high altitudes and compensate for the lower oxygen in some way if they spent enough time up there. And like I said many times, people did and do live at high altitude in cities such as La Paz and Bolivia, which is at a whopping 3600 meters or nearly 12,000 ft in elevation.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. Bert speculated that people and other animals who had sustained exposure to high altitude may produce more red blood cells for increased oxygen absorption, which was later proven correct. And after Bert's extensive research into high altitude physiology, the field really kind of opened up in the last couple of decades of the 1800s, with high altitude field stations established and expeditions organized to remote high altitude locations. These stations also served as home bases where people could study other disciplines such as astronomy, physics, and glaciology. And in some places like Pikes Peak in Colorado which is at 4300 meters or 14,100 ft or La Oroya in Peru which reached an altitude of 4800 meters or 15,700 ft. Railways were constructed to these sites so that the general public could also see what things were like above the clouds or so people could mine. Side note, La Oroya might sound vaguely familiar to you because I've mentioned it on the podcast before. In our Bartonella episode, I talked about how at least... I know, cast your mind back.

Erin Allmann Updyke

Right.

Erin Welsh

But in that episode I talked about how at least 4000 people died while working on the railroad to connect Lima to La Oroya.

Erin Allmann Updyke

Oh yeah.

Erin Welsh

This same railroad. And these 4000 or so people died from Bartonella bacilliformis, aka Carrion's disease.

Erin Allmann Updyke

Wow.

Erin Welsh

Isn't that... Connections.

Erin Allmann Updyke

There's so many, Erin.

Erin Welsh

I love that. By the early 20th century, scientists had made tremendous strides in understanding the relationship between altitude, oxygen, and health. But there were still a ton of details to be figured out, like how mechanistically oxygen is used and how it acts in various tissues as well as the steps involved in cellular respiration. That however, don't worry, is a topic for another day.

Erin Allmann Updyke

I was like oh gosh.

Erin Welsh

Yeah. And instead I want to close out this history section by talking about how the clinical picture of acute and chronic high altitude sickness and complications was filled in over the 20th century. This is the last time I'll say it but it bears repeating that not only have people lived at high altitude for tens of hundreds of thousands of years, but they've also recognized the negative health consequences of high altitude. And that's evidenced by the fact that there are many different local and regional names for altitude sickness. One of these was picked up by researcher Thomas Holmes Ravenhill who published a paper in 1913 titled quote "Some experiences of mountain sickness in the Andes." Endquote. In this paper, he classified mountain sickness into three primary forms. Puna of a normal type, puna was the word for mountain sickness that people in northern Chile used where Ravenhill carried out his studies, and that is what we would call today acute mountain sickness. And then two divergent types. Puna of a cardiac type, high altitude pulmonary edema.

Erin Allmann Updyke

Okay.

Erin Welsh

And number two, puna of a nervous type, high altitude cerebral edema.

Erin Allmann Updyke

Yeah.

Erin Welsh

Ravenhill's work was largely overlooked though until the 1960s when it was quote unquote "rediscovered". But in the meantime, a good deal of research on altitude sickness and severe outcomes was conducted primarily by South American researchers, including Leoncio Lizárraga Morla, who described the first cases of HAPE in Peru. In all of their publications, these researchers noted how quickly the affected person recovered after descending to a lower altitude, which is a useful thing to know. But their work was not really acknowledged likely because of the bias against scientific publications not written in English. And this is notable when high altitude pulmonary edema was quote unquote "rediscovered" in the US by Charles Houston in his 1968 New England Journal of Medicine paper, quote "Acute pulmonary edema of high altitude."

In this paper, he described a 21 year old skier in Colorado who developed quote "severe dyspnea, weakness, and cough" and had to be evacuated. At the hospital he was observed to have a bluish tint to his skin, difficulty breathing, and rattling in the lungs, but no evidence of heart disease. Houston suggested that quote "both acute and chronic anoxia may cause striking elevation of the pulmonary artery pressure, failure of the left ventricle, and pulmonary edema. Since exercise and severe cold, together with anoxia may have cumulative effects, this explanation appears to be the most probable." Endquote. You may have caught that in that description Houston also mentioned chronic anoxia which had been an area of interest for several researchers for decades. And that is the physiological changes that occur when spending time at high altitude as well as comparing populations of humans and other animals that had spent generations at high altitude with their lowland counterparts. One of the most prominent research in this area was Carlos Monge Medrano, who in the mid 1900s characterized chronic mountain sickness, sometimes called Monge's disease.

By this period, the field of high altitude physiology had grown immensely, helped along by military investigations during WWII into how pilots performed at certain altitudes, when to deploy oxygen, etc. By veterinary studies exploring how to breed cattle that thrived at altitude. And it was also helped along by medical researchers wanting to know how low oxygen levels from other things besides altitude, like decreased lung function, could be treated. And also by ecologists and evolutionary biologists who wanted to tease apart questions like do all mammals acclimate to altitude in the same way? What is the genetic basis of high altitude adaptation in humans? Are there ways that mammals evolve to live at high altitude predictable? And so many more.

Erin Allmann Updyke

So many.

Erin Welsh

So many. And here today to answer some of these questions is a very special guest, Dr. Jonathan Velotta, assistant professor at the University of Denver and my partner. We'll take a quick break here and then hear what Jon has to say about the evolutionary basis of high altitude adaptation.

Erin Allmann Updyke

Oh, it's going to be so good.

Erin Welsh

I'm really excited.

TPWKY

(transition theme)

Jonathan Velotta

Hi, I'm Jon Velotta. I'm an Assistant Professor of Biology at the University of Denver, my lab studies evolutionary biology and physiology of vertebrates. So we're interested in how animals have adapted to their environment at the physiological and genetic levels. One of the big things we're working on right now is adaptation to low oxygen and cold in a high altitude rodent, that's the North American deer mouse. But we also study the genetics and the physiology of ion and water balance evolution in species of fish.

Erin Allmann Updyke

I love it. I'm so excited.

Erin Welsh

It's really funny to say thank you so much for joining us today because we literally live together.

Jonathan Velotta

I'm right here.

Erin Allmann Updyke

I am looking at a Skype screen that's the two of them but they're actually just sitting right next to each other in the same room. It's fantastic.

Erin Welsh

Also I love that we are probably still two of the only people left in the world that use Skype.

Erin Allmann Updyke

Yes.

Jonathan Velotta

Yeah.

Erin Welsh

I think we have a little bit of superstition in terms of like let's not mess this up, we know that this works.

Jonathan Velotta

There are Gen Zers that don't know what Skype is.

Erin Welsh

That's actually true.

Erin Allmann Updyke

Well then.

Erin Welsh

All right, well let's actually get into why we have Jon here today.

Erin Allmann Updyke

Yeah.

Erin Welsh

Not just to talk about the pros and cons of Skype. And that is evolutionary adaptation to high altitude.

Erin Allmann Updyke

Yeah.

Erin Welsh

One of the aspects that I was thinking about though is just how difficult life at high altitude seems, right. Everything is cold.

Erin Allmann Updyke

Everything is cold all the time.

Erin Welsh

There's no oxygen, the sun is trying to kill you with high UV, you're dehydrated all the time. Why live at high altitude? Are there any benefits for animals living at high altitudes?

Jonathan Velotta

That was a question for me? Okay. Oh you forgot one which is that food is scarce, obviously.

Erin Welsh

Oh yeah.

Jonathan Velotta

So yeah, the challenges of high altitude obviously are hypobaric hypoxia as Erin mentioned. And so few animals really can and do live there and so that means that there's just fewer predators and competitors. So basically if you can deal with the environmental challenges then it's a fairly good place to live. So North American deer mice, for example, are really the only rodent lives at high altitude in the Rockies above tree line. And there are very few larger predators there. At lower altitudes in the forests where they also live, they're hunted by owls, foxes, pine martens, so lots of things like to eat them. And so at high altitude, they're probably relatively safe. They're also safe from other competitors, other rodents that live in very similar environments and eat similar food. So in terms of environmental conditions though, it's really challenging. So yeah, like you said, if you can evolve to deal with those environmental challenges, then you're relatively safe from other things in the world that are trying to kill you. And at high altitude we do see some predators occasionally. Like we've seen pine martens hunt deer mice at the summit of some of the mountains in the Rockies but that's probably relatively rare and they're probably not there living there or there very often but just coming up and then going back down.

Erin Welsh

Like a nice easy snack.

Jonathan Velotta

Yeah.

Erin Allmann Updyke

Little day trip up to the summit for the view and a snack. So what is the highest altitude that a mammal has been found at? And also what about birds? Do they still cruise around up there?

Erin Welsh

Yeah.

Jonathan Velotta

Yeah. So recently, like in 2020, there was a new record of the highest dwelling mammal by Jay Storz and colleagues and it's a mouse called the yellow-rumped leaf-eared mouse, so this is *Phyllotis xanthopygus* is the scientific name. I had to practice that one. So actually it was captured by hand on the summit of a volcano between Chile and Argentina, it's Lullillaco is the name of the volcano. So that's 6700 meters, so it's about 21,000 ft. So some of the highest peaks in the world do have animals. There are other high altitude dwelling mammals, like there's credible records of pika which are sort of like a rabbit, closely related to rabbits, at or around I guess 6000 meters on Everest.

And so yeah, that's pretty much as high as we've ever found a mammal. And again, the leaf-eared mouse at 6700 meters is the record. So it's not like these mice are day visitors up to high altitude, their home range is very small. So for a North American deer mouse, the maximum home range is just like an acre or so. And so they're living up there which is incredible because again there's not much to eat and obviously the oxygen is very low and it's very cold all the time. So you mentioned birds. So birds are interesting because they can fly obviously. And so birds can fly as high or higher than the tallest summits in the world. So there's a couple of birds that I think are good examples.

So Nate Senner and colleagues have tracked a migratory shorebird called the black-tailed godwit at 5000-6000 meters. And the amazing thing about this is that they're not flying over anything in particular, like no land structures, they're just flying that high to take advantage of what they think are better air temperatures and solar radiation that make for more efficient flying. There are animals, there are birds that fly over the Himalaya that have been seen flying at 7000 meters. But they sort of hug the land and so for them they are more so flying over land structures, whereas the god wits are flying to take advantage of that better air. One of the last things I'll say is that they're exercising this whole time, right. Birds aren't just cruising at altitude, so they are flying and flight is an incredibly energetic activity and birds do have very efficient breathing, which is one of the things that helps them.

Erin Allmann Updyke

That is amazing that they're flying that high and not just like holding their breath to go up for a little bit and then coming back down. Like what?

Erin Welsh

Yeah, that is really cool to think about how much work they're doing at that altitude. One of the questions that I asked Erin earlier in the biology section and she said I don't know but we should ask Jon this or maybe we both did.

Erin Allmann Updyke

Put you on the spot.

Erin Welsh

Was about whether physiological responses to altitude are proportional to the altitude. So like are you producing twice as many red blood cells as you are if you go up twice as high in altitude?

Jonathan Velotta

Yeah. I mean generally I would say yes. I don't think there seems to be really a threshold and acclimatization changes are mostly linear. And I mean at least the work that I'm familiar with is in deer mice, so there's been some work by colleagues of mine, Catie Ivy and Graham Scott, that have shown that breathing for example increases pretty linearly with decreasing partial pressures of oxygen. And then we've shown that red blood cells and hemoglobin concentrations increase steadily with decreasing pressure as well. So there's not a lot of great data I guess I would say but in general I think it's pretty clear that yes, as you move up in altitude, the acclimatization responses are proportional to that decrease in partial pressure.

Erin Allmann Updyke

Cool.

Erin Welsh

There you go.

Erin Allmann Updyke

Wow. I love that it was just like a yes. Yes, moving on.

Jonathan Velotta

I guess I could have just said yes.

Erin Allmann Updyke

So we talked about during this episode that a lot of humans have lived at high altitudes, like maybe alongside these deer mice for example, for hundreds of thousands of years. So do we see any genetic adaptations to this both in humans and in these animals? And what's the difference between acclimatization, when we talk about that, and adaptation?

Jonathan Velotta

Yeah. So I guess I do want to preface this by saying that human evolution is not my field but I would like to summarize here some of the really cool work that's been done by biologists and anthropologists. A lot of the work that I think I can talk about knowledgeably is by Cynthia Bell who's an anthropologist at Case Western Reserve. And you asked about acclimatization and adaptation. So acclimatization is like all of those changes that you talked about Erin, so red blood cell production, changes in breathing, those things that happen in the short term or within the lifetime of an individual that sort of give us more oxygen when we need it. But adaptation of course is an evolutionary process, it's where we see any change but in this case physiological change that occurs over generations because those changes have some sort of advantage. And so all those changes are based on changes in our genes.

To answer your question, humans do show adaptation to high altitude and it's really interesting. And so I think the best way to look at it is to take two examples of two mountainous regions in the world where people live and where adaptations to altitude have arisen. And so these regions are the Andes in South America and the Tibetan Plateau in the Himalaya. And so there are establishments, towns, and cities, in some cases really big cities, over 4000 meters above sea level. So that's above 14,000 ft. And we see that there are genetic adaptations to high altitude that we assume come from living there over many generations. And so Erin, you mentioned chronic mountain sickness and that's the association of chronic mountain sickness with polycythemia, which is overproduction of red blood cells. And then I think you mentioned hypertension, which is high blood pressure.

And so the incidence of chronic mountain sickness in some South American high altitude cities in Bolivia and Peru can be up to 15%+ in one estimate that I saw, whereas the incidence of chronic mountain sickness on the Tibetan plateau is much lower, about 1% or less. And this is from one estimate from about 2016. And so the Tibetan plateau is I think higher on average but most of the cities in which people live are probably similar. Some of the adaptations that we see in the Andes are really interesting and they generally are larger chest circumference and a greater total lung volume. And so this is likely an adaptation to just simply get more air into the lungs. Other adaptations in the region include higher on average hemoglobin and red blood cell concentrations and I think this is intuitive based on what you said, Erin, about acclimatization because more red blood cells improves oxygenation in the blood.

And so sort of to that end, there have been studies that have shown that increased hemoglobin and red blood cells is associated with higher arterial oxygen content. So they have more oxygen in their blood, actually more than when compared to some people at sea level. And the thing about this is that it may have a cost. And this would be sort of consistent with higher rates of chronic mountain sickness because more red blood cells sort of changes the content of your blood, it makes it thicker. And that could put a strain on your heart, which is a muscle, as it's pumping a more viscous fluid. And so if you couple that with other changes that you mentioned like pulmonary vasoconstriction, which again is the constriction of the vessels in your lungs, that all puts a strain on the right part of the heart especially as it pumps a thick blood through a constricted pulmonary vasculature. And so this could lead to an increased incidence of hypertension.

And not humans but I could talk about deer mice a little bit, just something I'm always finding myself talking about. They also have this increase in blood viscosity and vasoconstriction and this leads to an increase in the actual size of the right ventricle of the heart. And it leads to an increase in the pressure in the right ventricle which can contribute to things like heart failure. So yeah, that's some of the adaptations that are happening in the Andes. On the Tibetan plateau we see slightly different adaptations and this is really fascinating. Instead of lots of red blood cells which would increase oxygen carrying capacity, studies find that the concentration of red blood cells are actually the same as someone who is living at sea level. And this is very different because if you or I were to go to the Tibetan plateau, we would as Erin mentioned really increase the number of red blood cells to get more hemoglobin.

So this lower concentration of red blood cells should be disadvantageous in terms of blood oxygen level but actually advantageous in terms of blood viscosity, right. And so studies have shown that on average there is lower blood oxygen content in this region compared to those that live at sea level. And so to make up for this possible cost, other studies have shown higher levels of nitrous oxide in the lungs. And so this is a chemical that is produced by the body, it's a vasodilator. And so it keeps those lung vessels open and that allows for better exchange of oxygen between the lungs and blood. And this likely lowers the potential for hypertension. And so according to one study I read, the pressure in the arteries of the lungs is 28% lower in the Tibetan region compared to those in the Andes.

Erin Allmann Updyke

Wow. It is so cool.

Erin Welsh

That's so cool.

Erin Allmann Updyke

So, so cool.

Erin Welsh

It blows my mind honestly.

Erin Allmann Updyke

Yeah. Oh man.

Erin Welsh

So now that my mind is already blown about humans, I know that there's more to blow my mind about animals. So that was my really terrible segue into this next question.

Erin Allmann Updyke

That was good, I loved it.

Erin Welsh

Thank you. Which is do we see these same adaptations to high altitude in other mammals besides humans? And I know you talked a little bit about deer mice but I guess in general do mammals evolve to live at high altitude in predictable ways?

Jonathan Velotta

Yeah. I mean yes and no. It all has to hinge on oxygen transport. Where in terms of the physiology of an animal that happens does depend on the animal and so I can talk about a lot of examples of high altitude deer mice, some of the similarities and some of the differences. So deer mice also reduce the amount of hemoglobin and red blood cell production when they're at altitude. So that's similar to the Tibetan story that I explained earlier. And they also have reduced pulmonary arterial pressure. So there have been studies by some colleagues that I've mentioned that have shown that highland deer mice also have more capillaries and those capillaries supply more oxygen to their muscles which is really, really important for a deer mouse especially because they need those muscles to produce heat in a really cold environment. And they do that by one of the ways is by shivering and that requires oxygen.

Erin Allmann Updyke

I'm just imagining these poor little deer mice just shivering in order to stay alive for thousands of years. Like I'm the best shiverer? That's so sad.

Jonathan Velotta

Yeah. There's really strong selection on what we would call thermogenesis, the production of heat metabolically. And so I should really preface this by saying that deer mice are winter active, they really need this oxygen and they really need this shivering because they're active pretty much all year long. Going off of that, there have been some other studies, some by Zach Chevron and his colleagues, that show that high altitude deer mice are more effective at using fat as a fuel source during this shivering. And this is because fats are way higher in energy but they do take a lot more oxygen to burn. So if you can figure out, if you're a deer mouse, if you can figure out how to get more oxygen, then you can burn fat and shiver better.

Erin Welsh

Cool.

Jonathan Velotta

And there are lots of other ones too. I mean yeah, how much do you want? So there's a lot of animal species, birds and mammals mostly, that have evolved a hemoglobin that has a higher affinity for oxygen. Some birds and mammals have an evolutionary adaptation to just have intrinsically higher oxygen affinity. So this means they can pick up more oxygen. So in many hummingbirds, the higher the elevation that these hummingbirds live, the greater the hemoglobin oxygen affinity on average. This is true of deer mice too, deer mice that live at high altitude have a higher hemoglobin oxygen affinity and it is a genetic change.

And this change in affinity is caused by mutations in the hemoglobin gene. If I could riff at the genetic level for a little while, one of the things that we see is that there's a lot of mutations in animals, in a lot of different animals in a gene called EPAS1. And so this is a gene that codes for a protein, that's what genes do, that initiates the body's response to hypoxia. So it's a really important gene called a regulator. And all the things we talked about like red blood cell production, changes to the vasculature, these things at the genetic level are controlled by EPAS1. And so there are adaptive mutations at this gene that we find in high altitude animals including deer mice, also wolves, sheep, humans, birds, dogs, and even a snake.

Erin Welsh

Why? How are snakes up that high? I didn't know that like reptiles could survive at high altitude. That's amazing.

Jonathan Velotta

Me neither, I have no idea. I mean the sheep and the dog thing is kind of interesting because those are animals generally that people have brought to high altitude. And so their evolution at high altitude is more recent. And I think the really fascinating thing about EPAS1 is that this is all happening independently, right. These are very distantly related species of mammals, birds, and reptiles. And so clearly EPAS1, the mutation at EPAS1, has some sort of beneficial effect, we don't really know what that is. We have found that in deer mice the mutation in EPAS1 is associated with having a higher heart rate when you're exposed to hypoxia. So that should mean better pumping of oxygenated blood to tissues. But that's probably just one effect and a lot more research needs to be done.

I'll leave you with one final cool thing about animals, deer mice again, and that's that there are some really interesting studies showing that low altitude mice, so mice that live at sea level, produce low birth weight offspring when they're exposed to high altitude, so they have offspring that weigh less than they do if they were to breed at sea level. We would call this fetal growth restriction. And so there's some cool work going on by Kate Wilsterman and her colleagues that have been finding that in high altitude deer mice, so these are mice that are adapted to high altitude, they are protected from fetal growth restriction. And that in part has to do with adaptations in the placenta that improve gas and nutrient exchange from mom to fetus.

Erin Welsh

That is amazing.

Erin Allmann Updyke

It's absolutely fascinating. So you just covered like a million amazing high altitude adaptations in like the shortest amount of time. It was amazing. And we already talked about how difficult it is to live at high altitude. So I guess my question is do these high altitude adaptations themselves, as cool as they are, do they come with a cost? And do we know what that cost is?

Jonathan Velotta

Yeah. So I think I already mentioned blood viscosity in the association with hypertension. And so one of the other cool ones, at least that we've seen in deer mice, is that so there is this genetic variant for hemoglobin that I mentioned that's more prevalent at high altitude and it helps with picking up more oxygen in the lungs. And so one of the interesting things is that in mice with those genetic variants, when they exercise at low altitude they tend to do worse than mice without that high altitude gene. And this is presumably because having that variant does help with picking up oxygen but it also holds on to it more tightly. And so it has trouble giving it up at the tissues during exercise. So if you just stay at high altitude you're fine, but there is like a tradeoff there and that is a cost.

Erin Allmann Updyke

You can never go back to the beach.

Jonathan Velotta

Exactly.

Erin Welsh

We have one last question for you and it's designed to make you feel like you're back in grad school taking your prelims.

Jonathan Velotta

Great.

Erin Welsh

So apologies in advance.

Jonathan Velotta

I just had a flashback.

Erin Welsh

What do you think is the biggest unanswered question in your field?

Jonathan Velotta

Right. So I mean there are a lot of them obviously. But I think really the biggest thing is how changes to genes lead to adaptations of physiology. That is something that we know very, very little about. So aside from the work from Jay Storz that I mentioned on hemoglobin and some others, we don't really know about how genetic changes lead to physiological adaptations. We know there are genetic changes, we know there are physiological adaptations, we know there are genes that have mutations that are likely involved in adaptations, but we don't know how those mutations change, how the gene works, and how the animal works and all of that. So I think that is really one of the frontiers at least in sort of the evolutionary biology of high altitude.

Erin Allmann Updyke

Awesome.

Jonathan Velotta

Done.

Erin Welsh

Well thank you so much, Dr. Velotta, for coming on to chat with us about high altitude adaptations. And if any of you listeners out there are curious about Jon's work and want to learn more, check out his website on du.edu or whatever, we'll link to it on our website. I don't know the exact...

Erin Allmann Updyke

We don't have to have it memorized.

Jonathan Velotta

It's velottalab.com.

Erin Welsh: Okay. Is it? Oh yeah, that's right. You have your own lab website. Whoops.

Jonathan Velotta: You're welcome for making the long trek down to our basement.

Erin Allmann Updyke: Thank you so much, Jon, for coming all the way down to chat with us.

Jonathan Velotta: Any time, any time.

Erin Allmann Updyke: Genuinely it was really great to have you, we really appreciate it.

Jonathan Velotta: Well it was my pleasure. I've been a long time listener but first time caller.

Erin Welsh: How long have you been holding that one in?

Jonathan Velotta: I practiced that one.

Erin Welsh: Is there anything else that we need to cover before we do sources?

Erin Allmann Updyke: Just in case anyone was really dying for this information, we don't have numbers on the epidemiology of acute mountain sickness or chronic mountain sickness. Every study that you read on the incidence of acute mountain sickness has vastly different numbers. So that's why we just kind of skipped over that part. And I will link to a couple of papers about high altitude training for those of you who are maybe really into it because that was something we didn't touch on. That's all I've got.

Erin Welsh: Okay.

Erin Allmann Updyke: Well with that, sources?

Erin Welsh: Sources. I'm just gonna shout out one basically. And that was a book called 'High Life: A History of High Altitude Physiology and Medicine' by John West. Oh and also there was a great TED-Ed talk about how barometers work that I'll link to.

Erin Allmann Updyke: I had a whole number of papers on the physiology of acclimatization and the pathophysiology of AMS. I think one of my favorites was by Murdoch in 2010 in BMJ Clinical Evidence just called 'Altitude Sickness'. But I will list all of the rest of them. Jon, did you want to cite any of your sources?

Jonathan Velotta: Yeah. Can I give you all of my... There's like probably 25 papers in here that I summarized all for you guys.

Erin Welsh: That's a lot of work.

Erin Allmann Updyke: We will post all 25 of those and all of ours as well on our website thispodcastwillkillyou.com.

Erin Welsh: We certainly will.

Erin Allmann Updyke: Thank you also to Bloodmobile who provides the music for this episode and all of our episodes.

Erin Welsh

Thank you to Lianna Squillace for our excellent audio mixing.

Erin Allmann Updyke

Love it. Thank you to the Exactly Right network.

Erin Welsh

And thanks to you, listeners. So many thank yous and we're not even done yet. But we really appreciate you listening and we hope you liked this really deep dive, high climb, into high altitude physiology and history.

Jonathan Velotta

No comment.

Erin Allmann Updyke

And as always an extra thank you to our patrons. We can't express enough how much we appreciate your support.

Erin Welsh

It's true. Well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals.