

## Launching Episode Six: Combating Cosmetic Aging & Improving Skin, Nails & Hair

0:00

- Welcome to the Lifespan Podcast. Where we discuss the science of aging and how to be healthier at any stage of life.

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I'm David Sinclair. I'm a professor of Genetics at Harvard Medical School, and co-director of the Paul F. Glen Center

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for Biology of Aging Research. This series of podcasts is about why we age

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and things we can do to slow, stop, and even reverse that process. Last episode,

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we talked about really cutting-edge science and procedures that people are currently doing

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with their doctors and what they might be doing in the coming years. But today, we're going to talk about what you can do

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to slow, stop, and even reverse the aging of the outside of your body.

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And I'm joined today by my lovely co-author and co-presenter

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- Co-human. Co-ed. No. - Conspirator? - Co-conspirator.

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Matthew LaPlante. Welcome. - Hey. All right, let's do this again.

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You know this. I was not so excited about this episode. When you told me, when Wonderboy Rob told us

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that it was going to be about cosmetic aging. I poo-pooed this, then we prepped for it.

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We've been having great conversations over the last few days. I'm actually really excited about this conversation.

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- That's true. Especially the parts about improving your sexual function. I thought you were excited about the most.

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- That's not in this episode. We'll have an episode on that. No, today we're talking about cosmetic aging,

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and we're talking about the difference between interventions that are only aimed at appearance

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and interventions that might impact both appearance and aging. - And we had to cover a number of topics,

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including how to keep your hair, skin and nail looking young and even reversing aspects of that process.

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- And we should say here, there's nothing wrong with things that are purely aesthetic that only work to make ourselves look good.

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Because those things might not impact our biological aging, but they can affect us socially, emotionally, mentally,

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like it will make our lives better. So we're not going to poo-poo. I've used the word poo-poo now several times. So we're not going to denigrate

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interventions that are only aimed at appearances, but we are going to talk more about and center our focus around interventions

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that might also have an anti-aging effect. - Exactly. And there are coverups.

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We're going to talk a little bit about Botox and other creams. But really I think what's most exciting and most powerful

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are the technologies that are available now and shortly, that can boost the body's ability to fight aging

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and even reverse it. We put them into a couple of buckets. We've talked about this in previous episodes. Is the adversity mimetics which we love.

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Which is really slowing down aging and reversing it. Or the abundance mimetics that give you a short term gain,

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make you look good, but long term may not work or even have deleterious effects.

## **Estrogen, Progesterone, and Menopause**

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- Now this is usually the part in the podcast where I say, "Hey, David, we have to thank our sponsors."

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But actually there's something else we need to do because there was something we neglected to talk about

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in our last episode. Well, it was a pretty glaring oversight on our part.

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- Well, we focused a lot on testosterone, which is used by men and women increasingly, but we neglected to talk about other hormone

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that are not found much in men. Estrogen, progesterone, and this pertains to menopause hormonal therapy

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and overall hormone replacement therapy for women. So let's talk about that.

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- Yeah. And one of the reasons why this is really both interesting and important

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is because menopause effects the first part of our body,

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the first organ in a woman's body to really experience the effects of biological aging.

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- Right. Sometimes even in women's twenties, but late thirties, early forties, this can occur.

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- So this is often before your heart starts to show damage, your lung starts to show damage from aging,

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your brain, even. - Yeah. And there are ways of making sure that you go through that transition

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if you're a woman. In a more natural way. And so we actually called up a friend of mine, Cindy Meston, who's a professor in Austin

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who has given us some really good advice. Given that you and I are men, we typically don't know a lot about this.

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- And should not lecture on it. - No, we're not lecturing, but we will talk about how it pertains to aging.

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What the current thought about HRT actually is. - Well, can you take us through, we had this conversation several years ago

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and it stuck with me for a really long time. Can you talk about why it is that the female reproductive system ages earlier

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than the rest of the body? You started to notice this in mice - Yeah. In fact, that's one of the reasons we studied fertility in mice

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because we could get those experiments done more quickly. And we discovered, and we'll bring this up in a later episode,

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that we can reverse female infertility with molecules that stimulate. These were two ones that we work on.

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But today we're going to talk about the late part of life about how to replace those hormones. The reason you need to do that

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is that we've evolved as a species to have children up until the age of about 30.

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And then we should stop. Why? Because having kids as a woman is very dangerous. There was a time when,

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I think there was a 1 in 5 chance you would die from childbirth. - You needed to be younger or more vigorous to just get through that process.

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- Right. And then you have to put a lot of effort into raising those kids. It's not like an insect where you just let them blow away in the wind.

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You have to spend at least a decade. And these days, two decades, raising those kids.

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And if you keep doing that your whole life, it might take away from the energy that you put into the ones that you have.

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So for that reason, women have evolved to become infertile around the age of 40.

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- And that process that they go through is menopause.

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For some women it's brutal. - For sure. There's the well known things. There's mood swings, vaginal dryness,

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loss of sex drive, migraines, hot flashes, of course. There's also really serious effects on health,

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including increased susceptibility to heart disease. So this is clearly something that needs to be addressed.

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And there are increasingly better ways to be able to allow women to not just transition through menopause,

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but to continue having the right hormone levels to protect them against aging long-term.

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- And one of these things is menopausal hormone therapy, which is chiefly and has been traditionally chiefly

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estrogen replacement. Although increasingly other hormones are explored.

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And this is a treatment that can offer people a lot of symptomatic relief. There were concerns for a really long time

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that it had some pretty gnarly side effects itself, and even some could do some long term damage.

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We're learning more about that right now, though. - Estrogen used to be used primarily. And now, what we're finding

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is that the dual use of estrogen and progesterone in the right combination and ratio and timing

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is really important. And it may be that some of these side effects that people have been worried about and studies that came out early,

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particularly in the early 2000s about the increased risk of cancer are largely due to,

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I wouldn't say the misuse, but the lack of understanding of what the natural levels are for a woman.

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In fact, most women don't know what their baseline levels are in their thirties and forties. That's why Cindy actually,

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Professor Meston, recommended to us that women should get their baseline levels and measure during certain phases of their menstrual cycle,

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particularly in the luteal phase, what the levels are of estrogen and progesterone in their thirties and forties,

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so that when they reach their late forties, fifties, their physician can match those

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and continue the on at those natural levels for them. - And this continues a common theme that we've had in I think almost every discussion we've had

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so far in this series, which is unless you're monitoring, unless you're tracking,

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you have no way of knowing what your actual health state is. - Right. And so I've been using InsideTracker, one of our sponsors.

8:00

You can use a doctor if you want. But that's true not just for estrogen and progesterone, but for testosterone.

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Men and women typically don't measure their levels. They should be. And there's a sex hormone binding globulin called SHBG,

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which is important for binding all these proteins in the blood, these hormones. And if you don't measure that one as well,

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you're flying blind with your dashboard. So I would recommend measuring that as well. And if the levels of that become too high,

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SHBG it's called, then that can actually counteract these therapies. - Okay. And so, again,

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at the risk of lecturing on things like body parts that we don't have, suffice it to say a lot of the things

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that people have been hearing about menopausal hormone therapy for many years, the dangers of it shouldn't scare people off

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from having conversations with their physicians about this potential treatment.

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- Exactly. And even increasingly so as physicians and researchers like Cindy,

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are figuring out the right ratio and timing of these hormones.

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Increasingly, it's looking like there's a real long-term protection. So not just during the years of menopause,

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but extending that hormone replacement therapy out for decades seems to protect against the heart disease problems

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and bone loss. But of course, there are some downsides, particularly if you have a history of breast cancer. You don't want to be pumping yourself with estrogen.

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So please do talk to your physician about that. - We mentioned a list of effects that happened during menopause earlier.

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One of the ones that we didn't mention that relates to the theme of this episode

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is epidermal thinning. - Right. This is what happens to your skin as you get older

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and it's accelerated rapidly during and especially after menopause. - And we're going to talk about that more in a moment,

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but first, let's do thank our sponsors. - We definitely need to do that. Cause they make this episode

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and all the others freely available. Our first sponsor is Athletic Greens.

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9:54

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10:00

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along with vitamin C and zinc citrate for immune support. I've been drinking Athletic Greens for a number of years now

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as a way to cover all my nutritional bases. I'm often traveling and sometimes my diet just isn't the best.

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to claim this special offer. Today's podcast is also brought to us by Levels. Levels is an app

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that syncs with a continuous glucose monitor which they provide, and it interprets your glucose data for you.

11:03

I was so impressed by Levels that I recently joined them as an advisor. By monitoring your blood glucose levels,

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Levels allows you to see how different foods impact you. I've had fun running tests of my own, seeing how different foods impact my blood sugar levels.

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For example, I've learned that white rice really spikes my blood sugar, whereas potatoes don't. And as we've discussed on this podcast,

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having stable blood glucose is really important. Not only for daily mental and physical energy,

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but also for long-term health. So if you would like to try Levels, you can skip the 150,000 person waitlist

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and join today. You can go to [levels.link/sinclair](https://levels.link/sinclair) and claim the special offer.

11:44

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InsideTracker is a personalized nutrition platform that analyzes data from your blood and your DNA

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to help you better understand your body and reach your health goals. I've been using InsideTracker for over a decade.

12:01

And I'm the chair of their scientific advisory board. The reason I've long used inside tracker is because they provide the best blood and DNA analysis

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that I'm aware of. They make it easy to get your blood drawn. You can either go to a nearby clinic,

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or like I do, have someone come to your home. It's super easy. From there, InsideTracker presents your blood analysis

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in an easy to understand way and they give diet and lifestyle recommendations to improve your blood biomarkers

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essentially to optimize your body. Another feature that InsideTracker has is their InnerAge Test, which I helped develop.

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This test shows you what your biological age is, how it connects to your chronological age,

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and what you can do to improve it. If you'd like to try InsideTracker, you should go and visit [insidetracker.com/sinclair](https://insidetracker.com/sinclair)

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and get a 25% discount of any of their plans. So use the code Sinclair at the checkout

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on the [insidetracker.com](https://insidetracker.com) website. - Okay, let's get into this. A lot of people, I think, know this.

## **The Pinch Test, Epidermal Thinning, and Foot Ulcers**

13:02

This fact, but it still, I think, surprises some people. The largest organ in the human body is

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- The skin. - And it's sizable. - Well, it's 1/6 of your total body weight,

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which is massive. And it's the barrier to the world. And the health of your skin is super important

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for the health of the rest of your body and vice versa. - And monitoring the health of your skin can give you a lot of insights into the health of your body.

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When we were talking before, I likened this to going to the grocery store and looking at a piece of fruit.

- Right. If you see some bruises

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and some damage on there, you can assume that it wasn't handled very well,

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but also it might be old. So you give it a squeeze, you see how it is. And we'll talk about ways to do that with our own bodies

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to really have a quick test and even some molecular tests to determine how molecularly old we actually are.

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- There's one you've been doing all morning this morning. Do you want to do it now? - The skin pinch test. - Yeah.

14:02

- Sure. So what you do is you rest your hand on a table, so it'd be relaxed normally.

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And then you grab the back of your skin, pinch it up, and it should, if you're young, pop straight down in less than 2 seconds.

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Someone in their thirties and forties, it'll pop straight down. But once you get into your fifties, it's going to take many seconds.

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- And the chart that you found and I don't know what the scientific basis for this is,

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but the chart that you found said when you get into your like eighties and nineties, it can take, well, like 20, 30 seconds?

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Something like that. - Oh. Even worse. So for people like us, were in our forties and fifties, should be less than 10 seconds.

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By the time you're 60, it typically takes 10 to 15 seconds to come down. Over 70, between half and a whole minute to go down.

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- Okay. And you're 50 and yours went down right away. So that's good. - Well, I've been doing the right stuff for a number of years,

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but that's pretty good for someone my age, looks like yours - We'll also going to fix that on the video.

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Yeah. It also helps if you tense your hands. - We don't probably even need to say this,

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but like, it's just obvious. I am aging faster than you are aging, but I'm doing okay on the the skin popup test.

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- You are. There are other ones we can talk about later, like nail growth. - Let' stick on skin for a minute here though.

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Because one of the things we talked about right before the sponsorship break was epidermal thinning.

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This is a problem for women who are suffering from menopause It's also a problem for men.

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It's a problem for people as they age. And I think a lot of people don't understand

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or don't really think about it, at least, I didn't think about why this is such a pernicious problem.

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Why is it bad if we have really thin skin? In addition to the fact that we can't take insults well. - Right.

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Well, we tend to forget that our skin is the major organ in our body to protect us from death.

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You know, we've seen with COVID-19 what happens is once you get a pathogen in there, it'll run rampant.

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And so our skin is the main barrier. And as we get older, it can be damaged much more easily. You see an elderly people,

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the bruising, the ripping, the tearing. It's becoming paper thin. And so we need to protect it.

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It's not just about looking good in your forties, fifties, sixties, but in your seventies, eighties and nineties, it's super important.

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It's life and death as to how young your skin still is. - This really hit home for me when I met David Armstrong.

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- Yeah. So he's the US's top surgeon for ulcers, wounds in the foot.

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And he spends his whole life trying to figure out ways to reduce the number of ulcers,

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which is about 13% of the US has a foot ulcer right now that's about - Like right now.

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- 40 million Americans have foot ulcers. - Yeah. - And we don't talk about it. Cause these are people who typically are older

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and don't have a voice in society, typically. But he is on a mission to advocate for the cure of these things.

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And also he spends his life trying to cure people of these ulcers. But it's very difficult.

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The reason is these ulcers, because the skin is old, it doesn't heal very well. And typically it'll be open.

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A weeping wound and crusty around the outside. It looks like you've got a quarter size hole

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in the bottom of your foot. That just arises just by tripping on something, or stepping on a something sharp that's layering it out.

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- But if it's coupled diabetes, which leads to a loss of sensation,

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of feeling in the foot, this can be incredibly dangerous and lead to among other things, amputation.

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Infection, which leads back to this whole reason why we're talking about why it's so important

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to keep our skin as thick and healthy as possible.

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- And keep the feeling in our skin. Remember, our nerves are all in our skin. And as you get older, you lose that feeling. And there's a story

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that we wrote about in our book, Lifespan, where one of David Armstrong's patients had stepped on a thumbtack, a little nail,

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and it was in his foot, he didn't notice. And he only noticed days later because he could hear a tapping sound as he was walking.

18:01

- It's absolutely terrible. Every time I hear that story, I just cringe. - Well, it's a really big problem because often you can't make these heal.

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And then what David does and all these other surgeons is to cut around that scabby site.

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And it just gets bigger and bigger and bigger. And eventually you've just got this open wound. Next thing you have to do is cut the foot off.

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And then you keep cutting and cutting. I think after about five years of getting one of these big ulcers,

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you are almost certainly going to die. It's worse than getting a cancer diagnosis. - And there's a lot of people probably listening right now

## **Skin and Biological Aging**

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and go, "Oh no, this is never going to happen to me. I don't have to worry about that. I'm super healthy. I'm not going to get diabetes." But we're all aging.

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And I think most people can picture their elder self. And when they do, they see their skin,

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it's a little more wrinkly, it's a little more saggy. It's a little thinner. And this actually means something

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more than just appearances. And we know this from this 2012 study,

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where researchers took the photos of about 300 elderly people and they gave them to another cohort of people to rate.

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They rated for the age. - Is that the Lothian Birth Cohort in Edinburgh?

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- Yeah. Yeah. - All right. So they looked at people from 1921 onwards

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and it was fascinating. They rated them for a bunch of things, their age, their health, attractiveness, facial symmetry.

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- This is just based on the appearance on the photograph by the way. - Right. - Like, no, you're not meeting these people. We're not taking any tasks, we're just looking at their photos

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and saying, "Are they healthy or not? Are they old or not?" - So what did they find?

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- They found that if you follow those people out seven years from the time that that photo was taken,

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there was a really high degree of predictability that the people who were rated as older looking,

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whether or not they were actually older chronologically or not, if they were older looking, they were more likely to die.

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- Well, that totally fits with what I hear from my friend, Nir Barzilai in New York. He's at the Albert Einstein College of Medicine.

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And he studies centenarians. These are families, peoples that tend to live over a hundred.

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Not to be confused with centurions, which are Roman soldiers. Sometimes that's mixed up. But what he sends me sometimes

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are photos of his centenarians, the father and the son. And both those guys that now imagining in my head

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look really young. Not just the guy that's a hundred who probably looks 70, but the 70 year old son looks 40.

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And so this is fitting with the idea that you are really as old as you look.

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- When I read about the 2012 study, I immediately thought,

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"Oh, you know what would be really interesting? Is if now we could take those photos and then test those people's biological ages

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with a DNA methylation clock. - A Horvath clock. - Horvath clock, which we talked about in prior episodes.

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And lo and behold, somebody had already thought of this. This often happens, by the way. You and I are talking about research and we like, "Oh, we should check this out."

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And then somebody else has done it. But another team of researchers did do it. And it turns out that it didn't correlate.

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There wasn't correlation between these people's appearances, even though that was predictive and their biological clock,

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but there's a distinction that needs to be made. - Well, they were measuring the blood clock in that case.

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So what we've learned since is that there are various tissues have different clocks. And it helps to have a specific clock

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for that particular tissue. Others have since gone on to make skin clocks. And they seem to work better

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for measuring the age of the skin. - And Mariana Boroni who's a friend and colleague of yours from Brazil.

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She let a study that was published in 2020, showing that when you do this, when you build this epigenetic clock

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based on methylation of skin cells, it does predict biological age quite well.

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- It does. And there's a good reason why skin is going to age probably faster than the rest of the body,

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though it's still a good indicator. And that is that it's exposed the elements. We know that if you grow up in Australia, like I did,

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that the UV light is going to create DNA damage that accelerates the epigenetic changes that lead to aging.

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So someone like me is going to have probably older skin than someone, my identical twin,

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if they had moved to Norway. - And like a third of Australians suffer from some sort of,

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is it skin cancer? - Yeah. It's skin cancer. It doesn't have to necessarily be lethal.

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But a third of Australians have something removed from their skin that could be a tumor.

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Now, what's been done since I was a kid is that all beaches have free sunscreen,

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which is great. Not in my day where we need to just sunbathe. - Like when you show up to the beach, there's like a little, - Yeah. Yeah. The press pump.

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Instead of having ketchup in the US, they have sunscreen. Well, now we have the hand sanitizer. But it's the same thing, right?

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It's like, - Don't use that. - So that's at the beaches? - It is. - You don't have to bring your own sunscreen.

- No, no, no. - That would save so much money.

22:57

Cause that sounds expensive. - Billions of dollars in healthcare costs in a country for just a few dollars of sunscreen. - That's a really great investment actually.

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- Yeah. Sometimes Australia does things really well. But the problem though is that,

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for those of us who grew up without the sunscreen, we have this damage that we are probably stuck with,

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though increasingly we're learning you might be able to reverse that damage as well. - And that was part of this study by Mariana Boroni as well.

## **Cellular Senescence, Ultraviolet Light, and Skin Aging**

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They looked at the application of senolytic drugs to these skin cells

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and then measured the results. - They did. So let's talk about skin aging from a really modern perspective,

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which is that skin is full of senescent cells. These are zombie-like cells that reach a point where their epigenome is so dysregulated

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that they check out of the system, they stop dividing. - They're no longer producing. - Right. They don't divide and we can stain them blue

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with a dye called beta-galactosidase. And they're pretty common in an older person.

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The problem is that they secrete these inflammatory factors and also what are called mitogens that stimulate cancer.

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So they're not good things. And in mouse and increasingly in a few human studies, we know that if you delete these cells, kill 'em off,

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you get rejuvenation of the body. It includes internal organs, you can treat diabetes with it.

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But the skin becomes rejuvenated. And in this study, what they did was they took out skin biopsies from people

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and grew them in tissue culture dishes, so it's ex vivo, and they could then treat them with senolytic drugs.

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They used a couple, a pretty common ones. One's called ABT-263 which is from Abbott's,

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also known as Navitoclax. And they also used rapamycin, which we've talked about before as a way of mimicking starvation in the body

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or fasting at least. And what they found was that those skin explants, as they're called, grew thicker,

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which is what you want if you're reversing aging, but they also could measure the clock. They had a special skin clock that they had built themselves

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out of measuring the DNA methylation chemical patterns during aging of skin. And there, they did find that this senolytic treatment

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reversed the age of those little pieces of skin. - The implications of what you're talking about

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in regards to the senescent cells are really interesting. Because again, what we're talking about is the body's largest organ.

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And it's not a system unto itself, it interacts with all of these other systems. So if we have senescent cells

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secreting these cytokines all over the place. They're not just staying in the skin, they're going to move other places too.

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So if you can lower the age of the skin, you can save the rest of the body.

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- That's exactly right. And James Kirkland from the Mayo Clinic has found that if you just put what we call it,

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what he called a dab of senescent cells under the skin, in a mouse, it causes the whole mouse to get older.

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So lowering the overall burden of senescent cells is a good thing. And where are most senescent cells in the body

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because of the damage from UV light, you get them mostly in the skin. - Okay. So one of the ways to do this potentially,

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to fix this problem potentially is retroactively, we can address it with some kind of senolytics.

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We can also do it proactively by just simply avoiding all that UV light, wearing sunscreen.

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Let's talk for a little bit about what's actually happening. How does UV light actually like make ourselves go bonkers?

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- Right. Well, the first thing to appreciate is, a little bit of sunlight isn't going to hurt you. In fact, you need it.

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- Vitamin D. - It's not bad for you. But you can overwhelm the system. So if you actually get sunburn, you get red,

26:37

there's inflammation, swelling of the skin, tenderness, then you know you've overdone it. And so what I tend to do is I go out a little bit each day,

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maybe for 10, 20 minutes, get a bit of sun, but not to the extent where I'm going to get burnt. And I always wear sunscreen out there

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if I'm going to be out for longer than that. So what's happening actually is that the sunlight is hitting the DNA molecule itself

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and causing two letters in the DNA, two chemicals, the Ts. Remember there's ACTG, four of them.

27:05

The Ts that are next to each other will link chemically. It's called a, a thymine-thymine dimer. And now the cell,

27:11

- If the sun fuses them? - The sunlight. Yeah, yeah. Photon will hit them and they'll become fused.

27:16

Like that. [Matthew laughing] And so if you've got a zipper, you can imagine what's happened to a zipper that's fused along.

27:22

How do you possibly open up that zippers? So you need to open up DNA to read it and to copy it. And now you've got these stuck together.

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- So you can't. They can't be opened up in it. - Well, it's a big bulge in the enzymes that read DNA, have trouble getting over it.

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So you have to remove them. Usually what happens is that the cell cuts them out and puts new ones back in.

27:41

- Okay. And when you do, when you kind of unfuse those, do you know what happens? You live long and prosper.

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- That also helps. Hang on. Let's see if I can do that. There we go. So what's actually happening though,

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is not what you might think. The old idea was that these thymine diamonds are actually mutagenic and cause mutations.

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But what we now know from studies from my lab and others is that the act of repairing that DNA

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damages the problem. And it's the reorganization of the proteins in the cell

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that ultimately lead to the cell losing its identity. - Okay. So I have not been as good as you have been

## **Collagen, Keratin, and Skin Health**

28:17

about wearing sunscreen. So I have to probably address this retroactively.

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Can I just like rub some rapamycin and ABT-263 on my skin

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and it's all good? - It probably would work. You have to be careful cause rapamycin suppresses the immune system, remember?

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- Right. - And right now, those drugs are not available, as far as I know, for topical treatment. But actually, Dr. Boroni, then took that finding

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and then use that little skin explant beta-gal stain, which is blue,

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to look for peptides, small little proteins that we talked about in the last episode.

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Which one of those 700 and something peptides, if any, had age reversal effects got rid of that blue senescent stain

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and reversed the clock? And out of those 700 and something peptides, she found a few.

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There were about 20 that looked good. And one of them she's actually put into a product that she sent me to try the other day.

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It's called OneSkin. And I'm not an advisor to this group or anything, but it did seem to work.

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It looked just as good as retinoids, which is the leading product that is used to reduce fine lines and wrinkles too.

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But I know she's developing additional peptides to put into her cream, not just this one that is starting to show some efficacy

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in human clinical trials. - And the thought process behind having a peptide in a cream is what?

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- So we don't know exactly how this peptide makes the skin younger, but one of the downstream effects, one of the benefits certainly is involving the COL1A1 gene

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that makes the protein collagen, which we've known for over 50 years to be an important component of younger skin,

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making it more flexible and thicker. - Collagen, of course, is really super popular supplement to put in beauty products right now.

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It's a protein, but it starts to attenuate after our mid-twenties.

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- Right. When we're young, it's the most abundant protein in the body. It holds together our bones and our skin.

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- This is why babies are all chubby and beautiful and plump, right? - Yeah. It's a wonderful protein,

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but we don't make enough of it as we get older. And that's why beauty products in particular, want to boost that production.

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But you can also smear it on, put it in powders, put it in drinks, take it as a pill.

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Energy drinks have it in it. The question though is, is it useful? Is eating collagen going to be good?

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Well, one thing I can say for sure is that collagen is made up of a lot of amino acids. You're going to get the right ratio of collagen amino acids

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from those products whether or not the collagen itself makes it into your bloodstream

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after being degraded in your stomach. - By your stomach acids. - Yeah. There's a big debate

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about whether these products are working by being broken down and rebuilt. Or actually make it into the body

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as an intact peptide of string of amino acids. And I would say the jury's well and truly still out on those things. - It is fair to say

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that as long as you pick a safe collagen product, there's likely not a lot of harm that can come from it.

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- Not at all. There's no harm in taking collagen. And probably what it's making sure is that you don't have any deficiencies

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in the amino acids you need to make this most abundant protein in the body. - What we know right now

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is that there's probably more benefit from retinol or vitamin C in terms of protecting your skin.

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- Well, yeah. Vitamin C is good for overall body's health. It's essential as an antioxidant.

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Retinae though is one of the most important aspects for preventing and reversing fine lines

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and wrinkles in the skin. - And these substance actually create collagen down the line, right?

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- Right. These retinoids have been shown for many years to boost the production of collagen. That's clear.

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They also do other things. They increase the growth of the epidermis and the stratum corneum, which are important parts of the skin,

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make it thicker. They also can actually lower skin pigmentation by about 60%.

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A lot of people want to have even colored skin. They make fibroblasts grow,

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basically stimulating cell growth, which is really important. They lower the lipid. So that's why it's often used as a defense against acne.

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And in fact, you were telling me earlier that you've used that before. - when I was a kid. Yeah. - Yeah. - It dried out my skin something awful though.

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I mean, it makes you like super susceptible to sunlight. So you have to wear sunscreen when you use it.

- Well, that's true today.

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If you put it on your skin as an adult, you have to be careful from the sun, but mostly you end up with dry skin. So you have to make sure you're moisturizing

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while you use the retinol products. And there's another thing that's important about these. They are what are called MMPs,

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this metalloproteinases that break down the skin and you want to inhibit those as well.

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Which is what retinols do. Actually, what they do is they go inside the cell and there's a receptor inside the cell

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that binds to the chemical that you're adding. And they then go in and turn on certain genes that provide all of this extra cell growth

33:04

and other benefits to the skin. But you have to be careful because if you overdo it, you get really dry skin.

33:09

And if you get it into places like your eye, it can be really unpleasant. - Oh god, that sounds awful. - Yeah, don't do that.

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- They also have an advantage of creating keratin or promoting keratin? - Right. So the keratinocytes are lower down in the skin.

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So keratin is a super abundant molecule as well. That's important, like collagen, for the flexibility.

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It's an important component of not just your skin, but your hair and your nails as well. And your retinae can promote the growth of the keratinocytes

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that make keratin. - Let's take a little aside here and talk about nails. Because this is sort of like,

## **A Quick Aside about Nails**

33:43

you know, skin, hair, nails. And a lot of people forget that this is a pretty good,

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or like a lot of people might not know that this is a pretty good indicator of your state of aging.

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- Yeah. It's a pretty fun one. I learned this a number of years ago when I was at MIT, that the rate of your nail growth

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is a really good indicator of how you're aging or not aging. And so every time I have to cut my nails,

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I'm thinking, how long ago did I cut my nails? It's all born from a study from 1979,

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where they glued on these little measuring tapes onto people's nails and measured them over years, in fact,

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and there was one individual, Mr.Bean actually, who measured his nails for most of his life.

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- Like literally his name was Mr. Bean? - Yeah. - Like the, - He might have been Dr. Bean or Professor Bean, I'm not sure. But we have that graph.

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And actually, looking at thousands of people, we now know for sure that the rate of nail growth

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decreases about half a percent per year. And if you measure that, it's a really good indicator

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of how old you are biologically. I don't do that, but I do pay attention to whether my nails are slowing down in their growth or not.

## **Autophagy and Retinoids**

34:46

- I don't because I bite my nails, which I know is a terrible habit, but I like to say now that I'm just engaging in autophagy,

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which is, you know, good for my lifespan. - Right. Taking that keratin and putting it back in your stomach. - Right. Exactly.

34:58

- But autophagy actually is a function also

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or a result also of retinoids. - It is. There's Ana Maria Cuervo down at Albert Einstein College of Medicine

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is a world leader, probably the world leader in understanding autophagy, the recycling of old proteins in the cell.

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There's shallow autophagy when you skip meals, there's deep cleansing, what's called chaperone-mediated autophagy,

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which is after three days of fasting, these retinoids control that pathway of autophagy

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through a protein called LAMP2A. What's exciting about Ana Maria's work is just this year, she published that if you upregulate that mechanism,

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this chaperone-mediated autophagy, mice live a lot longer. 30, 40% longer.

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So it's truly a longevity mechanism that we can control with these retinoids. - But there's something a little bit counterintuitive here

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because retinoids actually turns out to maybe not engage, It's connection with the autophagy

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isn't necessarily positive for lifespan like we think in other cases.

36:00

- Right. As we keep saying in these episodes, there's a balance between hunkering down during adversity,

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and mimicking that and going hell-for-leather, burning the candle at both ends with these abundance mimetics.

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And it looks like retinoids, retinoids are the second type that they stimulate the body to grow

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because the body thinks it's a time of abundance. But it might be at the expense of long-term skin health.

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Because what it's also doing is toning down, shutting down this CMA, chaperone-mediated autophagy

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that is shown, at least in animals, to extend their lifespan. - So retinoids long-term bad for the aging of our skin?

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Jury is out? - Unclear, unclear. - Unclear. - So what I would say as a scientist, might work, though it needs to be tested,

36:45

is use retinols if you want to reduce wrinkles and lines, but not every day. Give your body a rest.

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Perhaps when you're fasting, don't use it. And so you get that cleansing in between the growth periods.

## **Resveratrol, NAD Boosters, and Hyaluronic Acid**

36:57

- Okay. So let's talk about one more thing that everybody associates with cleansing antioxidants.

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But I know you're like, at least in terms of like oral antioxidants, you're not a big fan.

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You don't believe that they work the same way that people think they work. What about when they're in skin creams? Cause you see that all the time.

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Every skin cream's got like, "Loaded with antioxidants." - Right. So you said, what I believe. Well often I don't use that term believe

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because I'm a scientist and I like to report what's in the literature. And what's in the literature on antioxidants

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is kind of depressing for longevity. Over the last 30 years, a lot of different antioxidants have been tried.

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Ingesting them, injecting them, genetically modifying mice, putting it on skin. Very few results, if any.

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There is one antioxidants that seems to work pretty well for longevity and that's resveratrol.

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But as you know, I don't believe resveratrol is working primarily through its antioxidant activity. Instead, it's activating our body's defenses

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and mimicking adversity. - So there are topical creams that have resveratrol in them now? - There are an increasing number of cosmetics

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that have resveratrol in them. But resveratrol is probably not working primarily through its antioxidant activity.

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It's pretty weak as an antioxidant. What's likely happening is the resveratrol is turning on the sirtuin activity,

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which then turns on antioxidant enzymes, but a lot of other good things, revving up metabolism, increasing blood flow,

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getting oxygenation into the tissue as well. So I think that resveratrol is a really great component of a cosmetic,

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but not for the reasons that you might think. - Are there other NAD-boosting molecules

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that are in skin creams right now? - Well, I'm actually working on a way to boost NAD in the skin. That product's not ready for primetime yet,

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but already people have figured out that if you boost NAD levels, it's good for the skin. Often you find nicotinamide or nicotinic acid

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or molecules related to those in cosmetics. And they've been shown to actually have quite beneficial effects on the skin.

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Thickening, for example. Mostly, people think it's because of the B vitamin, vitamin B3,

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but actually, probably what's going on is it's turning on again the sirtuin defenses of the skin. - There's one more molecule we should talk about

39:00

as we're talking about topographic creams before we move on to other remedies. That's hyaluronic acids, HA.

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These are really, really popular right now. - Well, yeah. They're really important for the plumpness of the skin and the ability to flex.

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So when you do that, this is collagen, but it's also HA involved. And it's not just in the skin,

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HA is found throughout the body. And what's super interesting about HA is that it's found in abundance in long-lived organisms.

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It seems to be involved in protecting animals, in particular, from cancer. One organism we've talked about before is the naked mole rat

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Actually, one of our children, Alex, is handling and helping to raise naked mole rats

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up at the University of Rochester. So I get photos of these naked mole rats. They have beautiful skin by the way.

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Nice and smooth. I think we call them a condom filled with walnuts? - In an earlier episode,

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we did refer to them as a condom filled with walnuts, which does not at least invoke in my mind, a beautiful animal.

40:02

- But it's very smooth and supple. - Beauty is subjective. - Moving right along,

40:07

what's found is if you take out these cells from the naked mole rats, and this is Vera Gorbunova's work

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where Alex works in the lab. Those cells, they were found to produce this jelly-like substance in the dish.

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And when she looked at what it was, it was hyaluronic acid. And then she found out that if you take away that hyaluronic acid,

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the cells will divide and become more tumorigenic or cancerous. Conversely, what she's doing now is making a mouse

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that has heaps of hyaluronic acid in its body, with the expectation and hope that it will be resistant to cancer.

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Long way of saying that these products aren't just for beauty, they might actually be preventing cancer

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in the skin as well. - Your colleagues at Harvard Medical School, Kristina Liu and Janelle Nassim

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have said that topical HA does work really well as a moisturizer. But they've suggested

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that if the goal is to improve volume loss and laxity of the skin,

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that you might want to consider an injectable HA, does that make sense to you? - Well, it does. Cause HA is typically a big chain of chemicals.

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It's sugars put together and they don't get into the skin unless they're really small. So one way of doing it is injecting it into the actual skin.

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But even then it's hard for the cells to take it up. So one other way that's in some cosmetics is to have small chains of HA.

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Oligomers, they're called, to let them get into the skin and then let the skin synthesize those chains

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inside the cell where they belong and also outside. That can be done naturally.

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But also what we discovered in patented in my lab is that resveratrol boosts the HAS2 gene,

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which makes the enzyme that makes those strands of HA. - David, a lot of things we've discussed so far.

## **Botox, Skin Peels, and Microneedling**

41:47

At first, they seem purely cosmetic, but then when we've dive a little deeper, we realized there were some anti-aging implications.

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So I didn't want to move on from skincare until we talked about what is probably the most popular intervention

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for wrinkles, for aging skin, and talk about whether or not there are any anti-aging implications in Botox.

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- Right. Well, besides retinol, Botox is the most popular treatment. And let's talk about what Botox is.

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I think most people know, but let's just remind everybody. It's a toxin that comes from a bacterium,

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clostridium botulinum. It's found in foods. If you eat it, a lot of it,

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So you don't need much. - You're about to lose 'em. - Nanograms will kill you. In fact, if you have, what is it? A gram or kill a million people,

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and 2 kilos can kill all of humanity. It's that toxic. - And we inject this into our faces?

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- We do. And it's very effective at getting rid of wrinkles. There's no question. The way it works is it inhibits neurotransmission.

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And neurons are telling the muscles in, let's take my forehead, for example, are pinching off the muscles, they're tighten,

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and you get the wrinkles. So if you get Botox in there, the muscles will relax. And then the wrinkles will go away for six to nine months.

43:05

You have to keep repeating it though and keep getting injected in those spots. - But this is not a clearing out of cellular senescence

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or REX, differentiation of cells. This is just numbing the nerves.

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- Right. It's purely cosmetics, as far as we know. It's not medical.

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It's not treating headaches, which it can be used for. But that's okay. If you look good, you're going to feel better.

## **No Duh Stuff: Sun Damage, Smoking, Alcohol, and Bad Food**

43:29

You're going to have a better social life. All of that's good for longevity. So it's still worth talking about.

- Okay. Let's talk about skin peels now.

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Same thing? No real benefit? I mean, it just make your skin look nice and shiny and clean, but no real benefit?

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- I think this would be an area of just getting things smoother,

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not really changing the age of the skin itself. But there are some treatments that probably cause enough havoc and damage to the skin

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to induce minor stress, adversity. Hormesis, as we've called it. And that would be microneedling.

44:01

So I've never had microneedling done, have you? - I mean, I've had tattoos. Is that the same thing? - Probably. With some bit of ink.

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I mean, it sounds not too pleasant, but this is a machine that's putting thousands of holes in your skin.

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What's probably happening is that there's a hormetic effect. There's this release of all sorts of repair factors

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and could have long-term benefits on the age of the skin as well. But that certainly hasn't been proven yet. - Almost everything we've talked about today

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has some cost involved. And there are plenty of questions still to be resolved

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on a lot of these things. But there's some stuff that, you know, like I call it the no dust stuff that really obvious stuff,

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but we should probably say it anyway. You mentioned earlier sun damage, staying out of the sun's really important.

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Smoking is really bad for your skin. - That's probably the fastest way to accelerate aging in your body.

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And it shows up on your skin. There's no question. You can even see the difference in people. - A lot of people don't know this,

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but alcohol also shown in research to be pretty bad for our skin. So if you don't need,

45:06

- Right. I didn't know that. I only recently gave up alcohol having seen that study. - And sort of like along those same lines,

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smoking, alcohol, bad food, eating processed foods, eating foods that are rich and fats and chemicals

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and all that gross stuff. - Yeah. It's amazing how much your food can affect the aging of your body and your skin.

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And you can see the big difference if you've ever had a pet and you change the diet of the dog, for example. We see this in our mice.

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We feed them good food, and their skin and their hair changes radically. - And that's the important transition point there.

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The hair also changes as well. What's good for your skin generally is good for your hair too.

## **Hair Loss and Hair Graying**

45:42

Let's talk about hair loss. We're also going to talk about hair graying.

45:49

Look, I started going bald when I was in my mid-twenties. I was told to blame my mother's side of the family.

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Is there any truth to that, genetically speaking? - Well, there's a little bit of truth to that. There are over 600 genes that are involved in hair loss.

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And only about 20 of them are found on the X chromosome, which is what you get from your mother.

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Which accounts for about a 11% of male pattern. Baldness is what we're talking about here. If you're a female it's 50/50,



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whether it comes from your father or your mother, because these genes are carried on the X chromosome.

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So yeah, I mean, a little bit you can blame your mother's side, but most of it is fairly random with your parents.

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But there's a strong genetic component. No question. It can be slightly slowed with these treatments and modifications to your aging rate.

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But ultimately in this case, it's genetically determined. That said,

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no one's ever died from hair loss or hair growing. So it's not such a big issue.

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- And actually it could be dangerous to have long hair in some instances. - Well, yeah. Even in my lab, if you have really long hair,

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and you look into a centrifuge, it can be quite a mess afterwards. - Also, for people who do a lot of work with pyrotechnics,

47:00

long hair, bad idea,. - Right. Says the guy who lost his hair a while ago. - Yes. I'm safe from that.

47:07

But am I aging faster than other people? I mean, is that an indicator?

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Again, I started losing my hair really, really early. Is that an indicator that I was aging early?

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- Not in this case. We've evolved as primates, as descendants of these apes 6 million years ago

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to show off our age particularly as men. Because as we get gray, we lose our hair.

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We become more dominant. We seem to the rest of the tribe, we used to, that we were wiser and we had more influence.

47:39

- We were stronger, we made it through the other apes. That's why we look old. - Yeah. Well, think of the silver back gorilla.

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That's the dominant one, right? Same with humans. This was a sign that you should be given respect.

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Not so much these days in our society. It's more about staying younger. But in previous times,

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even just going back a few hundred years, being gray and distinguished was a real bonus.

48:03

- Okay. Why, just a fundamental level, does hair loss occur?

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I mean, I understand the evolutionary drivers, but at a cellular level, what's going on?

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- Well, it really goes back to stem cells. These are the cells that keep dividing asymmetrically, giving rise to other cell types

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and that they reside in the bulge of the hair follicle. And there are a variety of types. There are some that are just there

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to produce the keratin in the hair. There are others that are there, melanocytes to produce the color. There's a new type of stem cell.

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It's called the HAP, the hair follicle-associated pluripotent stem cell that people have found you can now isolate

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and turn into bone and muscle. We don't know what roles they exactly play, but what happens, what we think happens during aging,

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and was only recently discovered less than a few months ago, is that the important stem cells for hair regrowth

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get kicked out of the hair follicle. They get spat out, which was unexpected. We thought that they died, but they actually get expelled.

49:03

- This going to like shut out like a little can then. - Right. And there's a video of this that I tweeted about at the time.

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So what that means is that you want to prevent them getting expelled. But also you want to maintain their function as well,

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which is all about preserving their epigenome, their ability to remember the type of cell that they are.

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More externally, what we've known since the 1960s, is that the hair follicle shrinks and get small,

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cause in part by dihydrotestosterone. And when that happens, the hair becomes thinner and thinner

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until it stops going through what's called the Anagen Phase, which is the hair growth phase.

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As opposed to the other three phases, which are called catagen, telogen and exogen. - And this is really what a lot of the treatments

## **Topical Treatments, Pills, and Dihydrotestosterone**

49:47

are aimed at preventing. Let's talk about some of those. There's topical treatments. There's pills. There's some other stuff.

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But let's start with topical treatments. These are creams that you rub on your head.

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Did these things work? - Oh, they undoubtedly worked. This is minoxidil also known as Rogaine.

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It was first discovered in the 1960s from a group that was trying to lower blood pressure.

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So what it does is it stimulates nitric oxide production. Nitric oxide is important in Viagra,

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opens up the blood vessels. And they put it into patients and they found that they got extra hair growth.

- And these were patients

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who were dealing with high blood pressure and their doctors prescribed them their stuff. And they came back the next week and they're like, "What did you do to me?"

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- Well, a few months later, yes. Some of them got new hair. And then in the 1980s, it was formulated with an oily substance called DMSO

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to get it through the skin layer in the scalp and found that it actually does slow down hair loss. Mostly at the back of the head,

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but also here. Even though it's not recommended here, it does work if you apply it across the whole top, like that.

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- Retinae also works for promoting anagen? - Yeah. That's a little known fact.

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If you have some retinol cream, 0.5%, you can rub it on your skin to reduce wrinkles, but you can also rub it on the parts of your hair

51:03

that are thinning out or you don't want to lose hair. And especially in combination with Rogaine, minoxidil.

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It works quite effectively to slow that aging process. - Yeah. There's a study that showed after a year,

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if you combine tretinoin, which is retinae, with little bit of minoxidil,

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it resulted in regrowth in 66% of the people after a year.

51:26

- Oh. - That's a good result. I mean, if you're trying to regrow hair, that's a really good result. - Yeah, it is.

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- The problem with this stuff is you've got to apply it several times a day. A lot of people don't like the way it feels on their scalps.

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- Yeah. It's an oily substance. It doesn't look good, doesn't feel good. So most people stop doing that regularly.

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But there's an alternative that doctors are recommending, which is taking a pill. - Propecia. - Propecia.

51:48

Also known as finasteride. Finasteride, Propecia. This is a once a day pill that inhibits testosterone?

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- Well, more specifically dihydrotestosterone. - DHT. - Right. DHT is converted by 5-alpha reductase.

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It's an enzyme that's found throughout the body. Now, dihydrotestosterone is important in the body.

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It reduces fat. It's good for the heart, good for the mind. It has some other downsides. It actually helps your prostate grow

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as you get older and you need to go to the bathroom. So the real question is, what are the best levels for optimal longevity?

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And actually there was a study on that. There was a study of 3,690 men that found that the levels of that hormone were optimal

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if they were relatively low, but within middle range of 9.8 to 15.8 nanomoles per liter.

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And those were the men that lived the longest. - Which is interesting that you're saying there's an optimal level because there has been some studies also looking at,

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for instance, eunuchs, who don't have really hardly any testosterone at all.

52:47

At least not any that's been produced by their testes. And they tend to live a really, really long time.

52:54

So on the face of it, you might think like, "The less, the better." - Well, yeah. the testes are doing more than

53:01

putting up testosterone obviously. And cutting off testicles probably is affecting a lot of things, including the brain, depression as well.

53:07

- Not by the way, a longevity strategy that we advise. - No, we don't recommend that. Talk to your doctor first.

53:14

But what's amazing about eunuchs is that they live on average 14 to 19 years longer

53:20

than regular men that have deep voices. - That's better than veganism, that's better than exercise.

53:27

Like when we wrote this book, you told me that the number one thing that you learned about living longer was eating less.

53:37

- But - I have to change that. - those numbers suggest there is actually something else people could do.

53:42

- Right. Cut off your balls, if you're a man. - But don't do that. - Don't do that. But it's interesting

53:48

that eunuchs tend to live a really long time as do smaller people so the excess of testosterone and growth hormone in general

53:56

seems to be promoting an abundance memetic, okay? But what's really cool about these eunuchs is that,

54:03

I looked up the numbers, out of a bunch of eunuchs, 81 in total,

54:08

three of them became centenarians, lived to a hundred, which is unheard of in the normal population.

54:14

Normally, the chance in the US of reaching a hundred is only 1 in 4,400 people.

54:19

- So it's one in 4,400. And in the eunuchs, it was 1 in 30. Greater than 1 in 30.

54:24

- Yeah, exactly. That's a 130 times greater than the background rate, the normal rate. So clearly it works.

54:30

It's just not something you'd want to live with on a daily basis. - This might extend your life.

54:35

Like it'll make your life longer, but not better. - Well, and if it doesn't work,

54:41

it'll just feel longer. - This really relates to one of the problems

54:46

with inhibited testosterone, which is that it lowers sex drive. That's a potential side effect to Propecia?

54:51

- Yeah. There's a bunch, including mood swings. Well, you can be depressed and breast tenderness as well.

54:58

- Yeah. You really have to just hate the idea of being bald to go through or to subject yourself to a lot of this stuff.

55:06

- Well, I disagree. Because these are side effects that are in a low number of people.

55:11

So you could try it if you want to see how it affects you. And if it's fine, then good to go. But make sure you tell your doctor

55:17

if there's something else going on. - There's another intervention that has, as far as we can tell, almost no side effects whatsoever.

## **Frickin Laser Beams: Low-level Laser Therapy**

55:24

It sounds super cheesy and futuristic, fricking laser beams.

55:31

- Yeah. Laser beams. I didn't think this was real. It sounds crazy. You shine light on your head and your hair will grow again.

55:38

Come on. But I looked into it and it's actually been approved by the FDA as a treatment.

55:43

There are combs that have red laser light, and caps that you can wear. These are typically treatments

55:48

for 10, 15 minutes a day or every other day. And they literally have been proven, clinical trials,

55:54

to slow down hair loss, as well as regrow some aspects of hair in, not everybody, but in the majority of people.

56:00

- And this is called LLLT? - Low laser light therapy.

56:05

- Therapy. I think that's right. And we're not quite sure how this works.

56:10

We know it works, we're not quite sure how. There's a leading theory about mitochondria.

56:16

- Yeah. Some people think it's due to heat. I think that that's a bunch of BS. What probably is happening that makes sense to me

56:23

is we've heard about nitric oxide earlier about opening up the arteries and the blood vessels.

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Nitric oxide also controls mitochondrial function. And that laser light has been shown to dissociate this nitric oxide enzyme from,

56:40

what we talked about earlier in another episode, the electron transport chain. There are proteins that make the energy.

56:46

They're called the electron transport chain. There are five of those, and they're made up of multiple proteins.

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And number five gets disrupted by laser light. In fact, this nitric oxide, synthase,

56:57

which is a protein that we mentioned earlier for blood vessels, also plays a role here. And the laser light takes away that protein,

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that nitric oxide, synthase moves away. And now what you get is a bunch of free radicals in the mitochondrion,

57:09

which results in what we call mitohormesis, A little bit of what doesn't kill your mitochondria makes them stronger and multiply.

57:16

And probably that increase in energy is what allows those stem cells to stay young and rejuvenate.

57:21

- Like rejuvenating stem cells, which means that all of these strategies

57:26

for addressing balding,

57:31

the creams, the pills, the one that's actually having potentially seems to be having an actual anti-aging effect

57:39

is the fucking laser beams. - It is funny the world we live in. But it's beyond hair now

57:45

that it looks like shining red laser light, which can penetrate deeply into the skin, even into the sub layers

57:50

can be beneficial on the entire body. And this is why we're seeing a huge increase in the sales

57:55

of saunas that have infrared laser light as well. - Let's talk about platelet-rich plasma injection.

## **Platelet-rich Plasma (PRP) Injections**

58:04

Another thing that's gaining popularity for a variety of conditions. A lot of athletes use these

58:09

to recuperate after sports injuries, but people are increasingly using these

58:16

for hair loss as well. - They are. It's a platelet-rich plasma, PRP.

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And what you get done is you go into a clinic, they'll take out your blood, they'll spin out the cells, take the platelet-rich plasma,

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and inject it either into your veins for longevity. Or in most cases, put it into your scalp

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in many different places with a needle. They anesthetised it so that you don't cry too much.

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And what is probably happening is that this plasma is filled with a bunch of goodies. Exosomes we've talked about before,

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hormones, little peptides, probably what are called VSELL, very small embryonic like cells.

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We're get to that in another episode. This mixture of things probably helps the stem cells in the follicle

59:00

get rejuvenated, maybe even turn back the clock on those. But exactly what component in there that's working?

59:06

We really have no idea. - You know the point of frustration in irony, which is that blood banks and hospitals systems

59:13

are trying to get people to donate platelets, for lifesaving research and therapies.

59:20

But one good way to get people to get their platelets out of their body is to tell 'em that they can regrow their hair.

59:25

- Yeah, it's true. There are a lot of people who don't just care about feeling good and living longer, but also how good they look,

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and are willing to spend a lot of money on that. - Is there an anti-aging pathway involved in the PRP, do you think?

59:36

I mean, you noted these like the exosomes and the peptides, these are all things we talked about last episode.

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It sounds like potentially. - Well, undoubtedly. We know that when you fuse the blood systems,

59:47

the circulatory systems of an old mouse and a young mouse, the young mouse makes the old mouse rejuvenated and younger.

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We don't know all the components in there. There are some of them. There's one called GDF15, for example,

59:59

but we don't of what's in this mixture that promotes hair growth. When it's found, it'll be purified

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and probably be given as a cream or an injectable. But until then, it's this messy PRP treatment.

# Hair Aging, Stress, and Gray Hair Reversal

1:00:11

- Before we move on from balding to graying, there's this sort of like hair thing

1:00:19

that a lot of people are familiar with when they age and that is it stops growing on your head,

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it starts growing in other places. You get in your nose. Your eyebrow hair start to get long. You get in your ears.

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What's going on here? - We don't really know why hair starts growing in the wrong places, as annoying as it is.

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Probably I think what's happening is that we have this evolutionary program where we used to be a lot hairier,

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six to 10 million years ago. And those stem cells are still ready to grow thick hair in our ears, on our nose,

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wherever you don't want it to grow. And that the changes in the structure of the DNA,

1:00:55

what we call the epigenome, is changing over time. And that those regions that are normally silent,

1:01:01

in the ears. So you don't get hairy ears, are unraveling as part of the aging process. - So these are parts of ancient genetic code

1:01:10

that have been allowed to escape from the histones, and now they're readable by the cells.

1:01:15

- Right. And we become our ancestors, unfortunately. So shave or pluck that out for now.

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What that means is we would predict that if we can slow down aging using the methods that we've talked about in this

1:01:26

and other episodes, we should also prevent that process from happening, or at least delay it till much later in life.

1:01:33

- Would that be the case with graying hair too? - It could be. Because graying is part of not just a genetic program,

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but can be accelerated by things that are also known to accelerate aging itself, such as psychological stress.

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- This is really interesting because we know from some fairly recent research that stress plays a key.

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I mean, it's always been sort of known, "Oh, you're going to make me go gray." Right? My grandmother, "You're going to make me go gray." And I'll be like, "Grandma, you're already gray."

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But we've long known that gray hair is associated with stress.

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What's coming out now is that it doesn't have to be permanent. - It's been known for probably centuries  
1:02:10  
that you can have these binary colored hairs, where at the tip of the hair, it's dark. And then it's gray in the middle,  
1:02:15  
and then dark again at the bottom. And people have wondered what the heck is going on. And just recently in 2021,  
1:02:20  
a group of researchers had a look at what was happening in people's lives during that gray hair growth period.  
1:02:26  
And they found that they were remarkably stressful periods of those people's lives where they didn't stop working,  
1:02:32  
they didn't sleep, they didn't go on a vacation. And so I think it's very clear that stress can induce gray hair,  
1:02:39  
a loss of color from the hair. But what's also remarkable about that finding is that it proves that gray hair is reversible.  
1:02:46  
- Which means that what we're talking about here is an epigenetic effect. - Sure. I mean, anything that is genetic  
1:02:52  
is essentially irreversible. So this is an epigenetic effect. What I would imagine  
1:02:57  
is that after you've been for many, many years, it's going to be very difficult to reverse that.  
1:03:03  
But in the early phases, when you're getting this spattering of gray and color, gray and color, you are able to get those packages of DNA  
1:03:11  
back to where they were when you were young using some of the methods that we're talking about today. And we've talked about in other episodes.  
1:03:17  
- And this has to do with those stem cells that produce pigment. They're melanocytes? - Yep.  
1:03:22  
- And these sit right next to our hair shafts. - They do. And they inject the color as the keratin is being put together into that hair shaft.  
1:03:30  
And the prevailing theory as to why we get gray is that these melanocytes die through a process called apoptosis.  
1:03:36  
Hopefully that isn't true. I think it's true for very late in life. But what we're seeing in this new study is that they become dysfunctional before they die.  
1:03:44  
And that's a period that we have a chance to recover their function and prevent them from dying.  
1:03:49  
And there are a number of ways that I could think of at least, to reverse that and prevent them from dying.  
1:03:55

One way though, would be to use some of these adversity mimetics to get that epigenome to reset.

1:04:01

- That's what some researchers have done in mice, at least, in a fairly recent study, actually this year,

1:04:07

using a combination compound. Including cyclosporine, a minoxidil,

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which is the cream that we talked about earlier, and then another pigment-promoting drug. We dug into this a little today,

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and got really excited by what we found. - Yeah. Because the paper tries to obscure what this actual chemical is.

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This age-reversing and pigment-promoting drug. Turns out it's called tacrolimus,

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which is a very similar molecule to rapamycin or also known as sirolimus,

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which we've mentioned in earlier episodes is one of the main drugs that can extend lifespan and inhibit this complex of proteins called mTOR

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that responds to fasting. - And like cyclosporine, it's an immunosuppressant. Which means it's an adversity mimetics.

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It's showing your cells that times are not all that great right now. - Right. It's making your stem cells freak out

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that things are going to be rough. And maybe we should be rejuvenate and start growing a little better. I just want to mention this cyclosporine A,

1:05:04

it's really interesting. You said it's an immunosuppressant. It's used to prevent organ rejection. In my lab, we found it also rejuvenates mitochondria

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through actually making sure what's called the mitochondrial permeability transition pore or MPTP

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is preserved. Long story short, I think this combination of cyclosporin A for mitochondrial activity,

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minoxidil, which we talked about, improved blood flow. And this pigment-promoting drug,

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which is basically an analog of rapamycin, which simulate a fasting response,

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is the triple combo for hair repigmentation. - This is not yet ready for human use.

1:05:43

Undoubtedly, there's probably somebody trying this out in Hollywood. But as of right now, this is still sometime into the future.

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- I think so. You know, people are already trying rapamycin as a drug, 10 milligrams every week or so.

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This is only being done by a few people under doctor supervision, but I could imagine that there will be products

1:06:03

made available to the general public one day that would definitely restore hair color. It's not a miracle that this happens.

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It's just science and we're going to figure it out. - And just like another one of those cases where when we address an aging pathway,

## Targeting Aging Upstream

1:06:17

we're addressing things that are downstream of that aging pathway. And this really relates, I think, really well to a general theme

1:06:25

of what we've been talking about over the past few episodes, which is probably the individual problems

1:06:32

that come with aging that we talk about right now are not the things that need to be addressed if we can hit aging

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somewhere up to stream of those problems. - Yeah. And another important point is that when we learn how to reverse aging in the skin

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and rejuvenate the hair and get it to produce more color, those lessons can be applied across the body.

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Because all cells have a fundamental root cause of aging and the same defense pathways against that process.

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So for instance, rapamycin, cyclosporine, minoxidil, these could be used perhaps in really low doses

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and under clinical conditions, tested to see if they have rejuvenating effects in other organs as well.

1:07:09

- So maybe right now, we're trying to figure out how to help people keep their hair more colorful,

1:07:15

try to keep it in their scalp rather than on the floor. But sometime down the road,

1:07:20

we could be addressing things that are far greater importance to far more people.

1:07:26

- Right, And we foresee a day in my lab where you can take a pill, maybe three pills,

1:07:32

and you'll not just get younger, but your hair will regrow and become dark again if you wanted to. - So we've covered a lot today.

## Today's Takeaways

1:07:38

As always, if people want to go back, they can use the show notes, which are timestamped to find the thing that they want to talk about.

1:07:45

Just gimme a big picture here though, of everything that we've talked about and what's the big takeaway today?

1:07:52

- Well, the big takeaway is that we're on the verge of being able to reverse aging in the body internally, but also externally.

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And that'll be a world where people not just live longer, but feel better about themselves as well.

1:08:04

We've talked about injectables, edibles, smearables. It's a lot of ways of getting these molecules into the body.

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Not just ingesting them, but putting them on the surface and getting them into the layers where they needed to slow down or reverse aging.

1:08:17

And there's a lot to talk about about the future of all of this development and what we're going to be seeing

1:08:22

in the next 5 to 10 years as well, which we'll cover in a later episode. - At the top of the show, I mentioned that I had come into this topic

1:08:29

a little bit reluctantly. I didn't think we really needed to be spinning our time, helping people. - You thought it was a superficial topic.

1:08:35

- I did. I thought it was a superficial topic and I can admit when I'm wrong. - Rarely, but yeah.

1:08:42

- Once in a while. This isn't just about looking good.

1:08:47

This is part of the progression of the things that we've been talking about throughout the course of this series.

1:08:54

None of this negates. Also the importance of doing the exercise and eating well,

1:09:00

and engaging the circuits in your body that respond to adversity.

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- Getting enough sleep, don't stress, all of that stuff we talked about. - All that stuff is important. But then the outcome of that

1:09:12

is it can be that you look better. That's okay. - Right. So the moral of this episode is,

1:09:19

if you can keep yourself looking good by doing the right things, you'll probably end up living longer too.

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