

[MUSIC PLAYING]

From the campus of Harvard Medical School, this is ThinkResearch, a podcast devoted to the stories behind clinical research. I'm Oby.

And I'm Brendan, and we are your hosts. ThinkResearch is brought to you by Harvard Catalyst, Harvard University's Clinical and Translational Science Center.

And by NCATS, the National Center for Advancing Translational Sciences.

[MUSIC PLAYING]

After a surgical procedure, we often expect to receive stitches to close a wound. As patients, we expect closed wounds to facilitate healing and cleanliness. But what if we thought about this process differently? Could a wound left open heal more effectively than a closed wound?

After 18 years of experience in dermatology treating skin cancer, Dr. Victor Neel is finding that wounds left to heal open are no more likely to become infected than closed wounds. Now, Dr. Neel is trying to understand why. Dr. Victor Neel is a board-certified dermatologist an assistant professor of dermatology, and the director of Massachusetts General Hospital's Dermatologic Surgery Unit. Dr. Neel, thank you very much for joining us.

Oh, it's my pleasure. Thank you.

So we're going to talk with you about a project that you recently got a pilot grant for, and you're looking at how bacteria on the skin can affect infection after surgery. Tell us a little bit about your background and where you got the idea for this project.

Sure. So I'm a dermatologist. I've been in practice for about 18 years at Mass General. My specialty is surgical dermatology, so I had apart from dermatology, some extra training in skin cancer surgery and facial reconstruction. A lot of skin cancers-- most skin cancers affect the face, and to remove them, we create some damage, and the surgical reconstruction is part of that.

Since I've been at Mass General, I've treated about 25,000 cases of skin cancer, so I have a lot of experience treating skin cancer. And what I've noticed over the years is that some of the skin cancers that we leave open to heal do very well. So in selected cases, instead of surgically closing with sutures and doing facial reconstruction, we let a lot of the wounds that we generate after we remove the cancer just heal by themselves, and we actually call that second intention healing.

I incorporate about 40% of second intention healing wounds into my surgical schedule. So over the years, I've seen a large number of wounds heal completely open. That's a shock to me as a dermatologist and as a surgeon, because in medical school, we're not used to seeing wounds heal open. We close them. That's what doctors do. They usually close wounds.

But over the years, I've had the opportunity to see a lot of wounds heal open, and we've noticed a number of interesting things about them. Others have as well. It's certainly not an unusual thing to leave a wound open to heal.

Some of the things we've noticed but haven't really been well documented until recently have been things that were surprising. For instance, wounds that heal open-- so without sutures-- have an infection rate very similar to when we close them. So most people would assume that if you leave a wound open to heal, the risk of infection would be higher. So bacteria from the environment from-- the bacteria that live on your skin would-- you'd think that the longer a wound is open or the larger the wound is that you'd have more opportunity for infection. It turns out not to be true. So that was always interesting to me.

About a year and a half ago, I enlisted one of our residents, Sherry Yu at Harvard, and a medical student at Harvard Medical School, Gabriel Molina, to help me look at the data that I had accumulated over 18 years to look at the infections we had and to just characterize the types of wounds, the locations of wounds, the size of the wounds. And we noticed something that I had suspected for a while but we hadn't been able to document, namely that the size of the wound that we generate after skin cancer surgery really isn't directly related to the risk of infection.

Again, I think that was a surprise because you'd think that the larger the wound is, the more likely it is that it would get infected by bacteria in the environment. So that turned out not to be true. So even large wounds many square centimeters in size have the same risk of infection as small wounds as small as 1 square centimeter. So that was interesting.

The other interesting thing that we noticed from our data was that even though these wounds-- when they heal open, one problem with healing by second intention is that it takes a long time. So if you suture a wound, it heals pretty quickly, and that's a big advantage sometimes. The larger wounds take much longer to heal, sometimes a couple months. They're often easy to take care of, and our patients don't generally have problems taking care of them.

But we thought a priority before we looked at the data that the longer a wound was open, the higher the risk that it would get infected, similar to the observation about the size of the wound. And again, that turned out not to be true. So all of the wound infections-- and we documented several dozen over the years, several dozen over the years that I've been operating-- the infections always presented quite early in the healing phase, usually within 12 days.

So even though the wounds were open sometimes for months, exposed to the environment and all the potential pathogens that are floating around on your skin and in your home, if the wound didn't get infected within two months, it had a very low risk of infection. So that really was surprising, and we recently published that information in one of the journals, but it also led to some other ideas why this happens. What is the underlying basis for these observations? And that's how I got interested in the microbiome.

OK, so the study you're doing now is looking at the microbiome of the skin and how the organisms that live on our skin might influence that process of infection. Just to go back, for people who are not in the medical field, when you talk about leaving a wound open, you're still talking about dressing it and covering it somehow. It's not like an exposed wound. So could you talk about maybe what one of these wounds would look like?

Typical. Yeah, I actually sent Catalyst some pictures, and hopefully they'll be available on your website so people can actually look at some wounds and what they look like when they're healing. But essentially, the main dressing we use is just plain Vaseline that you could buy at the drugstore.

And dressing-- the dressing is really not to keep things out. The dressing that we put on is mostly to keep the wound moist. Wounds that are moist heal more efficiently. And as the wound is healing, it's sometimes-- it often-- well, actually, it always secretes some fluid until there is a natural barrier of skin. So it's more to prevent the wound from becoming messy rather than to prevent infection. So we'll have patients apply a thin layer of Vaseline and some plastic-backed gauze until the wound is-- skin has healed and it's re-epithelialized.

And again, that can take various amounts of time depending where the wound is. Wounds on the face heal very quickly. Actually, the wounds that heal the fastest on the face are on the lower lip. They heal at a very quick rate, and even a large wound will close within a week or two.

On the lower extremities, it's quite the opposite. Those wounds take a long time, sometimes up to two to three months to heal. But it's still the same protocol-- just a thin layer of Vaseline to keep the wound moist and a covering. We don't use any topical antibiotics unless we-- or oral antibiotics-- unless we suspect infection.

So you said that up 'til now, what was surprising to you is that this hasn't been done, that nobody has looked at what kind of bacteria colonize wounds when they're opened. Do you have a sense or a theory about why this is? Is there just a complacency?

No, it's definitely not complacency. Well, there are a couple reasons. One is in medicine, we try-- there are not an unlimited amount of projects to do. We have to sort of focus on what's clinically relevant, and until recently, we probably assumed that the pathogens that cause infection are the clinically relevant ones. So we've spent a lot of time creating antibiotics to kill them and figuring out ways to sterilize our instruments and our hands and to prevent pathogens from flourishing.

What has been under-appreciated is that-- and that's also for a couple of reason-- but under-appreciated that commensal organisms may have a positive role. The skin microbiome is kind of the poor stepchild of the gut microbiome. Gut microbiomes-- I don't know if you've discussed it on your podcast before, but that's received a lot more attention. It's a larger microbiome. So most of the organisms that inhabit the human, either outside or inside-- most of the organisms are in the gut.

And a serious condition that arises from the overuse of antibiotics is something called pseudomembranous colitis, and it's caused by *C. difficile*. And that's a life-threatening disease, and it usually occurs when doctors, for good reasons, have wiped out all of the cells and all the bacteria in the body. And *C. difficile* can colonize and in fact creates a terrible, life-threatening diarrheal disease, which is unfortunately very serious and claims a number of lives.

Well, it turns out that one of the reasons that *C. difficile* doesn't occur more commonly is that it's in competition with the billions and billions of normal bacteria that live in our gut, and when you destroy those with antibiotics, it creates a situation where there is a selective advantage for *C. difficile*. That's probably very similar to what's happening on the skin, and we just haven't had the tools until recently to carefully identify the organisms that are causing-- that can colonize normal skin and potentially prevent infection.

About a decade ago, we were able to-- not we, of course, but the scientists--

The science we.

Yeah. They were able to come up with very sensitive techniques of sequencing DNA in human swabs from human skin, and you can really identify all the bacteria that are present on the surface of the skin. A lot of them don't grow in the laboratory.

So all these years where physicians like myself have been looking at wounds and culturing them and sending them to the laboratory to identify pathogens, all these natural bacteria were kind of selected against. There are no special media in the laboratory that would allow them to grow. So we kind of knew they were there, because you can do special stains and see them, but we didn't know how to grow them. And if you can't grow something, it's quite hard to study it. And if it's not a pathogen, it's also less interesting.

So for those reasons-- because we didn't think that they were causing a problem, and we didn't have the tools to really identify them carefully-- kind of ignored them, and we hope to change that with some studies that Catalyst has allowed us to start at Mass General.

So the way we've decided to approach that is we're going to catalog the regional variety of bacteria in normally healing wounds. So in any given day, I might create 10 wounds doing skin cancer surgery, and a subset of those will be left open to heal. And we work on the face. We work on the trunk, anywhere there's skin cancer.

So what we'd like to do is-- and we started to do this already, and our patients are very anxious to help us, mostly because they're very thoughtful patients, and they want to contribute to anything that could lead to decreasing infections. What we've done is we're starting to bring patients back with open wounds, opened healing wounds, at different periods of time five days a week, two weeks out.

We know from our initial study that I described before that whatever's happening in terms of creating immunity to infection, it's happening in the first one to two weeks. After that, wounds are extremely unlikely to get infected. So we think we have the window of interest at one or two weeks.

So we're asking our patients with open wounds-- it may be on the lip. It may be on the cheek. It may be on the nose, the back, everywhere that we sort of do skin cancer and let the wounds heal open. We're bringing them back in a week, and we're analyzing, both by culturing-- so we're going to send swabs to see what the general microbiology lab is able to grow.

And we're also doing swabs to look at what's called 16S DNA, which is bacteria-specific DNA. It allows us, once we sequence it, to identify not only what kind of bacteria is present, but also the relative quantity. So we can really get a snapshot of the regional variation of what's normally growing when you allow a wound to heal by itself, open to the environment.

We think that once we characterize that, it'll give us a much better idea what the normal bacteria that may prevent wound infection-- what those bacteria are, and possibly give us maybe even a therapeutic option in the future. For instance, you might imagine that if we find a very common bacteria that is always present in wounds at a week and those wounds never go on to get infected, you might think that adding those bacteria to a newly generated open wound to colonize the wound prior to allowing an opportunistic infection to take over could maybe alter the course or even completely prevent infection going forward. So we're really just cataloging right now to really get a-- to see what the spectrum of normal bacteria that are growing in these wounds.

Is there a difference in the types of procedures that you see with infection, or is that not something that you're looking at, really?

You mean-- do you mean, do certain procedures predispose to different rates of infection?

Yeah.

Yes. Well, the thing that's fascinating to me is that the wounds that we close surgically, even though we have this a priori idea that those are wounds that will do better than wounds that heal open, there's a natural tendency, even amongst my colleagues who have a lot of experience, to surgically close everything. That's the way we're taught to do it, and that's the way a lot of people do it. However, I find that wounds that are closed, especially on the face-- some of the wounds have to be closed under a lot of tension with sutures, and those wounds are, in my opinion, much more likely to get infected than wounds that are left to heal open.

And why does that tension create the infection?

That's a good question. We think that-- if you think about it, if you and I existed 200,000 years ago, we have the same physiology now that, essentially, that we did then. We must have encountered small wounds all the time. I mean, it's only our modern society that has very smooth surfaces, and you could go a whole year without getting a scratch now. But you can imagine if we lived in a cave or on a big, open plain, we probably had small wounds all the time, and if it were so easy for us to become infected and suffer the consequences of infection and die that we wouldn't have survived.

So even though the human skin is extremely fragile, we've co-evolved mechanisms to heal open wounds, and certainly, one of them is our immune system. We have a very powerful immune system. Our hypothesis is that open wounds cooperate-- I'm sorry, that the immune system cooperates with the organisms that naturally live with us to prevent infection.

But however, when you suture a wound, that's sort of a situation that the human body would never encounter 100,000 years ago when we were evolving. There were no sutures, no suture kits, no surgeons. So that's a situation that the body has never encountered.

So to me, it's always surprising that the wounds that we suture close under tension heal as well as they do. It's not surprising to me at all that open wounds heal without a lot of consequences.

And what happens when you surgically close a wound under tension particularly-- and we try as surgeons, as reconstructive surgeons, to close wounds in a way that minimize tension. If you ask a plastic surgeon or a dermatologic surgeon why are you trying to close a wound without tension, their main reason they'll give is that it leads to less scarring, and that's true.

So wounds that are under less tension generally look better when they're done healing. But the other reason that it's advantageous to close a wound without a lot of tension is that that environment-- it compromises the vascular system. The body kind of freaks out in a lot of ways. The immune system is really not able to cope with a wound that is closed under tension as well as an open wound.

So that is one of the reasons that when a wound that's closed under tension does get infected, it can be a lot more serious. The bacteria seem to thrive in that environment, whether there is less oxygen available to the immune system or to the normal bacteria that the pathogen can thrive on, that whether that creates a different metabolic environment that is not good for wound healing-- there are a lot of theories about that. But those are not present. The tension of a sutured wound is a condition that's not present at all when a wound is healing open.

So you've talked a little bit about the immune system, how it responds when a wound is created, and you talked about white blood cells. And is there anything more that you think is important about in understanding how the immune system and the bacteria work together?

Yeah, that's actually a fascinating topic that's only recently being investigated, and it's still being investigated mostly in laboratory models. It's been hard to investigate in humans. So for instance, some things that have been determined-- that some of the commensal organisms-- there's an organism called Staph epidermidis, which is commonly found on human skin, and it's related very closely to Staph aureus.

However, Staph epidermidis is not a bacteria that causes infection, generally. And scientists in the laboratory have shown in recent years that the immune system cooperates directly with staph, Staph epidermis cooperates directly with the human immune system. They're passing signals to each other constantly.

And the human immune system becomes tolerant to Staph epidermidis very early in childhood. It's probably one of the first organisms that when you're delivered-- when you're delivered at birth, you're coated in bacteria from the birth process. And some of those organisms-- most of those organisms will immediately start to colonize the human and start to communicate with the evolving immune system.

When you're born, your immune system is very primitive, or it's prematurely primitive. It has to educate itself. And in the presence of these normal organisms, it learns to tolerate some of them. It's very similar to the theory now that you should be-- that kids who are restricted from dirty environments have more allergies later in life. It's because their early immune systems aren't educated the same way that other kids would be.

Similarly with skin microbiome, we start to develop systems that work together between the microbes on the skin and the immune system, and they're constantly communicating. So that's work that's recently been elucidated in detail, but it's just the tip of the iceberg.

There are dozens of different types of bacteria that populate the skin that we really know nothing about, and it's probably untrue that they're just hanging on for a meal. They're probably actively facilitating different functions of the normal skin, and we're just beginning to understand some of those functions. It's fascinating.

You made the comparison earlier between the gut microbiome. I wonder if there's a-- and then, you've talked about the idea that-- this bacteria just along for the ride, basically. Is there any-- has the idea that the gut microbiome-- I mean, I guess we do know that the bacteria in the gut provide a function, provide vital functions in digestion and regulating--

And it goes--

--body systems.

I mean, it goes further than that, apparently. I'm not a gut microbiome expert, by any means. But if you-- almost every week, there seems to be a new association between a normal human function and the gut microbiome. For instance, I was just reading that it turns out that Parkinson's disease and maybe Alzheimer's may be influenced by the gut microbiome. Obesity seems to be correlated with what kinds of bacteria are normally growing in the skin.

So it's really this hypothesis that the bacteria are just kind of living off of us is really quite not true, and it might even be the reverse. We might just be living off the bacteria. But in any case, there seems to be a reciprocal relationship that's evolved over time, and if you mess around with that by destroying bacteria, you definitely risk some adverse effects.

Surgeons are generally taught that we want to eliminate bacteria from the surgical site, and that's the teaching. And I think even at home, you get the idea if you scrub your skin more with soap, that's a good thing. You're killing the bad-- you're eliminating the risk of infection, and it may just be the opposite. It may just be the opposite.

So one of the reasons that-- I might have mentioned that the lower legs where we operate, they get infected at a 5- to 10-fold higher rate than other areas in the body, and physicians have hypothesized various explanations for this. Some are that, well, patients can't take care of their legs. They're not cleaning the area enough. They're just not taking care of the wounds. But it turns out probably the opposite.

So the lower leg is an area of the human body that has very low density of bacteria. There just aren't many there, normal or abnormal. There are a lot of different species that are present, but they're there in very low concentration.

When you sterilize the skin, either the surgeon does it when he rubs on antiseptics or you do it at home by washing scrupulously with soap, which is a great antiseptic, by the way, you're really destroying not just the potential pathogens, but also the commensal organisms that are just possibly useful for wound healing. And that creates an environment-- when you have a low concentration of bacteria, it favors pathogens. And the same reason we were talking about with pseudomembranous colitis, when you wipe out the good bacteria, you just have *C. difficile* hanging around, and that actually is a setup for infection.

So we've been teaching people how to keep their wounds clean all these years, and I'm not recommending that patients keep their wounds dirty by any means yet. But it may turn out that we've been doing the exact wrong thing. We've been really giving the pathogens sort of a carte blanche, an opportunity to get in before the good organisms do and colonize and create a barrier to infection.

So a lot of the teaching-- I love taking on topics where one of the possible outcomes is something uproots our common wisdom. I think it's just fun. And this may be one of those situations where we've just been looking at it completely the wrong way.

Wow. So you talked about-- a little bit-- the goal of the work, and you just mentioned upending conventional teaching. But what are the goal-- what's the goal of this pilot study, and how do you see this leading into future work? And maybe what kind of treatment could you see coming out of this?

So my biggest hope for this study would be that over the next four to six months-- we've already started recruiting patients, and it's going very quickly. We're getting a lot of help from Jeremy Wilkinson, who's at the Harvard core in the microbiome sequencing, and we have a lot of nice residents who are helping us. Sherry Yu and also Sameer Gupta are helping me with this work. We'd like to catalog the different normal commensal organisms that are present during wound healing and really just create a template or sort of a catalog, like I was saying, to launch into future studies.

So one, my biggest hope would be that if we could identify an organism that we could grow in the laboratory safely that has either a zero or a very low risk of causing actual infection, that we would somehow be able to use that as a therapeutic.

So you can imagine you go to the doctor or the surgeon. He performs a procedure, and before you go with a Band-Aid, we have a special probiotic Band-Aid that we give you that has a billion or 10 million normal commensal bacteria that would immediately be put directly in contact with the wound. And that would colonize-- instead of having this competition take place in an open wound with no bacteria and a competition between the bad guys and the good guys, we would deliver in high concentration the good guys. The wound would immediately be colonized. And then, going forward, the risk of infection would be severely limited.

So that would be great. That's going to take a while to develop, obviously. First, we have to identify which organisms are present and test our hypothesis, obviously in the laboratory first before we start purposely introducing bacteria into open wounds. But that's really the goal-- to promote the normal bacteria colonizing the wounds more quickly maybe, and offset their risk of infection with pathogens like Staph aureus.

If it's true that we can possibly intervene early in a wound infection and prevent it, one thing that makes that a more urgent priority is that the overuse of antibiotics has really touched every field in medicine, particularly in what we do. We often have infections that don't respond to many antibiotics, just from overuse. So this might be a way to mitigate the use of antibiotics.

There certainly are antibiotics that save lives, for sure. I mean, antibiotics have just changed the course of human history, but the judicious use of them going forward is critical because of the antibiotic resistance that's been generated by their overuse. So coming up with ways to decrease antibiotic use-- and maybe this could be one of them-- might be really important going forward so that when we do get a true infection in the skin that has the potential to create a lot of damage, we don't run up against a superbug as frequently.

[MUSIC PLAYING]

Next time on ThinkResearch.

So if we can develop new types of diagnostics that not only can be used at the point of care but also can inform on antibiotic susceptibility, that could enable us to have a greater arsenal of strategies for tackling antibiotic resistance.

Dr. Yonatan Grad of the Harvard T. H. Chan School of Public Health illustrates the importance of studying antibiotic-resistant infection. Thank you for listening. If you've enjoyed this podcast, please rate us on iTunes and help us spread the word about the amazing research taking place across the Harvard community.

To learn more about the guests on this episode, visit our website, catalyst.harvard.edu/thinkresearch.

[MUSIC PLAYING]