Chronic Itch
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Brian Kim, MD, FAAD, interviewed by Steven Chen, MD, FAAD

STEVEN CHEN, MD, FAAD: Welcome, everyone, to another episode in *Dialogues in Dermatology*. Today, we are excited to talk all about pruritus and itch. My name is Steven Chen, I will be your host for this episode. And I am delighted to be joined by Dr. Brian Kim, who is an Associate Professor of Dermatology at Washington University in St. Louis. His clinical and research career has really centered around atopic dermatitis and itch. And I am thrilled that we all get to learn from him today. Brian, thank you so much for joining us today.

BRIAN KIM, MD, FAAD: Thanks, Steven, for having me.

STEVEN CHEN, MD, FAAD: So I'm going to jump right in, because we don't have that much time and there's so much I want to talk about. The first thing is as a practicing dermatologist, we have so many patients who are itchy because they have a rash or they're just itchy in general. So just a big, high level question. What exactly is itch and how would you define it?

BRIAN KIM, MD, FAAD: I don't define it, it was defined by Samuel Hafenreffer, I think, a German physician, well over 300 years ago, as an uncomfortable sensation that elicits a desire to scratch. So that's really the definition of itch. And in recent years, we've defined it pathologically as chronic itch being when itch now lasts, rather arbitrarily, six weeks or longer.

STEVEN CHEN, MD, FAAD: So chronic itch, just basically six weeks. I feel like we use that six week cutoff for a lot of different things: for urticaria, for itch, and all that kind of stuff. So Brian, yes, absolutely we have that definition of itch from way back when. I'm curious how you organize the world of itch in your mind. When I have a patient come to see me, I was always taught to think about it as itch with rash and itch without rash. I'm just curious if you have an organizational framework for when you see an itch patient?

BRIAN KIM, MD, FAAD: I think it's very important, the conceptual framework that you laid out, is that there's lots of ways you can go about it. I think the point being is that if you have an itch with a rash, you're actually implying something a little bit more I think, in some sense. What you're saying is that you think the etiology of itch is related to primary dermatologic disorder that is said rash. And that's an important distinction because in the vast majority of those cases, if not all of them, if the rash is the cause, you treat the rash, atopic dermatitis included.—

--And I really fundamentally believe that atopic dermatitis, in its primary kind of form is a rash first, it's not an itch. And I know we say it's itch that rashes, but it really is a rash that becomes an itch. But then there are other conditions, as you're alluding to, that where it's really just itch. And it's unclear how much the rash, even if there is any part of this, other than that it came on as a result of the itch.—

--In dermatology we say, one of the first things we teach our first year residents, the difference between a primary and secondary process. And I think that's a fundamentally important concept in itch, as well. So is itch the primary process or is it the secondary process? And that heavily informs not just an intellectual, something I can pontificate about, but that it informs drug development, it informs personalized therapy.—

--Particularly right now, when there are essentially no FDA approved drugs for chronic itch, all you can do is take a personalized medicine approach. So then you need to think about what is pathophysiologically causing the itch in this patient, clinical trials, forget about it, in this patient, that's the problem in front of me. And big pharmacological trials, I tell my residents, "When you're in with a patient, the clinical trial does not matter anymore, because a clinical trial is a completely contrived tool that you design to get to a certain endpoint in a statistical way."—

--The patient does not care, in front of you. If you say, "Oh, we don't have any FDA approved that's not on-label," they don't care.

STEVEN CHEN, MD, FAAD: You're not showing your disclosure slide at the beginning of every patient encounter, saying, "We're talking unlabeled drugs here." So speaking of clinical trials and speaking of where the field is headed, can you tell us what's new in itch? I think a lot of us in our derm residencies, we learn a lot about the neuropathic elements that make up how the sensation of itch is transmitted. We talk about histamine, we talk about all these difference processes. But what's actually new in the world of itch, both from a pathophysiology standpoint and maybe from a therapeutic standpoint?

BRIAN KIM, MD, FAAD: I think that's kind of the "where are we at" question, which is we're at a very exciting place in 2021. I did this *Dialogues* a number of years ago. And it honestly wasn't that exciting for me, because I was talking about a lot of off-label stuff that I knew kind of works here and there, sure it was helpful. But we're entering a new phase, to your point, where now we're going to be backed up with clinical trials. We're going to have phase 3 clinical trial data that's going to prove it.—

--So what's happening in the field? Why has itch been ignored for over 300 years after being defined? It's one of the biggest in medicine almost, how did we miss it kind of scenarios. For one, there's a lot of things that there's some philosophical things that come into play. And then there are scientific things that come into play. And then there are clinical things that come into play. It's kind of the perfect storm of the disease that we would ignore for a long time.—

--I hope you don't mind me kind of getting into the historical elements of it.

STEVEN CHEN, MD, FAAD: No, I love it, this is great.

BRIAN KIM, MD, FAAD: --Because I think it also tells us how we can fall short and how we need to change the medicine. So who's the author that talked about the life of a cell, those great books about medicine and biology?

STEVEN CHEN, MD, FAAD: Oh, gosh, you're going to make me Google something, aren't you?

BRIAN KIM, MD, FAAD: I remember, because it was very influential in my kind of path into medicine. Anyway, he was talking about how in his father's generation what made someone a great clinician was that they could diagnose somebody. That was the paragon of excellence in medicine. I would say that's kind of the (s/l Ozler) model in some ways. It wasn't treatment, a lot of people don't realize that. And what it meant is that if you could walk into a room and hold a patient's hand and tell them when they're going to die, you're a great clinician.—

--And then he was talking about how in his era that it became the era of treatment. And I think the tail end of that is when I entered medicine. And then more than treatment, it became kind of extending survival and that's where checkpoint inhibitors. But I think the kind of next era of medicine is quality of life. And that's where itch falls in. And it's not about can we make people live longer, can we just put you on a machine and make you live longer, it's can you have meaningful life.—

--And that's where itch really comes in. Because it's really a quality of life issue. You're never going to die from itch. But you may want to die from it. And why did we miss it all? Well, I think a couple of things. There were some misunderstandings. For one, itch is a very shameful symptom. No one wants to talk about itch, we love talking about our pain. A high school athlete loves talking about how he injured his shoulder in the game and this is such, almost talks about it with pride. Itch is not like that.

STEVEN CHEN, MD, FAAD: That's interesting. I never thought about it that way.

BRIAN KIM, MD, FAAD: In fact, my patients are very embarrassed to even bring it up, let alone are they even going to talk about it. How are they going to advocate for it? How are you going to

have a foundation for itch? So that's gone. And then there was a scientific misunderstanding that goes back to von Frey, who was a great scientist. But there was this idea that, and there were some primary observations, that if you put spicules in the skin, it would cause pain but there would be an after-sensation that was itchy.—

--So the hypothesis that lasted for a long time is that itch must be a mild form of pain. Well, we have pain centers, chronic pain clinics, some things went bad. But we have pain. And the great thing about pain is that it is. But now we thought, oh, if we just funded more pain research or if we just understand pain better, we'll be fine, we'll solve this riddle. Never did. And then in 2007, Zhou-Feng Chen discovered the true bona fide first itch receptor, and this is why our center here was started.—

--Scientifically, that was a huge shift. And science matters, I think COVID has told us that. I feel like there was a time in medicine when science was just this kind of great thing that we learned and it gave us this way of talking fancy and then we just would leech people. But I think it's changed, where medicine and science is so coupled now, where within a year you can have a vaccine based on this technology, this idea. It's really changed. And that's definitely been my career and it's why I enjoy it.—

--What happened was that people said, "Oh, my gosh. We've been thinking about itch the wrong way. And there's a target we could hang our hat on and now we can actually go after this." And regardless of whether, that target I'm talking about is GRP, but regardless of whether that's an important target or not, which it very well could be, it was a conceptual shift. And it said, "Oh, this is something we can do." Then that happened.—

--So then what happened, a lot of the work that we did was we said, "Okay, well, if there are true itch pathways, there must be something more going on here between the immune system and the nervous system that would tell us that there are other itch circuits." And we've known for a

very, very long time this kind of ancient inflammatory axis that was evolved to kick out worms, which is the type 2 inflammatory axis. We knew it was strongly associated with itch, we never knew why, and we linked that.—

--And then what happened, now we bring this to clinical trials. You have these drugs that were already in development for atopic dermatitis, with the scientific premise that we're going to go after inflammation. And lo and behold, suddenly these inflammatory pathways are decorating the nervous system. And so then a lot of these companies, and you'll see this in 2021, pivoted a lot in terms of their design, their endpoints, the publications.—

--And realized very quickly, and drugs like dupilumab taught us this, is that itch really matters. Because the thing about itch is you don't know how much it matters when you're talking about a shameful symptom until you get rid of it. We almost learn more from actually doing something about it, because then the patients came out of the woodwork. And they said, "Oh, my gosh, I was miserable. This was horrible." Now they're talking about it. And then I think drug companies started to realize, "Oh, wow, we need to now think about this much more seriously."—

--I know that was longwinded but it brought us to where we are. Now, we have agents that were already in development, but now you have other agents that were now conceived in some ways from the get-go to go after itch. And now that's what we're seeing in 2021, with the new developments there. There are drugs and companies that are just saying, "We're going to go after itch, this is it. This is kind of how we started and this is how we're going to end it."

STEVEN CHEN, MD, FAAD: That's fascinating, thank you for taking us through that. Because I do think that it's easy to condense all of that into some, without really appreciating the path or the time and the effort that it took to get the field to this point, and so I think that obviously is so, so helpful to put everything into context. Would you mind telling us a little bit more about these kind of new agents that are coming out? How are they different than the agents that we kind of

force into using in an off-label way, when we actually get to target, based on new information, about these new itch pathways? What's different about what's coming out on the market soon, or what's being studied, I should say?

BRIAN KIM, MD, FAAD: It's funny, because one example would be the cytokine IL-31 itch. We knew about it for a long time. Stacy Dillon discovered it when she was at ZymoGenetics. And it took a number of years for Martin Steinhoff's group to show that IL-31 actually acts like a neurotransmitter, it hits the nervous system. And that science is really important because it informed the development of nemolizumab, which is an IL-31 receptor blocker, monoclonal, that's not approved, it's in development.—

--One of the things about it is that I think what it did was it informed even the clinical trials and it actually made itch as a primary endpoint. A lot of people I think don't realize this, itch still is a secondary endpoint for FDA approval for atopic dermatitis. So it's not a primary, despite it being the central symptom, the thing the patient cares about the most. But what happened with IL-31 is, and I'm putting my own speculation here, is that based on what happened, is that they said, "Look, we're not going to worry about inflammation. We don't even know if this drug is that great for inflammation, 31. It's a little mixed in terms of what it does inflammatory-wise. But we're going to just go after itch, because that's what this thing does."

--So that's one example. And then you have these other drugs that are emerging, like the kappa opioid agonist, Cara Therapeutics, Trevi Therapeutics are trying to push this through. And these class of drugs are, in my mind, in large part neuromodulatory. So all itch at the end of the day, whether it's inflammatory or not, has to end up in the nerve and it has to end up either in your spinal cord or your brain for it to have an effect.—

--So the idea is that if you can just modify the nervous system with neuromodulatory drugs, then perhaps you could have an effect on the itch, regardless of what's happening upstream. And so

that's a big paradigm shift, primary endpoints for these trials are going to be itch, and itch will be considered a disease entity of itself. It might have to be codified as notalgia paresthetica, uremic pruritus, prurigo nodularis, but these are truly itch disorders. It's hard to call these things rashes, like you said.

STEVEN CHEN, MD, FAAD: I think that speaks to our experience as dermatologists, when we see patients who come in, and as you implied and insinuated, there is, I never thought about applying the word "shame" to the symptom of itch before. And I think that's fascinating, because it is. I see a lot of very sick dermatology patients and it's usually not the sick patients who have that anguish, it's the itch patients that really have this burden, that they feel like they finally get to unload when they've gotten to the point of coming in to see the dermatologist to address it.—

--And it's so great to hear that the state of the science is turning toward looking at itch as a primary endpoint, as a disease entity unto itself. So that's wonderful to hear. Could you tell us a little bit more about your personal work in this field? It's always hard to brag about yourself, I know, but what are you most proud of in terms of your contributions to the field of itch and to the field of dermatology?

BRIAN KIM, MD, FAAD: I think what I'm perhaps most proud of is that we were able to make some key discoveries that made people take itch seriously. I think that's the thing. As I kind of alluded to earlier, I think that if you can bring real science to it, then you convince a very diverse group of stakeholders that this is a worthwhile venture. Whether it's patients, foundations, NIH, pharmaceutical companies, and all of these things matter.—

--I think that for me, the identification, some of it was just luck, but the fact that we were able to discover that therapies that were already in development could work in a very, very different way, that IL-4 and 13 actually act on the nerve, that these processes are very much dependent

on Janus kinases, that this is actually a totally new way to design trials, think about itch, look at high resolution itch. And that now 2021 is just a really gratifying year for me.—

--We're going to have probably four, five, six drugs approved along these pathways. And not only just that they're approved, but they're approved with these endpoints in mind that we've been talking about for the last seven years is being what we think is going to happen in our patients. And I think at the end of the day, the naïve part of me that I didn't realize before was I thought that if we made a great discovery that it would solve itself. But I've seen a lot of great science die in journals and never make it to our patients.—

--And it's unfortunate. So as a physician scientist, what I've realized is that what I always say is our papers are always the beginning of the journey. They might be the end of our scientific journey but they're the beginning of our journey to take this to our patients. And I'm proud that we've been able to do that, to some degree, and that hopefully there's less suffering from this. I mean, try telling your patient that there's no ICD time code for what they have. It's a hard thing to tell a patient.

STEVEN CHEN, MD, FAAD: That's so – just hearing you say that, there are so many potential approvals for drugs to relate to this. Like already in my mind, I've got like my five patients that I know that I want to try these drugs on, because they are the patients that have the burden of their disease is so, so heavy that I think the dermatologist really gets super-involved with our itch patients, because we know every symptom. We know when they can't sleep at night. We've spent so much time with them. And so I think that that's so exciting to think about the revolution that is hopefully what we'll see in 2021.—

--Can I ask, how did you find yourself interested in this area of dermatology? You've talked about obviously the importance of itch and the contributions that you've made. But what was the

initial spark that got you interested in studying itch and atopic dermatitis and all these new pathways?

BRIAN KIM, MD, FAAD: To be completely candid, it didn't start with me appreciating this unmet need. I also overlooked it. But my scientific career started with understanding the immune mechanisms that cause the rash. I was actually originally more interested in the rash. But what happened was we made a couple of key discoveries. And then I was left with kind of this kind of almost early midlife scientific crisis, where I thought what do I want to do next? I don't know if anything I want to do in this area of immunology is that interesting to me anymore.—

--And at that time, I was looking for a job. And they had just started this center for study of itch here. And I met with the neuroscientists here. And they were all excited about the immune system and I was all excited about the nervous system. And we started sharing ideas. And I realized, oh, my gosh, this is it. This is the huge uncharted area. And I remember the moment I realized that and I thought this is what I need, I need to become more of a neuroscientist.—

--And then as I started doing that, what happened was that we would, every time we'd publish a paper, our clinic would get flooded with these calls from all over the world. Because the patients always think when you publish a paper that means that there's a therapy like in a week, or they're very hopeful. And we thought, oh, my gosh, there's so much demand for this. So then I started to focus my clinic completely on itch.—

--I'm not a general dermatologist anymore, I haven't been for seven years. And there's a tremendous demand there. And in the clinic, it was a lot more just kind of helping patients one by one, case by case, evidence based medicine goes out the window because there's no evidence. And so it's almost like I was straddling these two crazy worlds, where I was on the one hand this hardcore basic scientist. On the other hand, you would almost think I was like this kind of holistic healer, because I was having to use anything at my disposal to try to help that

one patient. And there was this kind of gap and that gap hopefully will be closed by the clinical trials now.

STEVEN CHEN, MD, FAAD: That's so exciting. I would just point out the irony of you saying that I was a dermatologist who was no longer interested in studying rash anymore. Because itch, like everything we've been talking about, itch is its own thing. And it's amazing to see your work kind of impact that field and to see it really push the field forward is really exciting. We don't have that much time left, but if it's okay with you, I would love to leave some of our perhaps younger listeners with some sage words of advice from you. I'm just curious if you could provide any words of advice for potential future academic dermatologists who might want to pursue a similar career to you. What would you say to them as they're thinking about their future career?

BRIAN KIM, MD, FAAD: Obviously, it's a bit different, depending on who the young person is. But I think that what I would say is that you have to be very focused. And by focus, I mean that we're in a great specialty, there's so many great things about it. But there are also a lot of temptations away from the hard work that needs to be done and the hardship that's inherent to great accomplishments.—

--And I feel like a lot of people kind of get distracted. And I think that in the field, find what you're passionate about, find that unmet need, and go after it very, very tenaciously. Don't let up on it. And try to bring things outside the field into it. And try to just ask the hard questions. I think that even when we're in grand rounds, press the hard questions. It's great if you see an interesting case, but so what? Why?—

--What are you going to do about it? How are we going to press forward? I think sometimes we lose that a little bit in dermatology, because we're a quick in and out specialty. We see a lot of patients and we're high volume. But that would be my advice. I know it's a little bit of an almost

kind of a push, pushing advice in that way, let's do better. But I think that's how I genuinely feel. There are too many kind of distractions I think in this specialty, because there's so many things we can do. But ask the hard questions and go after them.

STEVEN CHEN, MD, FAAD: That's wonderful advice. I love the idea of I think we've all seen interesting cases and we've written, especially as medical students, we're writing case reports. And I think that's wonderful advice to say, "Great, you've written the case report. What's next? So what? What are you going to do to help that patient?" I love that advice. I think it's not just for our future academic dermatologists, I think that's for every practicing really physician out there, to really think about the next step. So thank you for that advice, I will take it. Even as an attending dermatologist, I will take it to heart in my own career for the future.—

--Brian, I want to thank you so much for joining me today for our episode for *Dialogues in Dermatology*, centered around itch and the new pathways and the new direction that itch is going. I just really appreciate all of your time today. Is there anything else you'd like to say to our listeners before we sign off?

BRIAN KIM, MD, FAAD: No, I think that's it. Thanks for listening and thanks for giving us the opportunity to kind of put itch in the forefront of dermatology in medicine.

STEVEN CHEN, MD, FAAD: Wonderful. Well, thank you for all your contributions to the field and specifically to the field of itch. And to our listeners, thank you for tuning in to another episode of *Dialogues*. Until next time, bye everyone.