Dr. Mariam Hanna:
Hello, I'm Dr. Mariam Hanna, and this is The Allergist. A show that separates myth from medicine, deciphering allergies and understanding the immune system.
The interventions we implement with our patients today could change their outcomes a decade from now. Did you ever hear the story about the patient whose family was too nervous to try baked goods ever? So they strictly avoided all forms from every man, woman, child that came within a two-meter radius of their household. Okay. How about the picky baby with texture and taste aversion issues that would launch the baked good at the parent, demonstrating how someone so small could have such a refined palate? Fine. How about the frustrating story of the child with milk or egg allergy who had been tolerating baked goods with occasional, maybe nonspecific symptoms who was then advised to strictly avoid, now getting ready to head off to school? One accidental exposure to a baked product in the past six months with anaphylaxis positive testing. They represent the unfortunate ones that represent the minority.

They're the milk and egg allergy that didn't go away by school age. The question today is, would their story have been different if we had not been as strict in infancy? So I'll say it again. The interventions we implement with our patients today could change their outcomes a decade from now. Today's guest is an international speaker who is passionate about this very issue. It's another perspective on food allergy ladders, early intervention, and how our counseling could actually change outcomes. It's my pleasure to welcome Professor Hourihane to our podcast. Professor Jonathan Hourihane is the professor of Pediatrics and child health in the Royal College of Surgeons in Ireland and Children's Health Ireland Temple Street. Since 2019, his primary area of clinical and research interests is in pediatric food allergy and anaphylaxis. He was a Fulbright HRB Health Impact Scholar to the Children's Hospital Colorado USA in 2020. He is a founding board member and is the current president of the Clemens von Pirquet Foundation and of the Irish Food Allergy Network. He has been involved in longitudinal, observational and interventional studies for more than 20 years now relating to both investigator-led and industry-sponsored allergy prevention trials in infants and more recently in the emerging field of immunotherapy for food allergy. He's actually a professor that really needs no introduction, but I did it anyways. Just for the sake of everybody listening, professor Hourihane, Jonathan, welcome to the podcast.

Professor Jonathan Hourihane:

Mariam, thanks very much for the looking forward to it.

Dr. Mariam Hanna:

So let's start by just telling us a little bit about where you practice. How does it look like when a patient gets referred? How long does it take for them to get that food allergy assessment, particularly in an infant?

Professor Jonathan Hourihane:

Yeah, and the Irish system is somewhere between the fully socialized practices of Scandinavia and France and Britain is somewhat like the Australian, and I think the Canadian model is that some of our patients have insurance and use it for access and other groups do not have insurance and have to wait in what's called the public service. The hospitals are largely public, so family doctors will be dealing with the elderly, the infirm, and the infant like you would always imagine. So they can refer a child to us directly, they don't have to go through a pediatrician first. And the other way we pick them up, and we're really trying to get hot on this, is by children who turn up in the emergency departments as a sort of an index that they might need our help sooner. Now, a lot of the time they don't need our help sooner because the attending trainee doctors just say, "Oh, it's an allergy, you'll have to go to the allergy clinic."
And it's usually urticaria. That doesn't need to come to us at all; the usual, and it's antibiotic de-labeling, but that's our route. We get babies to come and see us quicker. We can't leave them till they're three or four. So they are an intermediate group between the children who've genuinely had a life-threatening reaction and those who can evidently wait because we're conscious, and particularly for this podcast, that there's a time's arrow is active and part of this discussion because if you leave the introduction of these foods too late, we all know now from the British studies and others that the later you introduce foods in a preventive fashion, the less effective it is. And I think the same has been shown repeatedly for trying to modulate or affect tolerance induction in children who are three or four.

Dr. Mariam Hanna:

Absolutely. So some similarities and differences between our two healthcare system models and as well prioritization on infants needing to get in early. And already you're mentioning the role of early intervention in these infants. Can we go back to ladders specifically? When did you first start adopting ladders into your practice, and how would you say this has changed over the past five years or so?

Professor Jonathan Hourihane:
I can't really remember the specific thing. All I can say really is that as soon as the data about baked milk tolerant children being, or children being even all allergic children with milk allergy, were tolerant of baked goods, we immediately started liberating the completely draconian restrictions of no milk at all. And families either independently or

with a little bit of a nudge from us started giving small bits of biscuits or cookies, cakes, and muffins and stuff. And the problem was it's quite easy to say to a parent what a muffin looks like and what a jar of yogurt or some cheese or ice cream looks like. But the middle steps, they were hard to find and not a consortium; it was admittedly a forming milk company-sponsored program, the IMAP program to develop the ladder. I dunno where the term 'ladder' came from.

It's attributed to me. It's definitely not my invention at all. And the ladder concept here from that, the 12-step IMAP milk ladder was the first and there's now a six-step one; I'm old-fashioned and I think the 12-step one gives people more places to rest. The increases are smaller, I don't know why a baby should expect to do it faster than that.

Dr. Mariam Hanna:

Okay. If you were an early adopter, were there others around you that were more reluctant?

Professor Jonathan Hourihane:
Well, the data were convincing and the families were quite happy to do it. I think because in Ireland there are so few allergists, Mariam, the families are on their own for more time than they are in Canada, and they can't just ring up and tell me they want to come in this afternoon or Billy had a hive yesterday, we're coming to see you tomorrow. That access isn't there. So it gave them an autonomy, or it gave them a license to have autonomy in a way that they weren't doing it against medical advice, but we weren't pursuing them with it. We were just saying, "How are you getting on?" The big transition step was when you get from a solid food with milk in it to a white liquid or semi-solid like crème fraîche or ice cream. So that's a big step for 'em as well. And they did need some help through that.
The next big step for us was when we were doing a study in a related field of studying the threshold doses of foods, and we did the eliciting dose oh five study for peanut, which was published in, I dunno, 2018, but we were involved in a validation of the doses estimated with the FARP group in Nebraska of the sigmoidal curve with not many people reacting at the bottom, a lot of people in the middle, and then the high dose reactors, which has come to be a separate issue actually. But we were validating the dose because challenges are an incremental thing. So it's hard to know if anybody who's reacted in the challenge was due to that dose or the accumulation of the doses up to that point. So we did single dose challenges with milk with a tiny dose like not 0.1 mils of milk, I think is the EDO five of milk protein.
And we were doing this in a EU, European Union, so government-funded study. And then we were just giving that dose, and then they were going home, and then they were

on the ladders because that was our program already. And we noticed just clinical observation, good clinical acumen, that the children who'd had the single dose were going up the ladder much faster than the children who hadn't had the single dose because the single dose is raw milk, it's milk, so it's not on the ladder until the top. So we'd already shown them that wasn't going to kill them, and milk could actually be taken without any effort or consequence. And so then we got to the point of we did the study where we did the randomization of children to either having a single dose or not a single dose, but that wasn't until 2017 that started. So we'd had about six or eight years of unmeasured pragmatic ladder use in our service. And to be honest, I maintain that we've hardly had any problems with it at all. The people who don't manage it are identified quickly, they just don't get onto the ladder is really very few people get stuck once they get started. We've also shown I think conclusively that one of the things that stops people starting it is parental worry about it.

Dr. Mariam Hanna:
There are obviously two parties that you need to convince about incorporating the ladder, one being the physicians and the other side being the patient. On the physician side for allergists. Why do you think allergists should incorporate the ladders?

Professor Jonathan Hourihane:
Well, if there's no red flags in the referral and we ring the family and say, was there any signs of anaphylaxis or wheezing or if there's faltering growth, etc., we bring them in. But if there are no signs of anaphylaxis, we say start the ladders now at home without medical supervision. So that is that primary care, or is that community care, or is that self-care? Who knows, but it's certainly not university-led academic department professor-driven care. It's professor-supervised patient empowerment is the way we think of it. And to be cynical, the idea that you have to see your allergist to do anything, any dose increase is nonsense. And I think that's a self-interest that patients are not intelligent or safe enough to do something without you sitting them down in your clinic and getting two of your staff to sit beside them. I don't get that. The point I want to make about that is most of these children when they've reacted to milk, have reacted to a large amount of milk. They've had half a bottle of milk or they've had a teaspoon of yogurt or they've had whatever it is by starting baked milk, they must be getting a thousand or a hundred thousand times less milk in a non-allergenic form.
There are children where parents do rub milk onto their lip or onto their skin, but that's no validated test.

Dr. Mariam Hanna:
That's no validated test and happens here just as often as I guess it happens there. For you guys, you alluded to it, but how is our model of healthcare potentially impairing

rapid intervention in infants? So in the US and Canada I gather we have more allergists. There is a sparsity in certain parts of the country and each nation, but we do have more allergists per capita than what you guys will have in Ireland. Can you speak to that a little bit more for me?

Professor Jonathan Hourihane:
I think there's barriers between a patient and an allergist. I think you have family practitioners in Canada, in America, you've got primary care pediatricians and they all have a financial stake in the game of keeping the patients. And I think staying away from an allergist when you have milk allergy is not economic in the long run and it's not medically valid that somebody can look after this in the way that we're evidently showing is the best way to fix a child with milk or egg allergy. I think we may not have done the trials, but I think the trials are going to come from centers where there isn't such commitment to it. I don't think we'll be ever able to do a trial in Ireland. I don't think our population would tolerate it.
Now our standard of care is different. So I think allergists don't see people with milk allergy quickly enough. I imagine in Canada, I mean they may be four or five months after their first reaction, they've been told to avoid it, and then they've been put on a special formula and they've had their eczema, they've had their ad fixed before the allergy, let's stay off the milk until we get your ad fixed and then we'll put you on the milk. Oh no, your specific IgE is now 150, too late. This will be the first time I've said this in public. I think everybody's first reaction to milk. I think they're all amenable to this and it's the delay that is causing their specific IgEs to go up and then increasing their risk. I think even the ones who've got high specific IgE at the start, and we only measured that in our study blindly. We didn't get the results till after the study. There was a couple of children with high levels and they didn't go as quickly up the ladder, but they didn't abandon the ladder either.

Dr. Mariam Hanna:
How often do families end up approaching you or reaching back out to the office to talk about reactions or how quickly to progress or advance on the ladder?

Professor Jonathan Hourihane:
Yeah, that's a great question. They can ring up whenever they like. We have office hours contact. We don't have out of hours contact. We get a few contacts, but our staff reach out to them after two weeks and see how they're getting on. And most families have adapted to it. And we reassure them that your redness around the lips is, you can either treat through that. Other people prefer to stop it, and we don't really dictate to them if they should do that or not. If they're comfortable that one hive comes and goes after 15 minutes, we say stay at that dose until there's no hive and then move on. Whereas other families are not tolerant of that and want to drop back. So again, I think

we empower families to make their own decisions. I think we could ring them more often, but then we're going to be getting in their way is what we think and the families who are not going to do well are more going to help them do it because it's not the immunology that's the problem, it's the anxiety and contact with us could be a two-edged sword.

Dr. Mariam Hanna:
That's an excellent perspective. We have a whole generation of the bagel coffee and anxiety consuming parenting generation where anxiety is just readily taken up and they fly with it and to the detriment of being able to advance with some therapies.

Professor Jonathan Hourihane:
Everybody in this field knows that allergies make parents anxious and idle conversation in a coffee shop or at the side of a swimming pool with other people who've had a bad experience ups the pressure. We showed in our study that we measured state and trait anxiety in the mothers. So state anxiety is how you are today. You could just be tired after a long travel. Trait anxiety is who you are, and the mothers with high trait anxiety, their children did much worse with the ladders. So that's an inbuilt unchangeable personality trait of the parent, which affects the immunological outcome of a disease in children. I don't think that's had enough attention or enough credit because that was based on the clinical observation that every allergist has ever made that anxious moms often take steps much more slowly than we think would be most helpful, and that's not a criticism of anxious moms. That's who they are. And whether that group is a group who need more support is something we look at a bit more closely when they come into clinic.

Dr. Mariam Hanna:
I understand. How long would you take in counseling a patient in your practice?

Professor Jonathan Hourihane:
Sometimes if I can't get them on the phone, we just write to them. So there's no counseling at all. We give them website access. So if they're, by the time they come to the clinic now actually Mariam, they're mostly on the ladder and have read it up. So the counseling is really how they're going to proceed after the first few steps. If we talk about egg ladders, because we have an egg ladder as well, some of these children are back up to scrambled egg after eight weeks. I mean that's a showstopper, that data. So they're just moving along without our help and by the time they come to clinic or eight weeks after they've been in, they're back to which is usually the first form of egg that's offered. Nobody offers children raw egg, why would you? So scrambled egg. So we think that's strong evidence that we're getting in their way.

Dr. Mariam Hanna:
You mentioned some patients that it would not be right for, so I'm going to go back to this point for a second. We talked about parental anxiety may require more handholding but not too much. That could also have a negative kind of impact. You kind of alluded to some of the patients that have had a more severe reaction, but I kind of want to flush that out a little bit more. Which patients would you exclude from a milk or an egg ladder? In this situation?

Professor Jonathan Hourihane:
In our published study of milk allergy, we didn't have any children with anaphylaxis to milk even though they were picked up unselected. So that study is criticized. It didn't have children with severe milk allergy in it, but you can't make a child have severe milk allergy to get into your study. We don't have that phenotype because we're seeing them so soon. So I think this is a key point. I think they're all malleable or changeable if you get to them quickly. Even the ones who've got high numbers because they haven't had anaphylaxis. And in our egg study, we still include children with anaphylaxis in our egg study and we allow them again because it's due to food higher up, the dosing, the allergenicity is patently higher. We start them at home as well. So we don't think there's anybody who can't be offered the ladders, whether that first dose needs to be in hospital for medical reassurance, and I mean medical reassurance of the doctors.

I don't mean reassurance of the parents because parents do an awful lot of extraordinary things for their families in their home situation, oncology, CF care, all that stuff. The idea that somebody who has an allergic reaction at home on a medically or advocated ladder program, that accident is due to the doctor's fault or issue. I don't see that at all. Families understand that this is a dynamic process and I think a lot of the caution about the ladders is about the responsibility for what might happen. And I don't think there's many medical fields where risk is absent. So I don't see why allergists have to be so minimalistic about allowing a child to have reactions. Now, the reactions that happen on the ladder are nearly always mild. I think I've got an anecdote of one or two children who've had anaphylaxis on an escalation dose on a ladder, and we've got hundreds and hundreds of these children now; they're having these doses three, four times a week over 10 years.
So there must be 30,000 patient years of dosing, or that's an exaggeration. I can't remember. There must be hundreds of years of dosing done now. And most cases of reactions on the milk and the egg ladders on an appropriate escalation are mild. And the only anaphylaxis we've seen in our recent data for 180 egg allergic children was accidental exposures to forms of egg above that. And that was the same in our published milk study too. So I think that once you're tolerant of baked milk, maybe your risk of anaphylaxis is lower because you're already turning off your inactive immunosuppression.

Dr. Mariam Hanna:

That's fair. That's fair. And I actually like the comment that you made about in our specialty, we have to be more tolerant almost of risk with some of our procedures and in other specialties they accept this. And even for home-based procedures that they're asking to do,

Professor Jonathan Hourihane:

Asthma doctors don't get guilty when a child comes in wheezing.

Dr. Mariam Hanna:

Fair. You mentioned the older patients and because in Ireland you're able to assess them and get them started very early. Is older or miss the boat, they've waited three or four months to see the allergist or are we talking about a different age group altogether?

Professor Jonathan Hourihane:

Yeah, I think the tolerance window is open from whenever the first reaction starts. So whatever that is, four or five months, whenever that is, I think it's probably for milk, it's probably not that much open anymore, but by the time they're three or four years of age. And I think those children are a different group. And we use the ladder approach really cautiously in the older children who come from other centers or who've come back from America or Canada or Australia who've been on milk because there's a lot of repatriation of Irish people. So the older child, the seven or 8-year-old with milk allergy is a very different beast at all. And what we do with the ladder is we get them onto baked milk to allow them some safety and social reassurance, but they're not a group maybe that are going to consciously ever drink four liters of milk a day or have two buckets of ice cream. Their diet is already different. And I think just some baked milk safety to allow them some safety with prepared goods from other people is probably okay, but they still probably have to avoid the foods that are high risk for high dose exposure to milk like dairy, chocolate, and things like that. I think we would agree that they're a different group.

Dr. Mariam Hanna:
They're a different group, and this isn't a form of immunotherapy in that group. This is like risk mitigation, almost.

Professor Jonathan Hourihane:

Yes. At the present time, we don't enter children in that mid-childhood age group with high numbers into the ladder program hoping for full tolerance. We just want them to be baked milk tolerant to a level that will allow them to be a bit more socially confident.

Dr. Mariam Hanna:

Okay. Is this considered or would you consider this patient advocacy? You have actually mentioned it throughout our entire podcast, and when I reached out to you, I was trying to annoy you a little bit about our first ladder conversation and get your perspective and input on it. And you were very passionate to say, I want to talk about this. Do you consider this patient advocacy to do ladders with families or to pursue this with patients?

Professor Jonathan Hourihane:

What are doctors meant to be except advocates for health? Okay. We're in a situation where we deal with a largely non-fatal transient disease with milk and egg allergy. And the fatalities that we see because we see them so rarely are magnified and awful, there's no question I'm not diminishing their importance at all. So our care needs to be predicated on the likelihood of that for any individual person. And I'm very persuaded by the data from London a few years ago. It's a famous slide. Your chances of dying of food allergy are the same each year as your chances of being struck by lightning. It's that level of serious risk, and the rest of the risk is perceived risk and inconvenience. And we have to-make that information available to parents and children and teenagers who are the people who put themselves out there. So we have to advocate that this advice to tolerate the food that you're scared of is actually strongly in your interests. Does that answer your question?

Dr. Mariam Hanna:
More than answers the question. It's perfect. Okay. So on that note, I think this is a great time for us to wrap up today's episode of The Allergist with Professor Jonathan and ask for your top three key messages to impart to patients and physicians on today's topic, which we're going to dub dietary advancement therapies and advocacy. Professor Hourihane, over to you one last time.

Professor Jonathan Hourihane:
I have four messages if that's okay. I couldn't squeeze it into three.

Dr. Mariam Hanna:
I accept.

Professor Jonathan Hourihane:
Okay. The first message is that early introduction is the time-proven and research-proven prevention target for every child and every food. And it's reasonable that if there's a tolerance opportunity for other foods, that you take that opportunity without delay. Reintroduction of these foods to the diet of allergic children is a form of immunotherapy. I don't think it's just fixing their diet to allow them to eat foods that some unmeasured measure, unused measure would've said they were already tolerant of. And immunotherapy is basically graded reintroduction, let's face it. The third one is that this reintroduction, I think we're showing it repeatedly. It's safe to be done or started at home for milk and egg. And in the post-LEAP studies, we're asking children to eat peanut at home as well when they're not sensitized to it. It's a different thing for peanut because of the allergenicity of its unique single form with the baked egg and baked milk, it's different. And the final one, and this is the major one, delay is not the solution. Okay.

Dr. Mariam Hanna:
Delay is not the solution. Thank you, Professor Hourihane, for joining us on today's episode of The Allergist.

Professor Jonathan Hourihane:
It was a pleasure. Thank you.

Dr. Mariam Hanna:
This podcast is produced by the Canadian Society of Allergy and Clinical Immunology. The Allergist is produced for CSACI by PodCraft Productions. The views expressed by our guests are theirs alone and do not necessarily reflect the views of the Canadian Society. This podcast is not intended to provide any medical advice to our listeners. Please visit www.csaci.ca for show notes and any pertinent links from today's conversation. The Find an Allergist app on the website is a useful tool to locate an allergist in your area. If you like the show, please give us a five-star rating and leave a comment wherever you download your podcasts, and share it with your networks because as we just said, delay is not the answer. Thank you for listening. Sincerely, The Allergist