

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.

It's funny how some moments in life you remember with crystal precision. I'll never forget one question from my medical school interviews. I actually don't remember much of what happened during it, but at some point, one of my panel interviewers—were taking turns—one member asked me directly, "What is epigenetics?"

I fumbled my way through a response to that question, and I have no idea what I actually said, but I remember the question clearly. Because in the field of allergy and immunology, perhaps more so than anyone else, we get asked, "Why have these conditions become such an issue when our generation and our parents' generation and our grandparents barely had this?"

Epigenetics. And the "epi" portion of that word really is where the epithelial barrier hypothesis fits in nicely. Have you heard of it? It's interesting how much of an impact it's made in some conferences, in some parts of the world, and yet others haven't heard of it.

I've become obsessed with laundry detergent choices, using a dishwasher, and even my toothpaste. My family thinks I'm losing it, but I'll let you be the judge.

Today, I'm very pleased to welcome Professor Cezmi Akdis. Professor Akdis is director of the Swiss Institute of Allergy and Asthma Research in Davos, and professor at the University of Zurich. He's also editor-in-chief of *Allergy*, and former president of the European Academy of Allergy and Clinical Immunology.

His research has been instrumental in advancing our understanding of immune regulation, epithelial barrier dysfunction, and allergic disease, including the development of the epithelial barrier hypothesis. He's published more than 750 reviewed articles, and is internationally recognized as a leader in allergy and immunology. Professor Akdis, thank you so much for taking time to join us, and welcome to the podcast.

Dr. Cezmi Akdis: Thank you very much. It's a great pleasure to be here.

Dr. Mariam Hanna: Professor, can we start first by just the basics, explaining kind of the epithelial barrier hypothesis, where this has come from?

Dr. Cezmi Akdis: Yes, it's a great pleasure to talk here. Let me first talk about our main question when we were assistants. You know, everyone were asking us—our families, parents, professors—why are allergies increasing? Because allergies were not a big public health problem 100 years ago.

In 1819, for example, when John Bostock described the first allergic rhinitis case, it was not so easy for him to find so many cases. Charles Blackley wrote the first book about hay fever and hay asthma in 1873, and it took him three years to collect only 28 cases.

Today, 28 cases is just when we are in a bus—half of the bus have this problem, and it's a really big public health issue because, starting from 1960s, allergic diseases started to increase. This is asthma, atopic dermatitis, allergic rhinitis started to show a significant increase.

We can say that this increase was one of the main motivations of our work on epithelial barrier theory. It was written as a hypothesis in the beginning, and now we are more confident, but the start was about 20 years ago. When we were looking at atopic dermatitis in the skin, and we found that skin barrier is defective, and an immune system cell called T cell was going and attacking our own skin epithelial cell and opening the barrier. This was the cause of eczema, and this was our first understanding of epithelial barriers and their leakiness.

Then we showed the same thing in asthma around 2001, and then we showed the same thing in chronic rhinosinusitis, in allergic rhinitis. So we started to look at allergic diseases and found that in all allergic diseases, epithelial barriers are not as intact as in healthy people. So this was the starting of thinking of epithelial barrier theory.

Then we started a series of research, which was quite exciting, and we identified what is a barrier, what does a barrier do—for example, skin barrier, lung barrier, bronchial barrier, nose barrier, sinus barrier, and gut barrier, one of the most important. And we identified factors, what makes the barrier. The barrier is the epithelial cells that cover the surface, and the microbiome on it, and also many cytokines, chemokines, and protective factors to defend us, mainly against infectious diseases, but also anything coming from the environment. We have to keep them out; they shouldn't go into our skin, they shouldn't go into our nose or bronchial mucosa. So this was the starting of our understanding of epithelial barrier theory.

Then our research continued, and we found that the immune system is doing this: opening the barrier, attacking our barrier cells in asthma, in allergic rhinitis, in atopic dermatitis.

Then we continued our research. In the year around 2013, we started to understand that environmental toxic substances, such as detergents, such as air pollution, such as food antigens, enzymes and emulsifiers in processed food, food colorants, sweeteners, taste enhancers, and also in the air pollution group, diesel exhaust, micro- and nanoplastic, particulate matter—they were all opening the epithelial barriers and causing an inflammation.

That's how we started to call it epithelial barrier theory. And it has three main pillars. The first pillar is epithelial cells, which cover the surface of our tissues, surface of our skin, nose, lung, and gut. And the second one is microbiome that covers above this epithelium, that stays there to protect us, the good microbes within this microbiome. And then the immune system that causes immune tolerance, that tries to keep the immune system silent, not active, and without any inflammation. So these three started to make the epithelial barrier theory.

Dr. Mariam Hanna: Amazing. And in terms of the major environmental factors that disrupt this, you're basically saying like our entire Western lifestyle. Can we delve into that a little bit more? What are those major environmental factors in that?

Dr. Cezmi Akdis: There's actually an app, a non-profit app, and you can use this app to check whether there is any environmental substance that breaks the barriers in the food, in the cosmetics. So that's possible. The app is called Yuka, Y-U-K-A. It's a non-profit app, for this reason I'm giving its name. And it's done by scientists, and there's also American Dermatological Society website and other websites that give these substances.

In our research, we started to identify them one by one, and also group by group.

The first group is the cleaning substances: laundry and dishwasher detergents and rinse aids. The reason why we are talking about the start of allergic diseases from 1960 on—the pandemic increase, the rise in the numbers in our household, classes, in our friends, also in the armies and all around the world—one of the main reason was initiation of these detergent exposure with quite toxic and strong detergents. And the material that were introduced to these detergents exactly in 1960 was sodium dodecyl sulfate, it's called SDS or SLS. You can check it in your detergents and household cleaners, and shampoos, body cleaners, and laundry and dishwasher detergents. And also, from the year 2000 on, toothpaste started to use this material. So this is the first group. It's a very strong group, and because of change in surface tension, these detergents are tearing apart our epithelial cells and also directly killing our good microbes.

The second group is, starting from the year 2000, our lifestyle changed. We started to use more and more processed food. Package food came into our lives. When we were going to supermarkets in the year 2000, we were looking at a pizza or a sauce, and the shelf life of a pizza or a sauce was only seven days. Nowadays, when we go to the same supermarket, look at the pizza or a sauce, we see that it has a shelf life of up to six months. How did it happen? It happened by a change in food industry by adding enzymes, emulsifiers, antibiotic-like substances to these foods to give them a longer shelf life, but at the same time, they started to cause small inflammation in our gastrointestinal system. And afterwards, food colorants, sweeteners, taste enhancers were introduced to our ultra-processed food, and this ultra-processed food became quite toxic and problematic.

And the third group is air pollution group. Cigarette smoke is the first one here, which is affecting a lot of people; diesel exhaust; ozone; nanoparticles; micro- and nanoplastic; pesticides; and particulate matter, which is in the air pollution.

So these are the main common substances that I can talk about.

Dr. Mariam Hanna: What is the evidence that we have that says that these disrupt epithelial barrier integrity? Like obviously these are advancements in how we prepare food or how we clean products or make something more sterile, but how do we know that those specific products are the ones that are linked to epithelial barrier dysfunction or interrupting the integrity of that?

Dr. Cezmi Akdis: Our first research started from the skin, and nowadays we have a device to measure skin barrier very precisely. And it's called electric impedance measurement, and it measures whether the skin cells are touching each other and the electric current can pass from

these cells in the right way. So if the cells do not touch each other, that means the barrier is broken, and then the electric current has a resistance because there is some water, some inflammation in between. This we can measure.

So the first group of experiments, we put these substances in the skin of mouse, and after doing some security experiments, we started to do this for humans. And we checked human skin and human skin lesions for atopic dermatitis and human skin by putting certain substances. So in all these, we started to see that these substances—the laundry detergent and cleaner, body cleaner, and toothpaste group—we started to see that they are damaging the skin barrier. This is how it started in the year 2013.

In the meantime, we started to develop three-dimensional tissues in organoids, and in these organoids we grew the skin cells, we grew the lung cells and sinus cells, and we looked at their barrier and how strong they are attached to each other.

And then we made organs on a chip, very small 3 millimeters organs, like a 3 millimeter gut, a 3 millimeter lung, a 3 millimeter sinus tissue, and we were able to look at all of these. One cell is like 10 micrometers, so in 3 millimeter there is about 300 cells, and we can see how these cells are interacting with each other. This is quite sophisticated for the normal listeners, but I can say that this started with mouse models, human models, and nowadays, we are now starting a study in several hospitals and also in NIH, and we are directly exposing, with permission, healthy humans to these substances and looking at what happens to their microbiome, what happens to their skin barrier and gut barrier.

Dr. Mariam Hanna: That's fascinating. And walk me through, how does the epithelial barrier hypothesis help us with the allergic march, the atopic march that we've talked about for so many generations now? Does this help explain this?

Dr. Cezmi Akdis: Yes, we work with a group of physicians who are organ-specific experts in the meantime, and we started to understand that epithelial barriers are quite important, and at the same time, they are responsible for multimorbidities and comorbidities.

So a child who has food allergy at the age of one year may develop eczema around this time, and afterwards, at the age of five or six may develop asthma, and at the age of seven, eight, nine may develop allergic rhinitis. This is called the atopic march.

But nowadays we are seeing it in a different way, and multiple and relevant to each other or irrelevant diseases are happening together. This is called multimorbidities or comorbidities, because if the family is exposed to these substances, and this is happening in the children, that they develop food allergy and eczema very quickly, and then they develop asthma afterwards, and it becomes a big health problem in the family, a health burden in the family, that the child has many allergies. And this is currently happening, as you know, from many patients.

We identified five criteria to look at these diseases. And nowadays, we know that this curve of increase is not only allergy and asthma, because we are also seeing autoimmune diseases, and we are seeing metabolic diseases. It's linked to obesity, it's linked to type 2 diabetes, it's linked

to thyroid diseases, it's linked to rheumatoid arthritis, osteoarthritis, fatty liver diseases, group of diseases that you wouldn't expect that they will happen because of exposure to these substances.

So the five criteria: One of them is very clear. If a disease shows increased prevalence after 1960s or around 2000s, which is not affected with the changing method of diagnosis. Everyone can easily say we are diagnosing in a better way, but there are certain diseases that didn't change, the diagnosis is the same. For example, looking at fatty liver. You put the ultrasound to the liver, and within a few seconds, you can see that whether there is a fat deposition in the liver or not. Or you do gastroscopy, and you see that esophagus is inflamed, eosinophilic esophagitis happens, and then you do the biopsy and the diagnosis is the same as we were doing when we were assistants in 1985, '86, and that was the time, and the same method is used still.

So this is the first criteria. The second one is a little bit sophisticated, it's epithelial barrier defect, so you need a device to measure epithelial barrier, and also some cytokines—IL-1, IL-25, IL-33, TSLP—and several chemokines are released from these epithelial cells.

And the third criteria is an important one, and it's called microbial dysbiosis. Our healthy microbes, the commensal microbes, are decreasing, but instead of them, some opportunistic pathogens are increasing, like *Staph. aureus*, and pneumococcus in the respiratory area, *Moraxella*, *Haemophilus*, they are increasing, but the good bacteria are decreasing.

And the fourth criteria is to see multimorbidities, to see comorbidities in patients, that these diseases are happening together.

And the fifth criteria is—we are still working on it and publishing a good paper—this is called circulating inflammation, and we can identify that there's inflammatory factors in the circulation of these patients. And from these we can say that there is a leakiness problem of the gut, gastrointestinal system, or a leakiness problem of the respiratory system, and we can identify them. And this is quite new science.

Dr. Mariam Hanna: And does our knowledge now of epithelial barrier dysfunction allow us to start considering opportunities for early intervention, allergy prevention? I don't think we can get rid of thousands of products that have now made it into food industry, cleaning industry, but are there opportunities now for allergy prevention given what we know now from this work?

Dr. Cezmi Akdis: It is starting. I can say that it is not fully established, but there are, for example, for the nose, epithelial barrier-protecting creams.

And current treatments of certain drugs like dupilumab or inhaled steroids are also closing the barrier. We know that some of their effects are through closing the epithelial barriers, and this is true. And they are helping the patients by closing the barrier, at the same time by decreasing the inflammation. So this is happening.

But the whole drug industry is working on this a lot, and it's possible to avoid some of the substances. It's possible to, for example, produce healthy food. We recently published the

peanut anaphylaxis paper, and we identified two emulsifiers that are used in the peanut butter. And these two emulsifiers are making the peanut butter really allergenic. And this peanut butter, when there is these two emulsifiers, soy lecithin and DATEM, these are two emulsifiers... And when we have these two emulsifiers, and then we see an inflammation in the gastrointestinal system and induction of IgE. In mouse models we saw it first, but we are expecting that this should be also proven in humans in the short time, because our models of the three-dimensional tissues, which we use in the stem cell-made colons, we saw that this inflammation happens. Then we went to mouse model, and we proved it in the mouse model. Now it's time to show it in the humans. This epithelial barrier research is going, not in a very fast way, it is developing, and we are understanding, because we don't want to put humans in risk by exposing them to these toxic substances, so we have to go step by step.

Dr. Mariam Hanna: It's fascinating area, and fascinating how to see the impact of things like impact on peanut allergy and how we prepare peanut butter in certain parts of the world. Okay, biggest unanswered questions or controversies that remain in this area or in this field, what do you think?

Dr. Cezmi Akdis: Yeah, I think understanding and awareness is the most important part, awareness by the public. If, in the beginning of the talk, I counted the substances, and it is very easy to decrease these detergents. It's very easy to decrease these rinse aid, not even not to use them, we are not supposed to use these rinse aids, detergents that are toxic. So this awareness is very important. In our household, we can decrease the burden of these barrier-damaging substances. This is doable.

The second one is in our food. When you go to supermarket, please go to the fresh food, fresh fruits, vegetables, and make a raw food. And if you buy package food, read the package very carefully, and which kind of surfactants are in it, which kind of emulsifiers are in it, and which kind of antibiotic-like substances are in it, and try to avoid package food which has very long shelf life. And by using the app which I mentioned, you can identify these very easily. So this awareness is really good, and this awareness is also quite important.

In the other point is that to stay away from micro- and nanoplastic, don't use plastic utilities in the kitchen. Stay away from pet bottles, use glass bottles, and stay away from plastics, opening plastic packages in the house, inside the house. When you buy a TV set, don't open the big TV set package where there is children, just open it outside, and bring in the clean TV, not the package. So these are things, but these all need awareness, and societies like you who will educate the patients are very, very important in this.

Dr. Mariam Hanna: Okay, looking ahead, what would you most like to see this field accomplish next? What do you think?

Dr. Cezmi Akdis: I think it needs certain regulations. First, many governments in the world are very excited in this, including also the White House, and NIH, NIH is doing studies, and FDA, they are all interested in learning more, and also bringing regulatory solutions to this, and avoiding certain substances, and decreasing the dose of certain substances, and dose of

exposure of certain substances. So it's going on from many sides, but there is around 1,500 food additives. It is not so easy to go one by one all of them and identify all of them, and many people are doing this research, but it needs more research funding by the governments. And in Canada, the government should be aware of it, and they should not easily give you licenses to products that have these toxic substances which are well known, and follow the literature, because in this app also, if you click on the toxic substance, you can see what is published on it. And that's very, very good for the public, and that's very good for the doctors. And these are entering also to the medical studies. Now we have recently published in *Nelson Textbook of Pediatrics* what we know in this area, so new doctors will learn about this, and they will get educated by knowing these. What I am talking about today is generally in the medical education currently. This is a big achievement, but it will go to the doctors and continuous education will make bring more awareness to the houses and daily practice of the doctors.

Dr. Mariam Hanna: Brilliant. Okay, and that's I think awareness is a perfect way to end today's episode. All right, time to wrap up and ask today's guest, Professor Cezmi Akdis, for his top three key messages to impart to patients and physicians on today's topic, barrier epithelial dysfunction. Dr. Akdis, over to you.

Dr. Cezmi Akdis: Yes, my first message is to be aware of it and to make certain decisions in your household. And we are continuously publishing, and there is a website. In this website, we have suggestions for laundry, dishwasher detergents. We have suggestions for food colorants, sweeteners, enzymes, emulsifiers. We have suggestions for micro- and nanoplastic, and this website is called epithelialbarriertheory, all together, .com.

The second thing is look at your politicians, and whether they are aware of this, and whether they want to bring solutions. And you are a big actually, and you have to tell your politicians that, okay, but now there is major things changing, there is climate change, there is global warming, and there is many things that affect our lives and our children badly, please focus on these, and politicians should certainly focus on these and put more funding to the research and more funding to the public education.

And the third message is to drug companies, Big Pharma, and also regulatory authorities. So we need certain regulation to avoid some of the toxic substances, and we need also drug development, and speed up the drug development for certain substances that can close the barriers, that can heal the microbiome, that can put the correct microbes that will protect us, so there are many ways to do this, and we are continuously identifying these ways and focus on this to bring better solutions to patients.

Dr. Mariam Hanna: Brilliant. Thank you, Dr. Akdis, for joining us on today's episode of *The Allergist*.

Dr. Cezmi Akdis: Thank you.

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