Pediatric Nutrition
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TRANSCRIPT

The Early Nutrition Journey and MFGM: Evidence for Improving Cognitive Outcomes

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The Science & Structure of MFGM

Dr. Jimenez-Flores: I was invited here and when I saw that it was a lot of medical doctors/pediatricians, I was wondering why. And I think that dairy scientists have a little bit to say about the ingredient that brings us all together and it's called MFGM. I hope that at the end of my talk, you'll have learned more about the science, the structure, and what it is that we use for infant formula, what we have looked at from a different perspective, a biochemist's perspective, on MFGM and development of the brain and some of the newer things from neurodevelopmental biochemistry.

Here you'll learn about MFGM, and what is this membrane that surrounds the fat globules in milk. And the funny thing is that all mammals' milk have that in common. It's not just humans. Bovine, platypus, we've studied MFGM in platypus, believe it or not. And in the last 15 years, the literature has exploded with the link of MFGM and human health in modulation of the immune system, bone density, cardiometabolic health. But what I'm most interested in, and what is very important for today, is cognitive function and development, and the gut barrier functions which, kind of starting as we study this, explain what is the mechanism of action.

Well, the most important clinical data that we found are a plethora of studies, if you add up all the subjects, there are over 1,000 babies that have gone through experiments of breastfeeding, formula or formula with MFGM, and the important thing is the results have been the same and we have experts that are going to talk to us here right after my talk. They're real experts in the pediatric and the cognitive science of babies. But first we have to really look and demystify what you may all be thinking, what is this? And I'm sorry that baby has such poor nomenclature, MFGM is hard for a lot of people. I would start with membrane, the membrane that surrounds fat globules, but I'm not one of the founders of this. You know, judging by our mostly ladies' population here, none of you were probably born in 1975, [during the career of renowned dairy science researcher] Stu Patton and a time where scientists had to do their own drawings with ink, no AI involved. The mammary epithelial study was one of the first pictures of a little mouse and there's the fat globule being extruded and it being micro-encapsulated, that's what we food scientists talk about this, on the membrane that comes from the mammary epithelial cell. This is nature's way of communicating mother to baby in the most biochemical way. Whatever mother has in its very self, being of the mammary cell, is going to the baby through this little membrane. And then, one of the scientific contributions that I thought was very important on this side is kind of the first trials of a new technique, then new technique, of freeze fracture and scanning electromicroscope was done, believe it or not, on the milk fat globule and this is where we discovered that it was very heterogeneous. It wasn't a simple membrane. It had proteins, glycoproteins, it had gangliosides, a link with the brain and nervous system. The sphingolipids, of which we're going to hear exciting news in a few minutes, and the proteins and what is very important for us in food science, phospholipids, because these are surface active components and they do modify membranes of all living organisms. That's what I think is very important.

Now, of all the nutrients that are needed for brain development, they're nicely put in red, I am very interested in the lipids. Even though I started as a proteins chemist, the lipids called my attention and the long chain fatty acids. And this, for example, all this called the sphingomyelin, of course, plays a really preponderant role in this.

Now, why is the membrane that surrounds fat globules important to us? And if you look at the structure you'll see the similarities between the myelin sheet in all our neurons and the composition of the milk fat globule membrane are very similar. It has a conglomerate of proteins, of glycolipids and glycoproteins just as we have learned are there in the milk fat globule membrane. There's no question that mother nature designed a perfect food, but she designed it to go directly from the breast of women to the mouth of babies. But we industrialized, and so what can we do, what have we done, to start understanding that if we need to feed the population of the world, what changes do we need to make so that we make all these benefits to primarily babies, but I think in general to all the population, at least that's my belief and my motivation.

I subjected one of my students, Sophie Gallier at Cal Poly, to really understand the very fresh fat globules. We were fortunate that the cows were milked 500 meters, I don't

know how much that is in feet, I'm not that archaic. So, 500 meters from our lab, she ran, talked to the boys, you know, French girl, milking boys, you know what I talk, so they gave her the freshest milk that she then ran and put in the lab in a confocal microscope. And this is what you see here. We notice, yes, the heterogeneity, how it works and that it was, other than the normal proteins, was intact. Then, we did a very mild pasteurization, that goes only to 60°C, again I don't know how much this is in Fahrenheit but it was warm. And we saw that the proteins in milk, especially the whey proteins, were attaching to that surface. And it is not coincidence because what happens is there are very nice complex and biochemical components in the surface of the fat globule that do attract and dock whey proteins. Is that a problem? Well, relatively, because then the technology to get the primo quality MFGM after many things, technologies, decided that it was best to use it from whey. Why? Because, in many places, the milk to make cheese is very mildly pasteurized so it's not ultraheated or anything like that and, in many instances, we still have cheeses, legal cheeses, made with raw milk and they have to be aged for 60 days. But the whey is a fantastic quality. What we do, we pass it through a sieve, it's called a membrane, but I don't want to mix membrane with technical membranes, you know. You've got to be membranologists, but so it's a sieve, very tight porous. The sieve won't let pass anything that is bigger than 10 kDa.

With that, what permeates, what goes through, is lactose and minerals, thus concentrated the proteins in the whey. And now, I'm happy to see that because of this technology and that we understood what is important about whey, most, and I would say all of the cheese makers in California, are making more money out of whey protein than on cheese. The tail wagging the dog, some would say.

Here's what really is important for us to understand. The brilliant scientist says why don't we open a little bit the sieve and instead of 10, we put 50 kDa? What happens then is that the whey proteins permeate and so now we have lactose, minerals and a lot of the whey proteins. And if you reduce the amount of whey proteins and what you retain is the big MFGM particles, you get the beautiful ingredient that isn't reached in milk fat globule membrane components, and it has low amount of proteins. And that is what is added to the infant formula that has been used in so many clinical trials. How can we tell because there's so much about the trilaminar membrane and how can we say that if we add this ingredient to the infant formula it will work? We and other scientists start comparing what is particular about human milk and the proteins and the phospholipids have to do before and after.

This is human milk characterized by high sphingomyelin content and this is what happens when we reconstitute the infant formula. Now, because the fat is homogenized, the fat droplets are very small, but I hope that everybody can see here how the proteins and the glycoproteins by themselves and a very important physical chemical, a principle that is surface action, they do line up at the surface of the fat globules by themselves. That's perhaps one of the tricks on why the technology works.

Mechanisms of Action of MFGM on Health

Dr. Jimenez-Flores: I started exploring what mechanism and that came because, in a reunion like this, one pediatrician told me, you know, Dr. Jiminez, he called me Dr. Jiminez, seriously, why is it that this works? We're used to pharmaceuticals in which they know the mechanism first, they purify a component and then we use it and voila, there's ampicillin or whatever it is. And I started looking into [the fact that] really we need to know and clarify what's the mechanism of action. And to that, you cannot ignore all the nutrient parts of the mother, the milk is produced by all these factors, but here is what really caught my attention. Structural development in intestinal mucosa, wow, that was big to me. Intestinal immune maturation, we know that and we have unfortunately a plethora of babies that cannot drink mother's milk and we see the increased infection and increased problems with the immune system. And all can be tied, if you study it far enough, to the early set-up of their microbiome.

When we were studying this, a very brilliant student of mine, Erica Kosmerl, she asked, "Well, why don't we have more of this beneficial bacteria through life?" She did this paper in which, here's the amount of bifidobacteria we have, which is plenty in early life, and then because, in my case, too much tequila probably killed all the good bacteria, we're looking into what could be beneficial for babies, and some groups started very nice research and very nice results with the human milk oligosaccharides. But there's more to that in the story because there are complex oligosaccharides in bacteria that are fed milk fat globule membrane. Erica started studying what bacteria change when they are grown in the presence of MFGM. And she knows something, highly sophisticated measurement that they set a potential which is the charges on the surface of the bacteria changed drastically. Being a professor that is of unsatiable curiosity, I asked her, "Well why do you think that is?" The answer was that the bacteria grow an extra

exopolysaccharide layer and that makes them work differently than just fermenting and getting the goodies. The way that they work, when they have an exopolysaccharide, and this happens with bifido but with many other lactic acid bacteria too, when they're grown in the presence of MFGM, they get that extra exopolysaccharide which enhances the mechanism in which the probiotic bacteria work to defend us against pathogens because the bacteria—could be a pathogen or not—have docking components directly to the intestinal epithelial cells. But if we have MFGM interfere with those receptors and they don't bind to the stomach, they just get, I think the technical term is pooped out. It's technical.

Furthermore, Joanna, being a very high-quality Mexican scientist in my lab, decided to start measuring, well, can we decide how strong that is. She used an instrument called a quartz crystal microbalance, believe me it's not a common instrument in food scientists, and she found that there's 2 groups of bacteria, 1 that binds very strongly to the sensor made of gold or weakly and they kind of clump. Well, when she exposed those group of bacteria to intestinal cells, Caco-2 cells, they found that there's enough take of the bacteria, they really bind strongly to the epithelial cells while the other ones, they clump and they make a loose, highly clumped group of bacteria in your intestine. Either way, I think there's different mechanism by which they exert this antibacterial action.

What happens if you just put MFGM into epithelial cells. There's the epithelial cell labeled red and there's the MFGM phospholipids labeled green and when you put 2 and 2 together, it turns out that the phospholipids meld with the membrane of the intestinal cells. And that is significant. We don't know exactly what other effects may be because we need to study better the metabolism, but this is a fascinating story that tells us a little bit more and, as a result, the triacylglycerols increase in the membrane, phosphatidylcholine, but it reduces the cholesterol esters in the membrane. And when that happens, the membranes are more supple, they're more flexible.

What else do we have? Well, this is, to me, the pièce de résistance. Thus, if I contribute this, I probably be happy to retire sometime. Here is what happens, I hope that you can see the little graph. What is probably most important is the permeability of the layer in our stomach. If they're permeable, toxins can go through, other substances that we don't want and then create metabolic syndrome, at least inflammation of the worse kind. And when we put DSS, which is an irritant to mimic things that would stress the intestine, we can see that it creates these big holes, even in cell culture which is more resilient than not, and it depletes the mucus layer. You see these clumping things here, they're the mucins, so called, and all doctors know that if your intestine is healthy, it has a good mucin layer, the mucosa, the lining of the stomach, as my grandpa used to say in Spanish, but I'm just translating for you.

But if we feed those cells MFGM, here's what happens. There's no permeability which started the whole thing in the paper in 2011 and what we see in the cells is that they're healthy, the mucus layer is intact even upon that irritant and we know that this was going to be, for a doctor, so we cut the plate to make histological cuts and you can see where the healthy [area] looks, how the injured barrier almost absent of mucins and with MFGM, we have a plethora of the mucins. That's as much as I can muster of data that we can do in the lab to probably explain what you will hear after my talk which leaves me just with the last part, as my time grows out, on the gut-brain axis. You cannot work in food science without people drilling at you, you have to study gut-brain axis and, pray tell, what is that?

It's a communication of all the things. We have the microbiome, we have metabolites and activities of microme in the gut and the gut, and this is the most murky interaction, we don't know what the gut has to do with the brain except a dirty joke that I know but I won't tell it here. But my student, and she started as an undergrad doing research with us in Ohio State, started screening from bacteria exposed to MFGM and then increasing in neurotransmitters. The end result of this, and I'm very happy to tell, is that the immediate effect is happening, and we have now preliminary data, that's what it's preliminary so I'm not talking much about it, but I'm so proud of this, that these bacteria in the presence of MFGM are helping the intestinal neuronal system to mature faster because there are differentiated cells, they keep replenishing the neurons in the intestine and this is helping.

What other evidence that we have, you will have the expert telling you about myelinization and how sphingomyelin or other gangliosides, DHA, play a role in it, but being a crude type of scientist, we dairy people, I know it has a lot of problems but check this out. My friends in Ireland directly on a neuronal cell culture added the phospholipids of MFGM. When normal growth or proliferation of cells, they need fetal calf serum, very expensive and cruel, you have to cut the serum out of an unborn calf, fetal calf. And it's great for neurons. But guess what? Look at the rate of proliferation just by adding a product out of milk. Big

difference. Caveat, at very high doses, it could be toxic. Here we have evidence that there is a very important link between mom and the child's brain. Sounds romantic, but I think that's what motivates a lot of us scientists.

To leave you with some take-home messages, MFGM, I hope that you have understood, is very complex, but in the complexity is its value. We cannot purify 1 or 2 components of MFGM and hope to work the same way. The components in milk are nonpresent in the plant world. Very simple. Plants have no brains, no mammary glands for that matter, but that's immaterial, I've looked. And MFGM and its lipid components fortify the mucosal barrier fortify the mucosal barrier. That is a fact. And facilitate healthy gut microbiota and I told you why, because then the toxins and the pathogens have no room to grow. I think, and believe me, my mother-in-law, rest in peace, was one of the healthiest persons that I have [known] and she was brought up, according to her, with donkey's milk. Maybe the stubbornness comes from there, but I don't know, the healthy microbiome was there. And I think, and as research continues and inspiration to scientists continue, there's a very important link between the gut and the brain. And MFGM plays a very important role.

MFGM & the Developing Brain

Dr. Deoni: We heard eloquently from Rafael there on the basis of how MFGM might interact both indirectly and directly on neurodevelopment, either through directly acting as a precursor to many of the nutrients that we need in the brain or indeed through the microbiome and up through the gut-brain axis. Perhaps not surprisingly here that I'm here to talk a little bit more about does it actually have an impact on brain development because if I got funding or if I got a nickel for every idea that sounded great and didn't work out, I would never need NIH funding. We're going to have a little bit of a deeper dive to see if it actually pans out for us and whether this nutrient actually plays a role.

We're interested in early development and that's what our lab is particularly focused in on. And why do we care about early development? Well, I might be aging myself, but when I was at university, almost everyone had these posters that said something to the effect of everything I needed to learn I learned in kindergarten. And I would actually argue that kindergarten was sort of geriatric in terms of what you needed to learn. Almost everything you needed to learn and everything you needed to be able to learn had happened by the time you hit age 2. Maybe preschool, as it were. And just to draw your attention to that and kind of give some visualization to that, this is the first 1,000 days or at least the postnatal portion of the first 1,000 days, right? This is going from age zero up to about age 2. And think about all the amazing things that you learn to do over this time period. You go from a very fragile being to being, in this case, a very independent young woman who can take on the world. Right? You've learned how to take your first steps, say your first words, make new friends, understand how to manipulate your brother, get him into trouble, understand which of your parents you can manipulate to get whatever she wants. All these things, she will learn very, very rapidly and, as you'll hear from Dr. Colombo after me, we can label all these various skills that she will begin to develop over those first 2 years of her life. Obviously, vision, speech, emotional manipulation, we'll call it emotional development but certainly manipulation on her parents, math and logic. She won't be doing second derivative calculus, but she will certainly know if Stefan got more cookies that she did or slightly more marshmallows in her hot chocolate. Social attachment, now if she's a physicist, she'll never develop pure social skills, but all these other things will begin to develop.

Of course, these things will then act as the foundation upon which all the more complex functions will begin to scaffold onto your executive functioning skills, attention, working memory and other functions, such as that, again, John will go into more eloquently following this. But again, recognizing that those skills then are what plays such an important role as she goes on to schooling. If I can go back onto her first days of school, they'll obviously play a role through her schooling and her school career, and then obviously as she goes on to her professional career, perhaps she becomes an MRI scientist like her dad, begin to subject her brother to various experiments and they'll also begin to play a role as she goes on into her personal life and perhaps she becomes a mother and begins this cycle all over again and it will have generational effects.

As an imaging lab, we're really interested in not necessarily all the behavioral changes that are going on, but also what's happening in the brain, what are the neurological changes and adaptations that are really facilitating or allowing all of these amazing cognitive and behavioral changes going on. And so these actually are pictures of Mila. If you're an MRI scientist, you get very different photos of your kids. But these are her, these are just a few samplings of the various images. My wife thought I enjoyed babysitting. It turns out she just slept well and I could get her into the scanner quite often, so I had her at the lab pretty much daily. But this is her, again, across those first 2 years of life and you can see

just the remarkable changes, even on a macroscopic level. Right? Obviously, we have other microscopic changes. We have metabolic changes. We have physiological changes. But looking macroscopically, the first thing you see is how the brain has expanded. It's grown by about 3 times in volume and, of course, that's being driven by changes in the underlying tissue microstructure and organization.

For example, we have changes in the cortex. It has begun to expand in terms of its surface volume. It begins to thin, but overall the expansion continues so that gray matter increases in volume across this time period leading to more ripples and that's being driven, of course, by neurogenesis as well as synaptogenesis and changes in synaptic pruning. We also have changes going on in the underlying white matter, right? The communication pathways as those pathways begin to myelinate, again increasing the overall volume of the brain's white matter. All of this is driving changes in that overall brain volume, again alongside all those cognitive and behavioral changes.

To increase and sort of impart again the importance of the first 1,000 days or those first 2 years of life going back to my statement that almost everything you need to have is sort of set up by the time you hit age 2. These are just looking at those 3 main organizational changes and brain changes and if you were to imaginarily draw a line down at about 700 days, right, the end of the first 1,000-day period, the take-home message is that by the time you hit age 2, you've developed about 85% to 90% of your adult brain. All of you have continued to mature, but you will spend the next 2 to 3 decades of your life refining that last 10%. Putting that into context, 2 years for about 85% to 90%, the next 3 decades to refine the last 10%. It's a huge period of immense change and in biology, any time we have something changing very rapidly, it's also a time of sensitivity, right? It is sensitive to environmental insults, it's sensitive to genetic insults, epigenetic insults, etc. It's a period that we want to be taking special care of and really be promoting and protecting.

Our lab really focuses in on this process of myelination because it is fundamentally linked back to brain function and brain connectivity, but it also is almost entirely environmentally driven. If we think about this process of myelination and what it actually means, if I were to take this image and suck off all the structure, I'd be left with the underlying neuronal architecture. All the beautiful axons within the brain that link up all the different parts of your brain. Basically, in order to do anything, you need to send electrical signals across the brain. For example, catching a baseball would require you to see the baseball, so you need some interaction and activity back in the visual cortex at the back of the brain and it would need to send a signal through the thalamus and up to the motor cortex at the top of the brain. Now, when we're born, all these cables, all these wirings are basically bare and so sending electrical signal along them is an incredibly slow and energy-intensive process. You're basically sending an action potential point by point by point by point along that axon, much like you would with electricity through an electrical cable, right? Sending electrical signals point by point. And as I said, that's incredibly slow and takes a lot of energy to do.

In order to get around that, mother nature came up with this beautiful solution which is called myelin. It's a fatty lipid layer that gets laid around those neuronal axons in response to neuronal activity and that allows information to flow far more rapidly because rather than going point by point by point, it actually hops along that neuronal axon, creating an action potential only at the Nodes of Ranier. And that increases the action potential or the transmission of speed by about 1,000 to 10,000 times faster. It's like walking along this beach as opposed to hopping into an F1 car and driving along the beach. It's a huge increase in transmission and that allows the brain to connect it and to integrate information across multiple brain systems. And so that's why I say this process is fundamental to brain connectivity and brain function. And we can see that by taking this and looking at the extents or the impact of myelination on the functional architecture of the brain.

Here what you're seeing is what we call functional connectivity images, or connectograms, which basically show the connections within the brain on a functional level. You see those different balls which represent different parts of the brain. They are color-coded by different functional systems. Those yellow balls at the back are part of your visual system and the purple balls at the top are part of your motor system and then the blue and red balls are part of things like your executive function system, working memory, attention, social-emotional processing, etc. And all the green lines represent connections between them, areas that are actually talking to each other.

What you can see is that in a neonatal brain, when you don't have a lot of myelin, information can't flow rapidly and so you don't have integrated networks. Those networks are like little islands. What that means if I were to take a 3-month-old and put them somewhere in a high chair and toss a ball to them, what happens? Right, it bounces off their forehead and then they move their hand. Right?

Because their visual system saw the ball coming, their motor system was primed and ready to move, but they weren't talking to each other. But, as you get down and as you play with your child, roll around on the floor with them, tickle them, have them push around balls, maybe make some blocks, play with Jenga, do some Lego and Duplo, they begin to build up those systems. Myelination begins to occur, information starts to flow more rapidly and you can see how your networks begin to integrate into each other and become more complex. Rather than being like little islands now, they begin to become more integrated, they begin to share information across them and this allows more complex behaviors. This is, you can see now, how you go from this structural change to a functional architectural change to ultimately changes in overall cognition and cognitive abilities.

Now, where does milk come into and where does nutrition come into this? Well, I had mentioned myelination is fundamentally linked to brain connectivity, as we just saw, but it is also intricately linked to environmental stimuli. In terms of stimulation, but alongside stimulation you need to have the building blocks to actually lay down myelin. And so there are many nutritional needs for myelination. We saw many of them in the previous talk by Rafael. This includes the things that we usually think about, our usual suspects like our lipids and fatty acids, particularly looking back to those phospholipids, sphingolipids like sphingomyelin as well as minerals, iron, zinc, every vitamin that we have as well as choline. A number of those same nutrients that we were just hearing about in terms of milk fatty globulin membrane as well as within breast milk are right here. And, as I say, with the exception of iron which comes directly from mom into the fetus during the third trimester, all these nutrients are beautifully provided through breast milk, provided mom is accurately- and well-nourished and healthy.

This work, and unfortunately many of these nutrients haven't been provided in formula or not provided at a high enough level to be biologically relevant, and so this is thought to underlie a lot of the differences that we see, for example, in children who are exclusively breastfed vs children who are exclusively formula-fed and looking at cognitive outcomes, whether it's early cognitive outcomes, Bayley's, Mullen scales, for example, later IQ, academic performance or indeed even moving all the way up to income and job potential. And, of course, there are thousands upon thousands of studies. We could fill this room with the number of studies demonstrating the differences between breastfeeding kiddos and formula-fed kiddos.

Of course, there's a lot that goes into this, right, because not only is this related to nutrition, but again there's a whole environmental aspect to this as well. Can we actually come back and bring this back to link it back to milk nutrients? Are those cognitive differences we're seeing directly related or mediated back to those milk nutrients through potential brain developmental differences or is there something else that's happening over here on the left? For example, socioeconomic factors, birth outcome factors, etc, that might be explaining this. Can we link it back to these milk nutrients?

This is work that we began to do a number of years ago mainly because there hasn't been a lot of work actually looking at the impact of breastfeeding, early nutrition in general on neurodevelopment. When we started this, there was maybe 3 or 4 studies that had been done looking particularly at the impact of breastfeeding on imaging and on neurodevelopment using MRI as well as EEG. But the challenge being that the majority of these studies were really done in those older adolescents, right, and the reason being for that is that it's a heck of a lot easier if you have a child and you've ever had an MRI scan, it's a lot easier to put an 8-year-old into a scanner than an 8-month-old or an 8-week old. The downside though is that although we do see what we might expect, that increasing the amount of breast milk in a child's diet, increasing the duration of exclusive breastfeeding is associated with improved neurodevelopment, is associated then with improved cognitive outcomes, are these actually related to breastfeeding? Right? Can we actually link back to what's happening back here?

This is some of the work that we began to do a number of years ago, very simply really just taking a wild stab to say if we have imaging data from these younger kiddos, can we link that up and get associations between breastfeeding practice or early nutritional feeding practice and neurodevelopment. The challenges, of course, is that, again, if you've ever had a kiddo and you've ever had an MRI scan, these 2 things don't tend to go well together. And, typically, what you end up with is what you have on the right which is just a screaming child and that leads to screaming parents and that leads to very unhappy staff and that leads to very nonproductive NIH progress reports. None of this is good.

The key thing is try to figure out how to put these kiddos into that scanner which we could have a full lecture on the

pains and trials of putting sleeping kiddos into scanners, but nonetheless if you're able to do this and you're able to find parents who are willing to put their kids into a scanner, you can get some beautiful data. We have been doing this again for about the last 16 or 17 years, following about 1,800 kiddos with biannual scans matched up with environmental and health history and home history information and, from that data, we are able to show that, just as a cross-sectional finding, that indeed kiddos who are exclusively breastfed had improved myelination and brain development throughout predominantly higher order cognitive areas and then that was linked onto when we looked at cognitive development, processing time period using the Mullen scales early learning, very similar to the Bayley's if you're more familiar with that, but across the various domains, be it motor, visual, functioning or language, improved neurodevelopment.

Of course, this is cross-sectional so it can be biased, unintentionally, but it can be biased, just depends on where your kiddos stand. It's much better to have longitudinal data, so we went back and did this a couple of months or a couple of years later when those kids had come back in, we collected more data but again showing the same sorts of things. That, again, increased breastfeeding, exclusive breastfeeding, promoted improved myelination across childhood. That did not normalize with age. Those kiddos maintained that overall change and again, this was mirrored when we looked at the Mullen scales for cognition and across the various composite domains, be it overall IQ, verbal cognition, nonverbal cognition, improved neurodevelopment in those kids who were exclusively breastfed.

The challenge here though is, again, are we actually just looking at nutrition when we're doing this analysis? Sure, we are controlling for all sorts of socioeconomic indicators. Income, education, marital status, where they're living, etc, languages, but are we really pulling these things apart because we know, for example in the United States, that the biggest predictor of a child's cognitive outcome is how much the family's making and where mom went to school. Right? That accounts for about 60% of the variation in child cognition. How do we pull these things apart? The first thing we did was, well how about we just go back, rather than doing this comparison between breastfeeding and formula-feeding, how about we go and break up those groups of kiddos and actually see if there's differential across the different formulas, recognizing that formulas will have a different amount of iron, some have more choline, some have more iron, some have more DHA. Do we see differential development in kiddos who receive different formulas? We had that information, so we went back and we did that analysis and, indeed, we did see a significant difference across those different formulas. Anyone who says all formulas are the same is just wrong. But indeed, we see significant differences across these and this is tied back in a way when we look at the overall formula that you can see that there's a significant difference in a number of different nutrients, even up to 50%, almost 60% difference in these nutrients across these formulas.

When we take this information, we look at cognition, we see that these brain development trends are mirrored. So again, the formulas that seem to be doing better have better cognitive outcomes and the formulas that are doing worse have poorer outcomes.

This doesn't explain all the difference between the formula-fed kiddos vs the breastfed kiddos, but it's about 50% of the variation, 50% to 60% of the variation. Nutrition is playing a significant role. Now the question is, though, which nutrients are playing this role? What's driving this? Is it predominantly the lipids that we just heard about? Is it predominantly things like sphingomyelin, DHA, choline? Or is it something else entirely?

In order to figure that out, we went and purchased a can of each of these formulas. Well, first I took out a second mortgage on my home because, heavens, that's expensive stuff. Sent that off to a lab, had it analyzed, that's where we got our information about what was actually in the tins and then we just ran analysis to see which ones were associated with this improved brain maturation profile. The results in scientific format are shown here. In physicist format, they're shown here. But basically again, showing that across the brain things like our usual suspects, long chain polyunsaturated fatty acids, DHA, ARA, important for neurodevelopment across most of the brain. We see iron, folic acid being important across many parts of the brain, but we also see sphingomyelin and choline, again nutrients that we just heard about being important across the brain, including this thing—apparently I needed to take a little bit more sphingomyelin because I can't spell choline in the cerebellum there. But again, being important across the brain. Okay? So, this again now begins to bring us back to this hypothesis that we have that potentially MFGM and these various nutrients are, in fact, incredibly important for myelination.

How can we go and test that? Well, we can do an RCT and again coming back to this recognizing, kind of coming back

to the same slide that was shown previously that this makes sense, right? Again, all those single nutrients from fatty acids to sphingomyelin and for just a bit of knowledge, that sphingomyelinase, that step there between fatty acids to ceramide to sphingomyelin, in order to get through that because that's where phosphytocholine comes in, so it's not surprising then why we see those nutrients being so important.

Can we now go and actually prove this? Well, we did an RCT designed exactly for this where we had two formula arms, one that was a standard formula, one that's already on the market, a second one that was boosted for all those nutrients that we just highlighted that we think are important for neurodevelopment, but keeping everything else the same. The lipid profile was the same, the percentage of lipids to carbohydrates to proteins was kept the same, the calorie content was kept the same. The only thing being different was increasing the amount of sphingomyelin, DHA, ARA, iron, folate, etc, and you can see that this is being boosted not only relative to the control formula, but also to even human milk references between 3 and 6 months of age. We're really boosting these nutrients.

If we don't see an impact in this case, it's unlikely that these nutrients are driving that development. But indeed, what we found across the full 2 years of this study, so this was a 1-year intervention with as much—up to 6 months exclusive breastfeeding—as we can get, and then we followed these kids out to age 2 and we saw overall improved neurodevelopment in those kiddos who received that trial formula. Again, being boosted for those LC-PUFAs as well as sphingolipids, phospholipids, etc.

This is a trial formula. Makes sense, but now does it get back to MFGM? Right? Can we link this back into something that's actually happening because recognizing that, as was mentioned, in a breastfed kiddo, that's where they're getting these nutrients, right? They're getting them directly from mom's breast milk. We want to come back and see, do we get these same nutrients from improving or increasing the amount of MFGM added back into a formula? Now, how can we do that? Well, the first thing is I can call up Mead Johnson, for example, or Abbott or whoever and say could you make me a formula that was boosted for MFGM. I don't know how you do that. Can you go figure it out? Can you then get it FDA-approved and then send me a whole bunch of it for free? That's going to be a very quick conversation, I'm not going to get very far into that, right?

Thankfully, however, I didn't have to make that phone call because they did the study for me. As I mentioned, we've been following kids for about the last 16 or 17 years. We recruit and enroll about 150 to 200 kids every single year and we continue to follow them. What that means then is that we basically have a whole series of temporal cohorts, right? We can look at temporal changes that may have happened in the environment across that time period. And, in particular, we can look at the introduction of added MFGM formula, that happened around the tail end of 2017, the beginning of 2018, and look at kiddos prior to that and kiddos after that who received the exact same formula because now we can get a little bit more information about what's actually happening to those kiddos who are receiving that added bovine MFGM. We went back, we did that study. Of course, you notice that we stopped in 2020. I don't need to tell you why, I think we all want to forget about that but nonetheless we were only sort of limited to the first 2 years of life. But what we found is almost exactly what we began to see in our RCT where, again, looking for these kiddos and again matching these kiddos for SES characteristics and birth outcome indicators. We saw overall improvement in brain myelination, predominantly in motor-related regions, so you see the motor cortex there at the top, cerebellum at the back as well as the thalamus in the center and the corpus callosum, all being increased in those kiddos who received that infant formula with the added bovine MFGM.

When we look at overall maturation, it's about a 20% to 30% increase and that that was then linked, when we looked at cognition, we didn't see a change in overall cognition. We didn't see a change in verbal cognition. These might be because we were looking at these kids that were quite young, this is before age 2, so verbal development is just beginning. But not surprising, given our imaging results, we do see a significant improvement in overall motor development. We'll see then if those continue on and carry on and scaffold on to later cognitive outcomes through Dr. Colombo's talk.

Hopefully, I've managed to convince you that, indeed, this is one of those rare cases that a good idea actually panned out, at least in my lab. Normally, those fall somewhere. But in this case, the idea that actually these nutrients that we see being important that should be important for neurodevelopment actually do seem to be important on a neurological level, improving brain myelination. And these, of course, include nutrient like folic acid, iron, cholesterol, our LC-PUFAs that we hear so much about, but now bringing in the sphingomyelin nutrient that we're now beginning to learn more about. Certainly, as I had

mentioned, that these nutrients are amply provided in human milk, provided mom is well-nourished. That's a key caveat here that we want to make sure and support nutrition in lactating moms in order to make sure that they're providing as much of these nutrients as possible to their infant. And also partially explain the observed cognitive differences we see between breastfed and formula-fed kiddos. As I say, we're now beginning to get more and more evidence, I think there is some really beautiful work presented by Rafael, but we're now seeing more evidence saying that formulas that have supplemental DHA and now sphingomyelin being added on to that seem to promote improved myelination and brain maturation in healthy kiddos, not just our sensitive populations, low-birth-weight or preterm kiddos, but even in healthy term kiddos and this we're seeing both in RCTs as well as observational findings.

I'll leave you with one thought which is weird, given I just spent a whole bunch of time talking about nutrition, but remember that myelination and brain development requires not just the basic building blocks for a brain, but also stimulation. Really making sure that you bring that stimulation impact onto our kiddos is going to be incredibly important. And the biggest, biggest question by far I get in our lab is how do I make sure my child is smart. It's a weird question, right, not how do I make sure they're happy or healthy. How do I make sure they're smart? But nonetheless, I think taking all that, to answer all of those, the biggest answer that I've managed to come up with is just to love your child. You'll never hear another physicist say that, but I think that works out because if you love your child, you're going to get down and play with them, you'll spend time with them, you'll read to them and you'll provide them with the best nutrition you can. And if you put all that together, they have the best chance of succeeding and becoming their optimum selves.

Supplemental MFGM & Neurodevelopmental Outcomes

Dr. Colombo: I'm lucky to follow 2 such great speakers and to finish off the story about how we go from biology to cognition. I'm a developmental cognitive neuroscientist and I work in the area of early assessment, and part of my job, across the course of my career, has been trying to understand how to measure cognitive function in infants and young children and toddlers. And, as Sean has told you, it's not easy. If you have ever spent time with infants and toddlers or ever been one, you realize that it's, they're not the most cooperative folks.

When cognitive psychologists started to study the make-up of intellectual function, they laid out a bunch of basic components which I will call lower order cognition. These are things like sort of being awake, being alert, being able to pay attention, being able to select certain things in the environment and actually highlight them significantly or emphasize them for either learning or memory. And so that's attention, and which is sort of what I started my career studying. Then there's different kinds of memory. There's memory that we're all sort of familiar with, the idea that when you sit back, you remember, you reminisce about things that have happened in the past. And that's long-term memory and that's really important, but what's also really important is sort of the moment-to-moment memory that we have while we're engaged in a score listening or attending. And that's sort of working memory. And that's just as important. And so those 2 different kinds of memory are critical to our function. And the last thing, of course, is that you sort of put all that together and it leads to an action and that's the basic information processing system that we have that was formulated in the late 1960s, early 1970s, by Ulric Neisser. What's missing from this, however, and what psychologists figured out pretty early in the theoretical realm of this, is that there was nothing to run this lower order cognition. They created, theoretically, a series of executive functions, things to run things from the top down.

This turns out to be an interesting thing. Initially, it was just sort of a like, well there must be some sort of homunculus, there must be some person up there running the show or pulling the strings. But we now know that these functions are simply integrated decision-making processes that exist in the frontal cortex, the front part of the brain, that develop quite late and which take information from all of the other lower order functions and then basically integrate that information and sort of pull different information along the way to do things like inhibit responses, to engage in goal-directed behavior, to learn rules and apply them to a certain behavioral set of outcomes, to be able to change your mind based on what the changing environmental circumstances present and, in a big thing, sort of like problem-solving, the idea that you put all this together over a series of time, you develop strategic initiatives and you therefore are able to do all the things that I think really, really characterize us as being uniquely human.

If you notice, also, parents like it when their kids pay attention. They like it when their kids can remember stuff. But if you're a parent, the thing you want your child mostly to do are these executive functions and that's why I'm

arguing a lot of times that for parents, really, this is the thing that matters to parents. These are the things that matter. These are the things that matter to all of us and these are the things we should pay attention to.

These things develop in different ways. The basic vital function, if you were asked to look at the effects of an intervention on, early on, you'd measure basic vital functions, but the lower order components actually are developed pretty early, really during the first year, first year-and-a-half. The sort of the saturation of the bars here reflects the times when things are developing most rapidly in which they're both most sensitive to environmental input as well as being vulnerable to problematic experiences. And if you're interested in the long-term outcomes though, you want to look at these executive functions because they develop, and they develop later. They develop really into the second and third and fourth and fifth year of life. They're not always evident really early. In my academic research, I know that I can see some of the inklings of executive function develop late in the first year, but not much before that and this is a controversial position but it's something I think there's lots of data for.

When you design a clinical trial, you're faced with a number of different options and, again, I would point out back on the previous slide that depending on what you're interested in, you need to measure things at different ages and it's also the case that it's not always the same thing at every age. For example, if you were interested in the effects of probiotics on early development and you were measuring it in the first 8 weeks, you wouldn't measure executive function. You'd measure sleep, you'd measure state, you'd measure some basic things. But, as the child gets older, you're going to be interested in more complicated things and that's why, for example, it's common for us to measure lower order cognition things early and then, as the kids get older, you'd measure executive function.

When you design a clinical trial, you have to keep all this in mind and you have a number of different options. The first options that pediatricians are typically familiar with are screening tests. These are not very sensitive. These are basically designed to determine who's at risk for potential delays or who has already been medically, behaviorally compromised. Another common thing that's used—another common measure—are parent reports. They can be useful, they can be helpful. I worry a little bit about what you're really getting when you ask parents, but a lot of research suggests at least by asking parents about their children at different points, you actually do keep them engaged in the clinical trial. In many ways, that's what I really like about these things if I don't really like them as outcomes. The last one, the third one is standardized global measures, like the Bayley, like the Kaufman, like the Mullen, like the Griffiths that's used in the United Kingdom or, in Asia, there are different translations of these measures. These are measures that are based on basic IQ tests. They were developed back in the 1930s, 1940s by individuals trying to determine the early precursors of later intelligence and language. They're used predominantly . . . the most useful nature of what you would use them for is still identifying delay. That's what they were designed to do. A difference of 5 or 6 points there, they weren't necessarily designed for that, but people use them and people understand them. The last one is the one that I usually come down to in terms of what my preferences are. And it's backed up by the data that Sean just showed you that different nutrients differentially affect different regions of the brain and I showed you the chart before, the figure before, where there's different types of attention, different kinds of memory, those reside in different parts of the brain. And so you would expect that a nutrient might affect one thing and it might not show up in all of the different measures that you use.

We've typically opted, when we design a clinical trial, to use tests of specific cognitive skills. We're interested in measures of attention or measures of memory or measures of executive function or, in particular, subtests of IQ tests to see whether or not outcomes are specific to a particular type of function or parameter.

I'll give you an example of the way we go about testing executive function in very young children. And this is the modified Stroop task. It's based on an old 1930s test that we do, that you can do with adults, and you can look it up, it's really interesting if you want to engage in parlor games and things like that with your friends. But this is really simple and, in their unending creativity, psychologists have called these tasks the red/yellow task and the night/day task or the day/night task. And here you tap—and as we've mentioned at many points this morning, kids are not particularly cooperative—and so what I like to say when I talk about these tasks is you tap into the inherent evilness of a 2- or 3-year-old and what you do is you actually say, okay, you know what, what I want you to do is to fool the experiment or fool the guy who's testing you. What you do is when you see the red and it's on the task here to the left, when you see, there'll be a screen that'll show you a color and when the red one comes up, say yellow. I want you to fool him. And when the yellow comes up, say red. Okay?

You got it. And 3-year-olds love this because it's like. . . the other thing is that the night and the day, this is when the sun shows up, you say night. When the moon comes up, you say day. And despite the fact that it's kind of this crafty way to test these kids, here's what you're really asking them to do from a psychological or cognitive standpoint. You're asking them to learn the rule, right, when I see something, say the opposite. The other thing you're trying to do is you're also asking them to inhibit saying the right thing, inhibit saying the correct thing and also inhibit sort of the impulsive response to say, to blurt out what you're saying. And all of this might seem pretty simple, but for a 3- or 4-year-old, it's not that simple. And, in fact, they have to be occasionally reminded of the rule and the younger they get, the more often you have to scaffold that.

Another task that I really like is the dimensional card sort task, the DCCS, and here what you have are stimuli that can be sorted on more than one dimension. For example, like these tasks, these stimuli here, I can sort these geometric shapes either based on color or I can sort them based on shape. I can put red things with red things or blue things with blue things. Here, I'll give a child a stack of cards and I'll say, okay, sort all the blue things here and sort all the red things here, cool, or sort all the shapes, all the circles here or all the squares there. And in this case, what you're asking the child to do is, 1, learn the rule; 2, apply the rule; 3, pay attention to what they're doing to the exclusion of the other dimension because when you sort on color, you have to ignore shape. When you sort on shape, you have to ignore color. Okay, so you're doing that. This is the first part of it. Then, when the kid masters this, you move, you switch the rule. When you're testing a younger kid, you tell them, okay, now we're switching the rule because, but with older children and adults, you might just actually let them figure it out by yourself by changing the consequence. Oops, that's wrong, the rules changed, okay, let me figure out what this is. This is a measure of cognitive flexibility. After you have actually learned the rule, do you perseverate or can you actually adapt to changing conditions, changing instructions?

You get past that point, you get to the third one which is actually a conditional rule and here you put a border around the stimuli and you say, when the border is not present, you can sort by color. If the border is present, you sort by shape or whatever the situation might call for, it doesn't really matter, you can do either one. If you think this is easy, it's not. If you try it, again make up some cards and test your spouse after a couple of glasses of wine. And you can see it's really not easy. If the border is present, I sort on one dimension. If it's not, I sort on the other one. What you do here is measure, for example, the number correct across the initial rule phase, the shift phase and then the conditional phase. Or you can simply look at the percentage of kids that pass each one of these as they go along the way.

This is the example of these 2 tasks. There's one more task that I like. I'm not going to present any data on this, but it just gives you a flavor of what executive function is like. This is the go/no-go task and it's mostly used when we do electrophysiological measures, if we're doing like brain electrical EEB-ERPs or something like that. This is amenable to that, so you get not only a reaction time measure, but you also look at different brain potentials when kids are doing this. And here what you do, for example, and this is appropriate to the location, you present fish and you're presenting them boom, boom, one right after another. And when the child sees the fish, you hit the button and then their instruction is to hit the button as long as it's not a shark. And if you see a shark, you have to stop. And it's really interesting progression. If you get a 2½-year-old, they're just banging away, but then at some point, about 3, 3½, they'll bang and they'll see the shark and they'll hit and they'll wince because they know they've made a mistake. And only about 4, 4½, 5, that you start to see kids actually stop themselves. It's a cute little task and it gives you a sense of like, again, you've got to learn the rule, you've got to apply the rule, you have to inhibit the rule under certain circumstances.

Now we set out sort of the methodological parameters of how we measure executive function, I'm going to talk about MFGM. And we've done a bunch of things on MFGM, but the study that really put MFGM, I think, on the map is Ali Herndal's study in Sweden where he did the Bayley scales. He used the Bayley scales to assess the effects of feeding babies with MFGM for about 6 months. And this is the study outcomes were measured at 6, at 12 months. This is using the Bayley scales. The Bayley scales are good for what they are. I look at them as sort of a relatively crude measure of developmental outcome and if you see an effect on the Bayley, in my view, you've got a really powerful effect because it's like looking at something happening on earth from space because it's really far away from the individual components of attention and memory and executive function. But Ali found that, basically, on the cognitive subscale of the Bayley, you do get a significant difference in kids who were fed formula with MFGM as opposed to kids who did not receive formula. And, in fact, the kids fed

MFGM were actually quite close to breastfed kids in this study.

This is the 12-month outcome. I would point out that, in a subsequent follow-up at 18 months, they did not find differences on the Bayley. Some people don't like that when effects wash away. That doesn't bother me at all because what I like to think about is that, for some amount of time, a child's development has been accelerated and that acceleration allows you to do all sorts of other things and learn other things that are relevant to later outcomes. The fact that other kids who were not supplemented eventually catch up, I don't see that as a problem, necessarily, as long as we follow up those kids later on. And I'll show you what I mean in a little bit.

Our own studies were done on MFGM in Shanghai and with a collaboration of several pediatricians in different hospitals so that we could stratify the SES differences in looking at this. And this was a relatively major effort in enrolling 450 kids and basically dividing them into 2 arms, kids who received a standard cow's milk formula with MFGM and lactoferrin as well as the standard formula by itself. And here, we actually, again, were interested in the primary outcome being the Bayley scales although we measure a lot of things in between, including parent report and language.

The parent report measures, again, this was something that I was not necessarily in favor of, but I figured, well, it's a blind trial, it's a double-blind trial, the parents and children don't know what they're receiving, experimenters don't know what they're receiving, let's see what the parent report. This was a way that we were able to measure them at 4, 6 and 9 months, or at least keep them engaged in the study and, dang, if it didn't come out. You can see the *P* value on the very right side, on the Ages and Stages Questionnaire, which is basically how's your kid doing, what are they doing here, what are they doing there in this domain. In every one of those domains, communication, gross motor, fine motor, problem-solving, personal social outcomes, the kids were better, the kids who were receiving the MFGM and lactoferrin were advantaged. Again, surprising to me, just boggles my mind that this came out, but it was really there and you can see by the *P* values, it's a significant change. When we followed them at 12 months, we did the Bayley at that point, and we actually did see significant improvements favoring the MFGM and lactoferrin group. The kids on the cognitive subscales of the Bayley, they were much higher, as you can see there. There's a difference of about 8 points. On the language, they're better, and on the motor, they're better. There's a social-emotional scale and general adaptive which I don't think are particularly sensitive at 12 months, those didn't come out.

Now, once again, at 18 months, when we followed them, the differences went away, but I'll reiterate here, that doesn't bother me. We've got a big difference at 12 months, let's see if that advantage goes out and gives children an advantage later on. I would point out, once again, that we fed for 12 months and then stopped feeding the formulas. What you're going to see as we move further and further away from the feeding period, that these effects start to persist.

I got the call on a Sunday morning from my friend Collin Rudolph who was, at that time, the chief medical officer at Mead Johnson and said, hey, this study came out, we're going to have to follow these kids further, can you design a follow-up for us? I said, okay, that's great. These kids, once they get to this point, are eligible to be assessed with a preschool scale of intelligence, like the WPPSI, and then we also get some executive functioning, I'm going to throw some executive function outcomes in there.

When we did the WPPSI at 5½ on these kids and, remember, we only fed them for a year, we see significant effects on visual, spatial, and this was the thing that kind of blew my mind, if you've been paying attention this morning, you're going to see that there's been a lot of talk about myelination. On the processing speeds subtest of the WPPSI, we saw significant advantages for the MFGM group. This is exactly what you'd expect as a behavioral outcome if, in fact, it's affecting myelination. Furthermore, all of this, if you add, you can see the trend here. You add all those things together, you get an overall measure for a full-scale IQ score. There's a significant difference there favoring the MFGM group.

Part of my day job is running a research institute at the University of Kansas that focuses on intellectual and developmental disabilities. It's very, very hard to move IQ. People don't realize that many have tried to improve IQ and many have died doing that. It's just not something that you see. Having been pulled into nutrition, I've seen now 2 or 3 times when you get a change in IQ as a function of what you feed early on. To me, that's one of the most remarkable things in my career to have seen and I'll just point that out to you because we take this, oh yeah, you changed IQ, you improved IQ, that's a big deal.

Oh, remember the tasks, the red/yellow and the night/day tasks, the day/night tasks, the Stroops? Kids who received MFGM and lactoferrin at 5½ years did better on the executive function tasks there and they also did better on the DCCS, particularly when they got to that phase where it's conditional. They, we followed them, so at 5½ they did the rule, the initial rule learning, they did the initial shift, but then when they got to the point where we made the shift conditional, they actually, the kids who were fed MFGM and lactoferrin 4 years earlier did better on this task, more of them passed this phase of the task. That's pretty much that Lighthouse test.

There's one more test, one more clinical trial that I want to talk about and it's the COGNIS trial that was run at the University of Grenada in Spain by Ana Nitto-Ruiz. And here they, again 170 infants were randomized to 18 months, feeding for 18 months, again standard cow's milk formula or MFGM and some LC-PUFAs. And there was a Bayley scale administered at 4 and 6 years, I'm sorry, actually the Bayley-IIIs, I think this is just a regular IQ test at 4 and 6 years as well as tolerability and all the safety things that typically happen.

The K-BIT, which was, it's not the Bayley, but it's the K-BIT, was assessed at this time and, again, you have vocabulary changes, changes in language that are significant with the intervention formula being above the standard formula and very close to breast milk. And then you get a significant effect on full-scale IQ. Once again, remember, it's really hard to move IQ and here we've seen 2 examples of it just this morning.

That's the story. I think, if you look at the breadth of the talks today, we've gone from bench science, understanding the nature of MFGM, its biological actions to what it does in the brain and now what it does in terms of things you can see in infants and children. What we're seeing, over and over again, is that MFGM really produces meaningful and powerful effects on child outcomes, particularly in language, IQ and executive function. This is really surprising to me how powerful these effects are. The other thing is that these effects persist from the point of feeding, which is typically anywhere from 12 to 18 months, and these effects persist out to childhood and school age. And this very strongly is consistent with the idea that these components are affecting brain structure and function.

Questions and Answers

How did you define MFGM and are there a minimum amount of ingredients, such as phospholipids, that meet the definition of MFGM?

Dr. Jimenez-Flores: I don't define MFGM. Nature designed it and made it. MFGM is designed by itself and my point is, if you, like me, cow's milk or mammals of all kinds and I do that because my professor had a collaboration with a guy in the museum in Washington, DC, the Smithsonian, and he was Mr. Milk and so I'm not kidding you when I say that I have analyzed milk of elephants, of bears, of kangaroos which have a different milk in each teat, and the milk fat globule membrane, that membrane that surrounds every droplet of fat in milk, has the same composition, virtually. And mostly for phosphatidylcholine, phosphatidylcholamine and sphingomyelin make one-third, one-third, one-third of the phospholipids. That's what defines MFGM. Now, physically, what we add to infant formula, how is that defined? Well, that's defined mostly by the industry that could make the ingredients I described, but the amount that is added to the formula is enough to mimic what is there in human milk, no more, no less. We need to have the same amount of phospholipids that mother's milk have which, by the way, a lot of the triglycerides will vary with the diets of the mother, but the membrane lipids don't. You know why? Because there's a function designed by nature which is lactation and if we don't have those components in that, in those conditions, milk wouldn't be secreted.

We always think of myelination tied to IQ, but does faster transmission of messages also improve social and EQ or emotional intelligence performance?

Dr. Deoni: This is a challenging question. Myelination, as I say, its role is to facilitate rapid transmission and coordinated messaging across the brain. When you think about social interactions, social skills, emotional-social regulation, all those require multiple brain areas talking to each other and integrating information across multiple brain systems. As John had mentioned about executive functioning skills require not just the ability to do something, but also inhibit other things while you're doing that. Pay attention to what's going on, receive feedback from the person's facial expressions, change your input on that. All of that again, so there's no direct anything that's going to require that integration of signals across multiple brain systems that is going to be directly leading back to processing speed of myelination. Although it might not seem that improving processing speed or transmission will relate to social programming, social-emotional regulation, it will be involved in some ways. Again, because it's such a fundamental process.

Do you see any changes in basic visual processing skills, like refractive?

Dr. Colombo: You see real differences in these really, really complicated later skills and is it just due to something really, really happening very early. I don't know. We didn't measure, we didn't do any visual acuity or refractive errors or contrast sensitivity measures for vision in any of these children as a part of the protocols. But this is the kind of thing . . . I like this question because it asks whether or not a particular advantage seen early in a very low order process can lead to improvements later on in higher order processing. You do see that in DHA where, for example, you improve visual acuity by feeding it, feeding DHA to preterm infants or even to normal-term infants. That difference goes away by 12 months but being able to see better for 12 months than everybody else then gives you a leg up and you see differences in executive function and outcomes.

Is this effect dose-dependent on MFGM?

Dr. Colombo: I would point out, with deference to my colleagues in the nutrition sciences, that calculating a dose for MFGM, since it's not a single thing, is, I don't know if it's possible but I do know that the formulations that are used basically seek to equate the level of MFGM in formula with whatever there is in breast milk, but that's as much as I can say. I don't know that a dose . . . you would have to dose individual components, I think, rather than the MFGM.

Can you briefly explain the difference between naturally-occurring MFGM vs added MFGM?

Dr. Jimenez-Flores: Natural MFGM is just the structure. Chemically, you cannot tell the difference because once you isolate it, it has the same components, phospholipids, glycoprotein, glycolipids, etc.

The other question related to this is what is the relationship with human milk oligosaccharides and MFGM?

Dr. Jimenez-Flores: Well, in human milk, the complex oligosaccharides that babies cannot digest but the bacteria are floating. We don't have the milk of humans selected like the way that we selected the cows to produce a lot of milk. In cows, we do have those complex oligosaccharides but they're attached to the proteins and that is because a cow produces about 15 to 20 kg of milk a day. I don't know of a woman that would produce that much, but it is through the genetic improvement.

Are there differences between full-term vs preterm mother's milk in MFGM?

Dr. Jimenez-Flores: I don't know how to tell this, but there's a difference between what we call colostrum and real milk. And colostrum, although it has some fat, any fat that is in milk, anyway, does have a membrane and that's something that we need to equate with donor's milk which is my last question here. Donor's milk is just a variation among humans. My daughter right now is lactating, she freezes her milk and I can see her the morning milk has more fat than evening milk just because I was babysitting for a while and I know milk so I was looking at it. Those are the differences. Freezing and thawing is basic microbiology, the bacteria do not grow in the freezer.

Can you talk a little bit about the process of doing MRI in infants?

Dr. Deoni: In a word, carefully. We obviously can't sedate our kids, we can't use the make go to sleep now drugs, so that's out. We basically spend all of our time waiting for kids to fall asleep and then gingerly moving them into a scanner and then doing a lot of work on the scanner to keep it quiet. Our scanner runs at about 60 dB, about the sound of a library so it doesn't just wake them back up again but it's an arduous process of patiently waiting for children to fall asleep and then gingerly moving them into that scanner and not disrupting them. I will say, although you might think immediately that, oh, like 3-months-old, 6-months-old are easier, 2-years-old are a pain. Absolutely the exact opposite. A 2-year-old will take longer to fall asleep, but when they fall asleep they are a dead thing. You can roll them down, you can carry them, kick them down the hallway, they will not wake up. A 3-month-old will fall asleep continuously, but they wake up at the sound of a pin drop. Very disparate, depending on who, what's happening.

Why is MFGM not introduced as a health policy in all formulas?

Dr. Deoni: I'll just put a mirror up and say because you haven't demanded it. But I think it should be. I think it's ethically absurd and morally reprehensible that it's not, particularly given the information that's now coming. I don't know what more you need, but . . .

Dr. Jimenez-Floes: I think that it's also very important for an audience like this to help our regulation officials and, remember, milk is regulated by the FDA to really demystify all these things of what we're adding to infant formula, but most important to convince them, as our data has shown, that science is an active conversation, but this conversation is taking the side of there is an advantage of adding MFGM, not only to infant formula, but really to our diet.

Why do you use the Ages and Stages Questionnaire instead of the Bayley at 4, 6 and 9 months?

Dr. Colombo: If you're doing a study with 450 kids, the amount of person power needed to do a Bayley at 3 times during development during the first year, not to mention getting people into the laboratory, the ASQ can be filled out by parents in a matter of minutes while they're waiting to see a doctor or something like that. The Bayley would take a much more extensive amount of time and would wear the child out. The ASQ represents sort of a quick and dirty measure, and it's mostly got to do with convenience.

Should MFGM be regulated?

Dr. Colombo: I worked for a long time on DHA and what was really interesting from our standpoint, and as a researcher who leads a research institute, we struggle with the assessment of impact. What impact has our research done, made in society? I'll point out that early on, we did a lot of work on DHA where we gave DHA and then the control group as a placebo. We went in for an NIH grant a number of years after that, after our initial studies had come out, and we were told flat out that we could not run a placebo group anymore because that was unethical. As a measure of sort of the impact of your work, the idea that we would propose a study where kids would get no LC-PUFAs or no DHA became something that we would not consider. That was great progress and I suspect the same thing will happen with MFGM eventually.

Dr. Jimenez-Flores: Just my comment on the regulation is we're facing, and this is totally political and a point of view, we're facing a decrease in the interest and belief of science in our society and that's a tragedy and I hope that it starts with doctors, pediatricians, telling people how important science is in the development of humankind.

Question about necrotizing enterocolitis.

Dr. Colombo: I'm not aware of any effects on MFGM on NEC. Certainly, in the Lighthouse study, I can comment that we obviously measured tolerance and it was well-tolerated. We did see significantly fewer adverse events in the MFGM-lactoferrin group. Those kids were healthier, which is another path through which you can affect cognition, by the way, in keeping with a lot of Sean's comments about like nutrition is one thing, but the effects of it are actually mediated through all sorts of other environmental conditions. I am not aware of any specific effects on NEC. Do you have anything?

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