

Prenatal and Early Life Risk Factors For Chronic

A Web-based Training

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A Web Based Training

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Introduction and Brain Development

When and where how does it really get going? And the subtitle is how adversity gets under the skin, that's really what we're looking at. Diabetes is in some way a natural endpoint, if you will, to a complex web of adverse experiences some of which happened before we're even born.

So our model of diabetes then is nothing wrong but it has been too small. We've been thinking that it was only about genes that we inherit and our lifestyle choices diet and exercise. And because we haven't been able to affect genes very well, at least not yet, we've kind of been beating our patience over the head with the lifestyle choices issue. And it's not that it's not important but as Dr. Phil would say "how's that been working for us". Not incredibly well under the circumstances. Perhaps our model is little bit too small. So it's not clear that these alone do not explain all of diabetes risks. And it's also becoming clear that the roots of diabetes overlaps with the roots of other chronic problems in our communities; health problems like heart disease and depression but also substance abuse and ethnic violence, learning problems and others. As for understanding where the roots of these things come from where finding a whole lot of overlap and that helps us understand why were seeing so much of what we see.

So let me give you an example.

This is a study that - takes so many years for these health risks to play themselves out sort of speak in terms of people actually getting the disease downstream- means that you have to look at older people in order to see sometimes how this works. So this study looked at children who were born in Helsinki between 1934 and 1944 so of course now they're 70 years of age and older. Of this cohort born during those years 320 of them had a unique experience. They were evacuated abroad during World War II. There was a real concern, a real fear that the Nazis would cross the sea there and invade Finland. That did not end up happening of course but there was a real threat but that might have occurred. And so to protect these children their parents sent them away from their country, from their family, from all their support systems as it turns out. And on average they were as little as five years of age at the time of evacuated and they were gone for about 1 1/2, a little over 1 1/2 years. Sixty years later compared with children who are not evacuated these are still children who went through the stress of World War II but did not get separated from their families in this manner. The folks who were evacuated 60 years later are twice as likely to have heart disease and hypertension and almost one and a half times as likely to have diabetes and close to twice as likely to have depressive symptoms. And as the study says as the first to show that early life trauma predicts higher prevalence of heart disease and type 2 diabetes in late adulthood. Our smaller model of diabetes would not know how to explain this because they control for all of the things like health (inedible) and the other things to do that. But you can see the study there that relates to this particular thing but it gives us a hint that there's something much larger than just genes we inherit and diet and exercise choices explained for all of our risk for chronic disease.

So, for diabetes risk it matters what happened to us as adults. Yes our diet and exercise choices matter of course count but we have to remember that many people have access

only to food with poor nutritional quality even if there's plenty of calories and we need to remember this is actually another stimulus to overeating. We talk about obesity as being over nutrition but in fact it is only over calories. Most people in the world, who are obese, actually are under nourished when it comes to almost everything other than fat, carbohydrates, and some proteins but the micronutrients are often in very short supply. And when the food you eat doesn't have a lot of that in it, you have to eat more of it to get that and that is again a stimulus to overeating again. Also stress and trauma to us that happens to us as adults matters. But it also matters what happens to us as children just as that study we just talked about from Finland demonstrates. And you're going to see a pattern here that not only does it matter what happens to us as children, it also matters what happened to us when we were in the womb. It also matters what happened to our parents and to our grandparents; there is now evidence clearly leaking that as well. And you can see that the recurring theme here has to do with nutritional quality and with variations on stress and trauma. These are the two recurring themes that will come back over and over again as we talk this afternoon.

You don't have to believe me on this, this is from a wonderful report that came out of Harvard just a couple years ago. But "adverse pre- and postnatal experiences can have a profound effect on the course of health and development over a lifetime...biological events that occur during fetal and postnatal life predisposed the child to an elevated risk of subsequent problems in physical and mental health". So we're talking about pre- and postnatal experiences long before we even have any memories these things are happening. What happens in us has affects that last.

And this was just in JAMA a couple months ago, "...confronting the origins of disparities in physical and mental health early in life may produce greater effects than attempting to modify health related behaviors or even improve access to health care in adulthood". And that's pretty profound to make that kind of a statement. That if we can just address these roots, the early origins of these disparities we see in physical and mental health, that's more important than modifying health related behaviors which of course what we spend a lot of our time doing in our clinics. Not that it's not important, but that it is probably not as important as what happens in the early life.

So one way of looking at chronic disease then, one framework might be, that chronic diseases it the product of multiple stressors and risk factors which accumulate over the lifetime and in all those areas that are listed there. Those stressors affect both the body's physiological regulatory system, as we'll talk about, and in fact our likelihood to have healthy behaviors or not. Different health trajectories, so to speak, are the product of and this is important - not only the risk factors as we'll talk about those but it's easy to lose hope when we think only about the risk factors- but it's the product of risk and protective factors.

Sometimes we can affect the risk factors and we need to do that wherever we can, and we'll talk about some ways to do that. But even if we can change poverty and we can change some of the things happening in the homes of some children we can increase the protective factors and changing that ratio matters a lot. While stressors have effects

throughout, life the body is naturally vulnerable to them during critical developmental periods. Which by the end of this I hope you will believe the prenatal and early life times are.

Well after all those heavy kinds of things I like this quotation because it actually sums it up just as well in some ways. “What you walk around with are the first 2 to 5 years of your life.” What gets imprinted, imbedded (whatever term you like) in those early years lasts.

We're going to look here at the brain for a moment. The developing brain is remarkably shapeable and adaptable organ. The brain's exquisite sensitivity to experience in early childhood allows traumatic experiences during infancy and childhood to impact all future emotional, behavioral, cognitive, social, and physiologic functioning. That's pretty amazing when you think that again we don't have conscious memory of our time during infancy and early childhood but yet something is happening that affects all of those areas for the rest of our lives.

And these early life risk factors combined they take their toll on the brain again for the rest of our lives. All of those areas that you see there are the things that we know are often hard in communities of poverty and culture because of all the issues of racism and other problems that have happen. And as you look at that list the more things that you have on that list and the worse they are you can see by the quotation at the bottom that these are associated with lower IQ scores as early as age 2 to 4 and more behavior problems by age 3. Again what happens early has lasting effects on our abilities for the rest of our lives.

So let's take a look then at how this might be happening. Sorry this is a little bit crooked; I'm not the best scanner in the world. But just to orient you to the left is conception, so the first few segments there are of course our in-utero period. And you can see were not actually to talk in the slide about the in-utero period; it's going to be early life. Then you see our first-year in months and then starts going to years and then decades all the way up to the final demise on the far right. And what these curves are showing are two important things. One is experienced dependent synapse information, as you can see there. And what that is as you know brain cells talk to each other across synapses and we think that the brain is when born somehow complete but only gets bigger or something. And in fact that's not true at all. A whole lot of brain development happens after we are born and in this critical area if what pathways are developed through the brain. If you are lucky enough to be born to a family with good appropriate adult you can bond and attach to with the things you can play with they don't have to be fancy toys, but something that helps promote your gross and fine motor development. All those kinds of things happen in a good way you will develop these wonderful complex webs of Nero pathways that will serve you for the rest of your life. As the Nero-scientists say “what fires together wires together”.

If you are not so fortunate to be born in such a household and you're born into one where the TV is babysitter and there's no good appropriate adult to bond attached to, the brain

will actually prune the pathways that are not used and let alone not create the new good ones that you'd like to have in place. The other things these curves are looking at is, as you can see, neurogenesis and the hippocampus that simply means new brain cells in part of the brain that helps us learn and remember. Without a good hippocampus we don't learn or remember anything. So you can see where these two things could be critical for us for the rest of our lives.

So let's look at the first of these curves which is that dotted curve and you can see that it peaks around age 3 months or so. And we see this clinically. One example would be all of us who do newborn care know that part of the newborn exam is to take an ophthalmoscope and to look in the eyes. One of the things we were looking for is congenital cataracts and, not that it's a common thing, but you want to find them if they're there. Because if you do not find them and treat them, get them fixed before the child's first birthday, you may later be able to make the eyes see but you may not ever be able to make the brain see. Because you can see that this window has pretty well closed by not long after the first birthday.

The second curve looks at the parts of the brain that help us to understand and produce language. And you can see that peaks around eight months or so. And this is important in so many ways. You might think well eight-month-olds don't have the peak of their language development; they are not spouting Shakespeare at the age of eight months. But the pathways that will later allow them to do so or to learn their own native language or a second language or just simply to be very verbal and functional in this world those pathways are being laid down at their peak around age 8 to 9 months of age. And so you can see where parents that are reading to their children, talking to their children, this would be very important. One of the differences between rich kids and poor kids is that rich kids hear three times the volume of words that poor children hear. And those words tend to be illustrative and descriptive and conversational, creating those nice rich complex brain patterns. Whereas poor kids not only hear fewer words that the words they hear tend to be more negative and critical and all the other things that do not contribute to good brain pathways.

So the third curve then is this big long dark curve which of course is what we call our higher cognitive functions it helps us to survive and think and process information and you can see that that peaks around age two or so. So this is long before the schools even get at our kids. By the time they go to school between ages five and six; you can see it's already starting to be on the downward slope. Still a lot happening; still a lot of stuff that happens in those early years of school but you can see that the peak happens in the pre-school period. We used to think that IQ was something that was genetically determined completely based on whether your parents were smart depended how smart you were. But as we saw in that last slide things that happen in a child's life can have a huge impact on IQ. And in fact IQ can become fixed by about age 10. Another example of this is if you learn a second language before about age 10 you will speak it without an accent. But if you learn after that time, you can see how far down that curves you already are by age 10, you will speak with an accent. Just like my high school French.

The next slide are things that, of course, are good for developing brain and bad for it both pre- and postnatally. And we talked about how important micronutrients are not just enough calories but enough of the micronutrients. Sensory stimulation activity and social interaction we just talked about on that last slide. You can also see the things that are bad for the brain. Of course if mom is drinking or drugging or smoking during pregnancy you know that's bad for the development. We know that if mom smokes during pregnancy, for example, that increases the child's risk to get diabetes later in life which seems like why would that be? But we'll kind of talk about why that is. And you can see down that list, it includes chronic stress for the child and mom during pregnancy.

So let's look at an example of what's going on with childhood obesity. Obviously childhood obesity is a big risk factor for adult obesity. This is a study done trying to understand what's going on with that. So they took a bunch of three-year-old children and they measured everything they could think about in terms of their lives, as well as their height and weight and waist circumference and all the rest of it. And they waited four years until they turn seven. And at age 7 they looked to see you which of these children had become obese.

And they look back at all the data they had on them from when they were three years of age to see what would have predicted who would be obese at age 7. And as it says next to number six, it was not the number of calories that these children were consuming or if it was junk food or even if they had been breast-fed. What matters was, especially number two and number three, what the child's birth weight had been and this weight gain in the first year of life which sometimes gets called catch-up growth, sometimes called adiposity rebound in the literature. But it means children who were born small for gestational age or even normal to a very quick catch up to not only the average weight but they just keep right on going right on up into the overweight and then obese categories very often. So some people might look at that information and think that we might need to put infants on diet but that would be a mistake to think that that's what this is about. What this is about is a reaction, a reaction to what? Something that didn't go right in pregnancy as we talked about.

So next sections of the talk are going to be divided up here by how the International Diabetes Federation said are the causes of type 2 diabetes. The first and third are the ones that have been parts of what we thought of as being a model for diabetes, the genes we inherit and the lifestyle choices we make. We are also going to talk about some other things that kind of expand the model especially on genetics but also this fetal origin business why that makes the difference in risk for diabetes later. And even though we'll talk about stress and relation to those first three we won't actually have a lot of time for discussing them directly.

Genetics

So genetics – let's take that first one, and of course it matters what genes we inherit, and that's what we thought about in terms of genetics for a long time as being important. But only 15% of the genes in ourselves are turned on at any given time, so something must be going on for those other 85% that are just hanging out waiting. Well waiting for what? Well, waiting to be needed based on reaction to the environment, and doesn't that make sense that humans have been so adaptable over the years that there would be some number of genetic cards so to speak, that we have in our hands that we can play depending upon the environmental needs. Enough food, too much food, hot climate, cold climate, on and on, we've been able to roll with the punches because we had choices of genes that we could actually turn on or turn off.

The thing about this 'epigenetics' which is this turning on and off these switches, if you will, of the genes is that turning a gene on or off is not always a reversible thing if it happens at the developmental stages of life, such as prenatal and early life. And we actually know the body's on and off switches, and on this slide here is kind of a cartoon description of that and this is from a wonderful article in the New England Journal in July of last year. And if you want to turn a genes on this is what we do: that blue curly line is DNA and you can see that nothing in terms of gene sequence is being affected – that blue line is not being affected in any way in terms of no one is breaking it apart and inserting other nucleotides in there – it stays the same. What is changing is those orange football-like things up there called histones. Histones are proteins that DNA winds around to kind of organize itself. If you take the DNA in any one cell and stretch it out, it's about 6 feet long – cram it down to a little tiny cell nucleus, obviously packaging is very important in terms of whether RNA can even get in there to transcribe that section of DNA.

If you want to open up an area of DNA so that RNA can get in there, you put some acetyl groups on your histones – that's what that 'AC' is up there. You also stick a transcription factor on a 'P box' which is your promoter area. These things will turn a gene on, so to speak. If you want to turn a gene off, you get rid of those acetyl groups on the histones – you get rid of the transcription factor, and you stick some methyl groups on the promoter area to kind of block that, because the promoter areas is sort of like the ultimate on/off switch for the genes. There are methyl groups there, that completely blocks other things from being able to get in there and that gene is effectively turned off.

So Epigenetics then helps us understand... we've known for a while that this idea of nature versus nurture, which you know the question has been asked “Which of those is more important?” We know actually that now that's an absurd question – it's not either/or, it's that both of them interact with each other quite a bit. As the story I'm about to talk about describes, nurture affects nature. This study was done in rats and if you take rat pups that are raised by nurturing mothers –and if you're a rat one of the ways you do that is you lick and groom your pups on a regular basis. And it's now been shown that literally the gene which affects stress hormone receptors gets turned on in rats that are raised by good nurturing mothers, and these rats grow up to be very stress-resilient rats. They're pretty mellow, the kind that if put in a new cage this rat is like 'hey this is kind of cool I

can look around and see what's going on here' – not stressed by it. But rat pups that are raised by neglectful mothers, the gene which affects their hormone receptor is turned off—these rats grow up to be very stress-reactive; you put them in a new cage they will cower in the corner in fear. And you might say “well how do we know that they didn't just get this inherited?” They've taken rat pups that were born to mothers that were nurturing and mothers that were neglectful, and reversed them so that they were actually raised by the other type of mothers. Plus they've actually been able to measure the DNA methylation on those genes to know which of these have been turned on or off.

So as they say there is no change in gene sequence, the changes are only in gene expression, hence these kinds of effects are called 'epi'-genetic, or 'above the genome' so to speak.

Epigenetic mechanisms provide a potential pathway by which early experiences can have lasting effects on behavior.

And as Daniel Goleman says “It is biologically impossible for a gene to operate independently of its environment: genes are designed to be regulated by signals from the surroundings. ...”

Fetal Origins

Now let's take a look at the second area that the International Diabetes Federation said was related to diabetes risk. And that's Fetal Origins. As we've said, we know if mom is drinking or drugging during pregnancy that's a real problem for the developing fetus. And as we will talk about some more, mom's nutrition during pregnancy is also critically important even more than we've ever known, in terms of pregnancy. We talked about smoking – if mom of course has diabetes already by the time of pregnancy that significantly increases the risk for diabetes in her offspring. But if mom herself was low birth weight, she is more likely to in turn deliver a low birth weight infant – holding everything else equal and that doesn't seem to make sense until we're understand this new science. And if mom is stressed during pregnancy, or even if she herself had adverse childhood experiences in her own childhood, she is more likely to deliver a low birth weight or preterm baby.

So let's just remind ourselves of definitions here: 'preterm' simply means being born before 37 weeks of pregnancy or gestation. And being 'low birth weight' or 'small for gestational age' simply means that no matter what gestational age you're born at – there are average weights, whether you're born at 32 weeks or 38 weeks, there are averages for babies that age. And these babies are born small for whatever gestational age they were born at. And you can be either or both 'SGA' and 'preterm' or neither, of course – but they both increase the baby's later risk for chronic diseases as we'll see.

Here's an example: this is a study that was done in moms who had depressive symptoms before conception and early throughout their pregnancy. And they of course had what is the hormonal equivalent of depression, which is elevated cortisol, and low serotonin and dopamine levels. Remembering that serotonin is the neurotransmitter that Prozac affects.

Serotonin and dopamine are involved with feeling good and thinking well, and going about your life in a good way. So this is the hormonal equivalent of depression. These moms were more likely to deliver their babies prematurely, and those babies were likely to be low birth weight or SGA. The newborns of those moms themselves had the hormonal equivalent of depression: elevated cortisol and depressed serotonin and dopamine levels – just like mom – and they had the newborn equivalent of depression. In this literature they call it ‘suppressed neurobehavioral profiles’. And all that means that the infants were not as interactive or alert, and all the other things that would correspond with infant newborn depression.

And if you think depression in pregnancy isn't common, this study was actually done in an HMO; and HMOs tend to actually be filled with people who are white, middle-class, and employed. In other words, folks who are less likely to have all of the struggles in life that many other people do, and despite being a lower risk group, in this study almost half of these pregnant patients had depressive symptoms and half of those symptoms were severe. And the risk to deliver a preterm baby went up as the depression severity went up. This is a huge problem. Well you might say “well the babies will be fine once, you know, now that they're no longer connected to mom, to the placenta, those hormones of mom will wash out and the baby would be fine.

Well unfortunately it didn't work that way – this study looked at adolescent girls who were born to mothers who had significant anxiety during their pregnancies. And these adolescent girls had increased stress hormones and depressive symptoms. Now we're talking 15 years after they were exposed in utero to mom's anxiety and the corresponding hormones, and this is huge issue. So we'll talk about, back to diabetes then and this whole thing.

This is a meta-analysis looking at studies around the world showing that this inverse relationship between birth weight and risk of diabetes. In other words, the lower your birth weight, the higher your risk of developing diabetes later in life. And of course in our population it's actually a 'U-shaped' association – meaning it was Native American patients were more likely to get diabetes both with lower and higher birth weights, as we'll see in a minute in terms of how much insulin resistance actually starts in the womb. So again... and this is now another study looking at people who were born in Europe during stressful times of the Great Depression and World War II. Letting their early life experiences play out in terms of disease experienced many years later, and in this large cohort of people born in Sweden during those years – both, whether you were born with low birth weight (SGA) and/or preterm, were both strongly associated with later developing diabetes. You might wonder why that would be.

Babies of obese moms – and this is obese moms, this isn't diabetic moms necessarily, these are just obese mothers, developed insulin resistance in the womb. This is Diabetes Care from June: maternal obesity creates a significant risk for the next generations with metabolic compromise already apparent at birth. So again, long before all of the nice prevention programs get started, children are starting out 'behind the 8 ball' so to speak, with increased risk by birth. And similar to the study we looked at earlier, in this study

rapid weight gain in the first three months of life is associated with risk factors for heart disease and type 2 diabetes by early twenties. So something is going on in that prenatal life that is really bothering people and creating the risk for them later in life developing diabetes and heart disease.

And this is a term we don't usually use: "Fetal Programming of type 2 diabetes." This is just from Diabetes Care a couple years ago "the intrauterine environment may modify gene expression permanently. ...might also be inherited transgenerationally, affecting the health of future generations. ...During intrauterine life, there waves of epigenomic modification, intimately associated with growth and development, and opportunities galore for environmental factors to influence these processes. A fetus thus programmed travels a path of limited options." That's pretty powerful stuff.

So we're gonna talk about this slide now cause it's actually going to help us understand what's going on in prenatal time. And this is from an article just a few years ago in Physiological Reviews. So it's kind of hard to understand at first, so we'll talk through there's kind of two things that are happening in pregnancy that we're going to talk about. The column on the left, substrate restriction means poor nutrition during pregnancy and before pregnancy actually, because a lot of the nutrition that goes to make up the baby's body actually comes from the stores that mother has in her own body. So that means her nutritional experience before pregnancy matters a whole lot as well. So on the left column is the substrate restriction or poor nutrition – on the right is going to be stress hormones affecting the pregnancy.

So let's take that nutrition one first ...I have a simple mind – the way I look at this is this way: If you have a blueprint for a house and you know the house you want to build, but you look and you see that you don't have enough bricks to build the house and you can't afford to buy any more bricks – you have to make some choices. You have to either leave off a room so you can have bricks to build the rest of the rooms or you have to make all the rooms that you do build smaller. And in essence that's what happens here – there's not enough nutritional building blocks during pregnancy available for the growing baby. The brain gets first choice as always, but the rest of the body may not get what it needs. And you can see on the side it often results in a decrease in cell number. Meaning that, it's not... the body doesn't make that choice not to build a room. It doesn't say t "well we don't have enough bricks so we're just not going to build a kidney." Instead it takes the other approach and builds a smaller room, so that there's a few less nephrons in the kidney, there's a few less liver cells in the liver, there's a few less beta cells in the pancreas to make insulin, there's a few less heart muscle cells and so on and so on. If it's a little bit of a decrease, no big deal, it will probably never be a problem to that child even once they get older, but the more that occurs, the more that there's a decrease in cell number can actually affect overall organ growth and even overall fetal growth. Which is what were seeing in small gestational age babies.

This is a huge issue later in life especially, as we'll see. Then on the right side, if mom is stressed herself during pregnancy or if her own stress hormones set points have been set so high because of her own previous difficult experiences in life, she's flooding that

placenta with stress hormones. Now there is an enzyme in the placenta that can buffer some of that so the normal bumps of pregnancy are not a big deal; that cortisol will not be a problem for that baby, but if mom has a lot of stress hormones flowing around it's going to be a big problem. Because that enzyme gets overwhelmed it does go across the placenta, and that cortisol and other hormones do then change the set point.

The way I think about it is: if you're building a car you're working on the gas system – if you have something that is making you rev the engine faster for the rest of your life, every time you hit the gas pedal even a little bit you're gonna get a whole lot of gas flooding the system, and an overworked car. And that's basically what happens here, is while these set points for this unborn child are being set, if there's a lot of hormones coming from mom then that child becomes cortisol-resistant just as they can become insulin resistant if mom has a lot of insulin floating around because she has trouble with glucose. So I know that's a little hard to understand in some degree but those are the two areas: decreased nutrition resulting in poor fetal growth, including at the organ and cell level, and a whole change in set points of a lot of things in the body including the way we respond to stress. You put those two things together and those five boxes in the middle – these things combine then to decrease the ability to synthesize insulin and increases, this cortisol does this, it puts out this child will put out more glucose from the liver. And it's said that the brain gets first choice of nutrition, the organs get second choice – what often gets the short shrift most of all is developing skeletal muscle. Because the body figures “well we can live without some of that most of all.”

Now you may say “that's not such a bad thing, okay this child won't become the next Olympic decathlon champion” – but it's more than that. Muscles are actually of course one of the best ways that we burn glucose, so later in life if we have less skeletal muscle to use the glucose that we have floating around, it's just one more risk factor for diabetes. And we also see that there is a decrease in the heart and the liver's functional capacity right from the get-go. And that box on the far right shows us that there's changes in the stress HPA axis hormone and things that regulate growth and appetite – now you're not even born yet and those things are already in place. So then as you can see in the darker boxes toward the bottom, now the child is born and there's enough macronutrients – there's enough carbohydrates, fats, and probably protein but this child comes out now starving. Those cells are starving and this is where that catch-up growth happens in the first few months to year or so of life. The child comes out in the beginning, to start with, with increased insulin sensitivity in these starving cells, so eats more, the growth catches up – but you can never recreate cells in an organ in quite the same way after birth as you can during the key developmental times in the in utero period. So you never quite make up for what happened in those organs before birth. The amount of cortisol floating around – we know that cortisol puts fat in the worst place, which is a abdominally or in the visceral area. And you can see that as time goes by, all of this combines to decrease the kidney's function to create obesity and then finally at the bottom, some years later the combination of heart disease, obesity, and diabetes. So what happens in the prenatal period matters a lot.

So we now know actually as I said in the beginning that what happens to your grandparents affects your risk for diabetes mortality. And some fascinating studies coming out of Sweden about this – but clearly showing that when your parents and grandparents were in the womb themselves that's when the eggs are created, when a woman is in the womb herself. So what's happening to her mother then affects the eggs she creates that she will then pass on the epigenetic markers for. Sperm is created for puberty, so what happens in late childhood affects the sperm epigenetics that gets passed along – so interesting stuff coming out on how at least two generations back, what affected them affects us. So we talked about how these epigenetic changes in the egg and in the sperm are passed on, so it not only matters what happens to our mothers, but it also matters what has happened to our fathers and grandfathers.

And this just sort of summarizes what we've been talking about, is that prenatal under-nutrition and/or psychosocial stress creates all those things we talked about. That maternal cortisol can be reduced by the placenta, but it gets overwhelmed when there's lots and lots of stress hormone around. And that reduced cell development even including overall fetal growth when there is insufficient nutrition. And that stress hormones themselves actually constrict the blood vessels going into the placenta and can lead to a preterm birth all by themselves. And as we have said, if mom has a lot of stress hormones floating around that changes those set points for the baby's own stress hormones for the rest of it's life. And there's a thought that this might be 'adaptive prediction' – meaning that if mom is stressed then the baby is probably coming out into a difficult world and needs to be ready for that. And that it might be actually to the baby's advantage to be a little more stress-reactive, a little twitchy or a little more hyper-alert in such a circumstance, so possibly that's an evolutionary adaptation. And I told you earlier about a study in rats looking at if you are born, if rat pups were born to a nurturing or not parents, that it affects a gene which affected our stress reactivity. This has now been shown in humans in a study that was published a few months ago in Nature Neuroscience, that early life exposure to parental behaviors – nurturing versus abusive –creates epigenetic changes in stress reactivity for the rest of that person's life.

Break the Cycle

So I'm running a little out of time here so I want to (sorry if I make you dizzy here as I flip through some slides). I do want to mention an article which is in the current issue of Archives of Pediatrics & Adolescent Medicine, because it really brings home again, similar to the study we started out with, what happens in early life matters for us for the rest of our lives, physiologically. This is a study that has been going on for 32 years so far, mainly it's a white population actually on the South Island of New Zealand, and what they looked at, they'd been following these children since shortly after birth. Now they are of course 32-year-old adults. But they looked at three areas of childhood experiences; they called them adverse childhood experiences that happened before age ten: this is growing up in poverty, dealing with maltreatment of different kinds, and social isolation.

So they controlled for all of the established risk factors including – we just talked about birth weight at length and how much of a risk factor that is – so they controlled for birth weight. They got rid of all those changes we just talked about so they can just focus on

what happened in early life. And what they found was that what was attributable, the number of cases or percent of the cases attributable to early adverse childhood experiences was almost a third of depression cases, about 13% of elevated inflammatory states, and again almost a third of cases of the clustering of metabolic risk markers for diabetes and heart disease. So this is huge – looking at what happened in early childhood affects people years later. And as they found, as the severity of each adverse childhood experience worsened, greater numbers of age-related these risks for heart disease, depression, diabetes went up in a dose-response fashion. The tougher your childhood, the more likely your body is to have to adapt in some way to confront those challenges, and those stay with us rest of our lives.

So I don't want to leave you without a little bit of “Now what?” and again, sorry for making you dizzy as I go zippin' through because I want to talk about some things that we can do and in fact should start to do. Now that our model is not quite so small, now that we realize it's not just about the genes we inherit and our diet and lifestyle choices. But it's actually about the genes we inherit, the epi-genetic markers that we inherit, and the experiences we have in our early life, that all combine together to affect our brain development, to affect our body's development and our risk of things like chronic disease later on.

So we've talked about how depression in pregnancy had such profound risk for children being born preterm or small. So we need to find ways to break the depression cycle, and we know that children who are born to and raised by parents who are depressed: the children are two or three times more likely to be anxious or have disruptive behavior disorders or themselves to be depressed. And consistent with what we've just been saying, this article says “These offspring problems often begin before puberty, continue into adolescence and adulthood and can be transmitted to the next generation.” We know that's epigenetically. Treating children's depression is difficult and controversial – I think that's safe to say, with all the black box warning for kids on antidepressants, not that you don't do it but it is difficult and can be controversial. But in this study they treated the mothers' depressions and the kids got better too. It matters what happens, who is at home and how we can bond and attach to them in our early years and the care that they give us, etc.

So just as we talked about how things that happen badly in early life affect children 15, 16 years later, things that go well also affect us – remember that balance of risk and protective factors. In this study they took growth-retarded children meaning those small-for-gestational-age kids, so they have those factors we've been talking about. They were between nine and 24 months of age, and they and their mothers met every week for two years, and the intervention was a play session in which moms were taught how to be good moms. How to listen and talk to their children, help children to experience success and praise and reducing punishment, both the severity and the capriciousness of the punishment. And these children 16 years later were still doing better, long after the intervention because the intervention happened while the brain windows of development were still wide open and change for the better could make a difference.

In fact, James Paxton here on this slide is an economist at the University of Chicago, and he actually looked at the economics of early intervention in these neurological risk factors, and these quotations are both getting at the idea that it is much easier and better to try and correct things that haven't gone well while the child is still very young once you get over it becomes much tougher. An example is that it's much easier to teach a five-year-old to read than it is a 15-year-old to read.

Interventions

So I want to tell you about an intervention that actually is, has some funding hopefully going to be... it's attached to the health reform bill – so we'll see how it does, for home visiting programs – because this is a program that has been shown to make a difference in a lot of the things we've been talking about. The Nurse-Family Partnership was started by Dr. David Olds, he's now at the University of Colorado, and the intervention takes specially-trained registered nurses, RNs.

And the intervention's been looking at... worked with low-income pregnant women – often these are very young and unmarried, and only first-time parents – because whether a mom did it well or not, she's the second, third, fourth, or whatever-time mom. She has already been there and done that, read the book, saw the film, and she's not as “open” so to speak, to a different way, as she is when it's the first time and she's completely overwhelmed and has no idea what is happening to her body or how this will work for her. So they match these nurses with these young first-time moms, preferably by about 16 weeks of pregnancy – that same nurse then works with that same young mom every one to two weeks through the child's second birthday – so it's about two and a half years.

And the goals of the intervention are to improve pregnancy outcomes – we've now seen how critically important that is – to improve the child's health and development, again we've been talking about how critical that is, and the parents have to have a goal for the future. Traumatized folks often have a hard time seeing the future; all they can see is the here and now. So they actually have to have a goal of either to get in school or stay in school or get a job, get some training – something – so that down the road they will be able to care for themselves and their children.

So there've been three randomized controlled trials looking at this intervention and they go back as you can see to the late Seventies – and um, pretty impressive for this kind of a complex long-term intervention, pretty impressive numbers of participants in these three randomized controlled trials. And what those three randomized controlled trials have shown us is that indeed, this intervention does improve prenatal health, children are less likely to be injured; and these next two are very important indicators of child well-being everywhere in the world – that mom has fewer pregnancies, and there's increased intervals between those pregnancies. It's important for mom to be able to replenish her nutritional supplies, it's important for economics so that there's enough money to pay for what these children need, and on and on and on around the world... those two things there are huge indicators of child well-being or lack thereof. Moms are more likely to be employed, and the kids are more ready for school.

The moms, even though they're not the targets – so to speak, of the intervention – 15 years later, they themselves are doing better in lots of key respects here. Another paper from the study showed that they are better able to handle stress than folks who were in the control group; even 15 years later they're still able to manage their life challenges better. The kids are half as likely to be abused and neglected. That's huge – a huge decrease in a very critical risk factor for later... for lots of things including diabetes and heart disease.

And they also are more likely to be avoiding contact with the juvenile justice system – and again this goes out 15 years – they're more likely to be staying in school, lots of things... and when they go to school, and remember this intervention ended at age two, but three, four years later they go to school with higher IQs, their language development is better, and they have fewer mental health problems, because of this intervention. And these two studies here, uh one from JAMA from a few months ago, talk about how this is a very rigorously evaluated intervention that does all the right things.

So, and this is an article from some folks at University of Colorado talking, who did a... this article is actually looking at the disparities in child health in our American Indian and Alaska Native communities. And after talking about all the hard things that our children are dealing with in their health and mental health, they looked at interventions that had been used including Nurse-Family Partnership, and they concluded the article by saying “...we are placing bets on the value of early intervention, beginning prenatally with the mother's first pregnancy, and extending throughout the first years of life and beyond as one of the surest ways to begin to address past centuries of neglect and improve the prospects of American Indian and Alaska Native children in this century.”

And this last slide here is just some of the many things that we can do as we understand this larger picture of what's happening for risk, for all these areas – whether it's diabetes, heart disease, domestic violence, substance abuse, depression... on and on.

So the categories across down the left side are nutrition, depression and substance abuse, and parenting and it's in quotations because of course many people can be parents to children besides biological parents. And so this is just a list of many things that I came up with – I hope around Indian Country we'll come up with a much more comprehensive list, ones that make sense locally. But we should be screening for depression in family planning and prenatal clinics, in 'well child clinics' and WIC clinics. We should be making sure that our pregnant women and even women before conception have the very best nutrition possible. We should be supplementing fruits and vegetables into the WIC program. Here at Cherokee we've been doing a backpack food program – so many children do not have enough food, they get subsidized meals during the school day but on weekends and school holidays they go home to often little or no food. And so on Fridays these kids get an unmarked backpack full of non-perishable foods to help get 'em through the weekend and the school holidays – anything to get nutrition into these children and reduce their stress at the same time.

So there's a lot of things on there, and again we can all come up with other sorts of things that we can do, now that we understand that what happens when we are very young matters and it matters for a very long time – anything we can do to make a difference there is going to be... a payoff for years and years to come. Prenatal interventions, for example: we thought that if we help a pregnant woman hopefully we help her, hopefully we help her unborn child, but now that we're understanding epigenetics, the person we probably help the most is the unborn child's child. This is – as we're understanding these things – is changing everything about how we understand what's going on in our communities, both individually and collectively, and the types of interventions that we need to be incorporating into our programs.

And truly as we understand these roots, that they are so common to all these different problems as we've been talking about – if we prevent anything, we just may prevent everything. So I appreciate you guys hanging in.