MCH EPI Conference

Welcome, Introduction and Keynote

December 9 – 11, 2009

WANDA BARFIELD: My name is Wanda Barfield, and I'm the team leader for the Maternal Child Health Epidemiology Program in the Division of Reproductive Health in the National Center for Chronic Disease Prevention and Health Promotion at the Centers For Disease Control and Prevention.

Of behalf of CDC, I would like to welcome you all to the fifteenth annual Maternal Child Health Epidemiology Conference, where we aim to make methods and practice matter for women, children, and families.

CDC is proud to be a sponsor of this conference. Our conference attendance this morning is nearly 450 participants, this week in beautiful and warm Tampa [Laughter]. Many of you have participated through pre-conference trainings organized by the Association of Maternal Child Health programs, which included training on state MCH data record linkage, geospatial methods, and communicating epidemiologic findings to our intended audiences.

CityMatCH has also provided pre-conference training on perinatal periods of risk. So it's been a great start so far.

I would like to first thank and acknowledge the people who have been instrumental in putting this conference together.

First, Ms. Zarinah ‘Ali [Applause], who is the MCH EPI Team project officer and main conference coordinator. I would also like to thank Mr. Bill Boyd, the CDC MCH EPI Team's deputy [Applause], and I would also like to thank our partners, the MCH Epi Planning Conference Committee, Scientific Review Committee, and our partners, to include HRSA, MCHB, AMCHP, March of Dimes, NACHO, CSTE, ASCO, SPER, ATMATCH and ASPH, and last, but not least, CityMatCH, who has sponsored the conference, planning on-site operations and logistics for the last three years. I'd like to especially CityMatCH's Mark Law and Mattea Campbell-Langel Thank you.

[Applause]

Maternal and child health has been an emerging area in the forefront of news and policy. The ongoing H1N1 epidemic has raised important issues on the health of pregnant women and children and the need for evidence-based data to inform providers on the most appropriate prevention strategies, as well as diagnosis and treatment of this series disease threat.

As the discussions on healthcare reform continue, maternal and child health again is in the forefront of the discussion. Health insurance for all children is one of the first

bills proposed by the Obama Administration, and the current healthcare bills in Congress, they portend important changes in maternal and child health in the U.S.

More than ever, the field of MCH continues to provide data and evidence to inform major decisions on the health of women, infants, children, and families.

The field of MCH is growing, and CDC and HRSA have collaborated together, along with other MCH partners, to support this growth. We've increased the number of MCH training programs in academic centers, increased the number of graduate and post-graduate fellows in MCH epidemiology, and increased the number of CDC/HRSA field assignees in state health departments.

A 2009 assessment of epidemiologic capacity conducted by CSTE and the University of Michigan School of Public Health and funded by CDC found that MCH epidemiologic and surveillance capacity has progressively increased since 2004 to 2009 from 43 percent to 55 percent, and now ranks third among nine program areas in 2009.

But there is further work to be done and new areas in MCH to explore. To welcome you from the Maternal and Child Health Bureau, and so introduce our keynote speaker, I would like to turn the mic over to my colleague, Dr. Michael Kogan. Thank you.

[Applause]

MICHAEL KOGAN: Well, good morning, everybody. On behalf of Dr. Mary Wakefield, head of the Health Resource and Services Administration, and Dr. Peter van Dyke, head of the Maternal and Child Health Bureau, I'd like to welcome you to fifteenth annual Maternal and Child Health Epidemiology Conference.

We're both pleased and honored to sponsor this conference, along with or partners at CDC, AMCHP, CityMatCH, and all the other organizations that have contributed to the success of this meeting.

The focus of this year's conference is in a slightly different but important direction. For far too long the United States has lacked basic information on the health on mothers and children both at the national and state levels. Steps have been taken to change that over the last ten years, and analyses have opinion conducted with increasing sophistication. Some have led to successful programs, while in other cases there's either been little change or worsening of longstanding disparities.

Generally, public health departments have to focus most of their time, energies and resources on addressing immediate problem areas, such as infant mortality, preterm birth or low birth weight.

While it's well known that infants born low birth weight or premature are add increased risk of dying in the first year, much less work has been done on the broader context of people's lives, either during the time of pregnancy or much earlier. Further, due to the nature of public health departments, less focus is given to the long-term consequences of early-life experiences.

Yet there has been work underway to examine the root causes of disparities, to look beyond the time of pregnancy, to look beyond the boundaries of a child's immediate circumstances. And so all of the plenary sessions this year reflect a broadening perspective. We have plenary sessions on the life course perspective, both in terms of moving from theory to action, and in terms of family planning.

The third plenary session also focuses on non-traditional areas for this meeting by examining environmental health issues for children.

And, finally, for the first time, this conference is featuring a keynote speaker. Dr. David Barker is both a professor in clinical epidemiology at the University of Southampton and a professor of cardiovascular medicine at Oregon Health and Science University.

In every field there's superstars. When you think of music [Laughter], you think of the Beatles or the Stones. When you think of sports, you think of David Beckham. When you think of queens [Laughter], you think of Queen Elizabeth the first or Queen

Victoria [Laughter]. And when you think of MCH epidemiology, you think of David Barker.

Dr. Barker has published over 300 peer-reviewed articles, authored or co-authored seven books on epidemiology or maternal and child health. He's authored or co-authored 38 book chapter and has been awarded numerous national and international prizes.

But numbers don't tell the story of Dr. Barker's contributions. Beginning in 1989, his work on the early life origins of adult chronic disease changed the way many think about both early life outcomes as well as chronic illness. Named the Barker Hypothesis by the British Medical Journal in 1995, his epidemiologic research has shown that adult chronic diseases have their origins through malnutrition in the womb. He's continued to work with colleagues around the world on various longitudinal studies examining different aspects of this association.

His work has been featured in such publications as *Newsweek*, *Time*, *U.S. News and World Report*, and, for goodness sake, even a feature in *The New Yorker.* I've also been impressed by the large volume of papers by other authors in the last few years that has supported his research.

As the low birth weight rate has risen by over 20 percent in the U.S. in the last 15 to 20 years, and as we confront the increasing epidemic of childhood obesity in this country, Dr. Barker's research has profound implications for our work.

Now, before I welcome Dr. Barker, you're a fairly bright audience, and many of you have noticed that only Wanda and I are at the podium [Laughter]. There's a reason for this. Dr. Barker, unfortunately, had a family emergency this weekend. However, he has graciously agreed to send his slides, and we have a live audio hookup with him. So he's going to give his slides by audio hookup. So I guess the appropriate thing is to welcome Dr. Barker and say live, from England, it's Dr. Barker! [Laughter].

[Applause]

Keynote Address:

Fetal Origins of Chronic Disease

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DAVID BARKER: Well, Michael, good morning. Thank you very much for that very gracious welcome. I'm sorry I can't be with you, but you know the reason for that.

[Inaudible] can you hear me?

UNKNOWN SPEAKERS: Yes.

DAVID BARKER: So the background to this talk is our attempt to prevent chronic disease has been largely unsuccessful. There has been [Inaudible] in which we've looked for infant in adult life and [Inaudible] because chronic disease, epidemiology is getting out of control where cancer is rising, [Inaudible] childhood obesity is rising. We need to take a look.

So my slides show [Inaudible]. So you might think, well, that is natural selection [Inaudible] to hasten the age of reproduction. But the truth is if you take [Inaudible] they know the age at which we die.

My next slide shows a group of babies, and the point of the slide [Inaudible] each of those babies could have been very different had the [Inaudible] in the womb been different [Inaudible] recipe which we acquire at conception, a recipe that make [Inaudible].

The phenomenon, which is referred to as programming, is simply about malnutrition and this is my next slide, sorry malnutrition and other adverse environmental exposures during development altering gene expression and permanently change the structures and functions of the body.

Fortunately for epidemiologists, adverse influences during early development also slow growth and give us a marker that we can use to relate early development to later

health experience. So this is what Michael referred to that in 1989 launched a paper showing that across the range of birth weights in both men and women, there is a progressive decline in the rate of coronary heart disease as we move across am I still in contact? Sorry, I've been cut off.

UNKNOWN SPEAKERS: No.

DAVID BARKER: Have I lost contact with you?

UNKNOWN SPEAKERS: No.

DAVID BARKER: Okay. Sorry.

There is a progressive decline in death rates from coronary heart disease across the normal range of birth weight in both men and women. And it's better to be eight pounds than seven pounds and better to be nine pounds than eight pounds. And it's babies that are small because they didn't grow rather than because they were prematurely expelled who are at increased risk.

The next slide shows a similar chart for weight at one in men. It's sobering to think that if you were, are, a man, it would be more useful to you to know how much you weighed when you were one year than to go to your doctor and get your cholesterol

measured today. This suggests that there are powerful biological forces driving these associations with early size.

The next slide sets out the fetal origins theory which says that this group of diseases coronary heart disease, stroke, Type II diabetes, hypertension and osteoporosis originate through development plasticity in response to malnutrition during fetal life and infancy, and we are now seeing really surprisingly rapidly that a number of cancers are also involved in programming and originate in fetal life, and breast cancer is clearly one.

So the next slide shows a schema. On the left hand side you have what may be ten years ago some people thought might provide answers to disease. Something wrong with the genes does something to the body leads to disease. But on the right hand side of this scheme you've got the new world. Undernutrition, stress, hypoxia, other adverse influences acting at critical windows of development alter the expression of genes. And this may be adaptive or not. It doesn't matter. But the response to these adverse influences is altered gene expression.

Let me tell you a little bit about critical windows of development. Every system and structure in the body has a critical window, often very brief, during which it must mature. Most critical windows occur before birth. Only the brain and the liver and the immune system remain plastic after birth.

A good example of programming is the development of the sweat glands. Newborn babies do not have functioning sweat glands because they didn't need them. But they have to develop them once they're born. And every baby has the same number of sweat glands per unit area of skin.

According to the temperature at which the baby lives, more or fewer sweat glands become functional. In warm places, more sweat glands become functional. In cold places, fewer become functional.

Now, this process is complete by the age of three years, and then there is no more plasticity. My daughter in law is Swedish, and she grew up in a cold place, and she has huge difficulty in being in the tropics because she hardly sweats. And this is kind of a good glimpse of critical windows of development and how they make you appropriate to the place you are at during development, but it may become less appropriate if your circumstances change.

The next slide shows two babies. The baby on the right was seven pounds at birth and this little boy was no problem. The mother was healthy, the baby was healthy, the delivery was normal. The problem is that little boy is thin, and if you put your hand on his thigh, you would feel the bone. The boy is thin because he lacks muscle.

In the womb there is a hierarchy of developmental priority. At the top is the brain, and at the bottom are systems for which the baby has no immediate use. The baby does

not need its lungs because the mother is the lungs, the baby doesn't need a kidney because the mother is the kidney, and the baby doesn't need any muscle because there isn't anywhere to go.

So babies trade off low priority systems to protect high priority systems. And in the audience that I'm sad I'm unable to be among, there will be people with one million nephrons, one million functioning units in their kidneys, and there will be sitting there somebody who's got three times that number. The variation in the number of functioning units in the kidneys is very large, and it's because the kidney is a low priority fetal organ, and obviously it's better to have more nephrons than fewer nephrons because through life they die.

We know quite a lot about why people who had small body size at birth are biologically different this is my next slide, sorry are biologically different through their lives. They have, as I have just described, reduced functional capacity; fewer nephrons, less muscle. They have altered settings. They handle food differently. They're recipient to insulin. If you think about it, insulin's job is to take sugar from the blood and stick it into muscle where it's stored.

But if a baby has an inadequate supply of glucose, it's not going to store it in its muscle, it's going to maintain it in the blood, and the way to do that is to make muscle recipient to the effects of insulin so insulin done leave the circulation and go into the muscle.

And the third way in which babies people who are small at birth are different through their lives is they have altered hormonal production. They have different production of stress hormones and they have different production of sex hormones.

So that is not going to be the subject of my talk, but this is going to be the subject.

This next slide, a group of poor children. This is a picture taken in London in the year 1912. These children are queueing for food. Clearly, they are poor. The interesting thing about those children in the slums of London is that, as a group, through their lives they had good health. They had very low rates of coronary heart disease and very low rates of stroke.

So there are two possibilities which might explain that. One is that although they lived in an unkind world, they did not have problems with childhood growth, which we now know are associated with later cardiovascular disease. That's the first thing I will discuss.

The second and the way more interesting possibility is that all though they were born into a cruel world, they left a kind one. The mother's of those children mostly grew up in the rich farmlands which surrounded London, yet the families had little money, but they had exceptionally good food. They had five meals a day. So as girls and young women, the mothers were

well-nourished. They came into London seeking wages, and they worked in domestic service and in other things and they got wages.

But their babies lived in a womb that had been conditioned by 20 odd years of good nutrition. They were then born into the terrible world described by Dickens. And my next slide shows a description of the life they were born into. This is the poor of London. Their life is the life of savages with vicissitudes of extreme hardship and occasional excess. Their food is of the coarsest description, and any luxury is quick. Some wit said it sounds like traveling coach class in British Airways.

So the next slide shows a picture of Finland. I want to this is a clinic in Finland before the second war. The Helsinki Birth Cohort is the most detailed European or anywhere in the world cohort. The Fins had not only exceptionally detailed obstetric records from about 1920, but they followed their children up so that the growth of children was recorded, and these records were maintained.

And in Finland, admission to hospital, medication for chronic disease is all recorded in national registers. So I'm going to show you some data from the health Helsinki Birth Cohort, which is 20,000 people born before the Second World War about whose lives we know a great deal, and we also know a lot about their social circumstances because census returns, which are, of course, confidential in the U.S. and in Britain, are open documents. And so, too, are people's tax returns.

So the next slide, entitled "Weight Gain in Childhood and Later Disease," shows three piles of growth. What is on the better axis are their scores for weight. So in the cohort as a whole, children follow the white line. The average is the horizontal white line.

You will see three different lines. On the top in yellow is a group of people who, as adults in later life, were normotensive. They were healthy, they were fine.

Now look at the blue line. The blue line is the people who in they're later lives developed mild hypertension, or stroke. You can see there's no tiers on the horizontal axis. They were smaller than the people on the yellow line. And then they just didn't grow, and so their weight fell away. And this is, in a way, appropriate because stroke is a third world disease, and in the third world children don't thrive, and so that is what you might expect.

I'm going to come back to how that blue line is initiated, and the answer in short is that that blue line is initiated by poor nutrition of the mother when she was a girl. And I'll show you the evidence of that.

Let's look at the green line. The green line shows people who ultimately develop severe hypertension or coronary heart disease or both. At birth they were small. We know that. And then through the age of three, four, five, they started to have accelerated weight gain, and this combination of being small at birth and then having accelerated compensatory weight gain is a feature of western children. It's not

possible to compensate if you don't have food when you're two, three, four, five, but in western children, once they're free and able to move around and get food, food is available. And that path of growth is a common one, and I'm going to examine it further.

But that green line was not an option for London children, and that may be one of the reasons why they, as a group, had such low rates of heart disease.

Let me show you this. The next slide is entitled "The Prevalence of Hypertension." It's a group of 2000 people from within the Helsinki Birth Cohort who were examined at the clinic, and they are set out before you according to two parameters. One, they're weight at birth, and, two, their current weight when they were around 62 years of age. And what you're seeing in these bars is the prevalence of hypertension.

So you can see that the best place to be was the bottom left. Only four percent of people who weighed more than four kilograms at birth and as adults had low body weight, only four percent of them had hypertension as adults. But move your eye to the top right and you will see a group of people defined by being below three kilograms at birth but in the highest quintile of body weight when they were in later life. Among them, 64 percent of people had hypertension.

Now, there are two things about this. Certainly we can make sense of it. If you have low birth weight, you have fewer functioning units in your kidney, as I already

described briefly. And if you grow a big body, those fewer nephrons have to do more work. Now, work for a nephron is receiving blood to excrete waste matter from it, and high blood flows through the kidney destroy it. That is well known in kidney transplant programs.

So the group top right not only had fewer nephrons, but overworked them. And the group bottom left had many nephrons, and they weren't very heavily worked.

The other thing that this striking pictures shows is, well, look, we now know that the strongest predictor of hypertension known to epidemiologists by a factor of a huge effect is two simple measurements of body size; one at birth and one currently. So these must be powerful biological processes.

The next slide, before I leave children, is a slide from the Helsinki Birth Cohort showing a similar thing, but this time it's body mass index at two and at eleven and above are the hazard ratios for coronary heart disease among men and women.

And you can see that the lowest rates of coronary heart disease were experienced by men and women who at the age of two were in the highest third of body mass index but at the age of eleven they were in the lowest. So how could that work?

Well, we do know the answer to this. A child who has high BMI at two will tend to be muscular, because a lot of body mass index of two is muscle rather than fat. But after

the age of two, increase in body mass index is about fatness rather than about muscle because the critical window for muscle has ceased.

So the children on the bottom right of this in the yellow thing, they were sturdy, and then they didn't get fat. And the children on the top left in the blue, they were non athletic, non muscular children, and then they tended to get overweight. And if you read Bill Clinton's autobiography, you will learn two things. Firstly, he describes how he looked at birth, and he was a remarkably thin baby when he was born. So he would have been, for life, unmuscular. And he describes that.

And, secondly, for him, any increase in fat would be dangerous. It's very striking that two measurements of body mass index in childhood could predict nearly threefold variations in the eventual occurrence of coronary heart disease which has to reinforce the message of your meeting, which is that growth in childhood is very important.

So I want to move away from childhood and back into the womb. So the associations between early growth and later disease, associations between birth weight and later disease and infant weight, they're gradient. And many studies have now confirmed these associations. And what we all have to take on board is a highly unpalatable truth that variations in the supply of food from normal healthy mothers to normal healthy babies have profound long term effects on the baby.

So there the question is, well, how is a baby nourished? A baby is nourished partly by the mother's diet. But that is unlikely to be all that important. It would be too precarious. There are mammals that don't eat at all in pregnancy. Elephant seals come out onto the ice in Georgia and they mate and they have their babies and then they go back in the water and they don't eat at all. There's nothing to eat. And bears mate and hibernate and awake to create their suckling cubs.

No doubt diet in pregnancy is important, but the other three things that nourish a baby are the mother's nutrient stores before pregnancy, secondly, the mother’s metabolism, which is set up through her entire life from her early infancy, and there is also the placenta's ability to transport nutrients from the mother to the baby. And I'm going to dwell on the placenta because it is little studied, and it may well hold the key.

But if mother's diet in pregnancy doesn't matter, why should mothers eat in pregnancy? Some mammals don't, so why would we need to? Well, the reality is if women don't eat, they become thin and we know that that programs adversely the metabolism of the offspring and makes them insulin resistant.

This little family I'm looking at I hope we're still on the same page looking at three people in Holland during the famine, the wartime famine in Holland which followed the unsuccessful attempts to capture the bridge at (inaudible). And for seven months calorie intake was very restricted, particularly in the cities. And the people who were in the womb at that time bear the marks of it. They have high rates of coronary heart

disease and diabetes and an adverse lipid profile. So a poor diet in pregnancy does adversely program the baby.

Interestingly, the babies who are in the womb during the famine, they grew normally. So the conclusion from that has to be, a, that a baby can be adversely programmed but nevertheless grow okay, and the other conclusion is that the growth of the baby depends more on the mother's metabolism than on what she may or may not eat during pregnancy. And that, of course, everybody in the audience knows because if it was possible to manipulate the size of your baby by eating this or that or the other, then everybody in the western world would know that. And endless studies have then to that the mother's diet during pregnancy accounts for only a small amount of the variation in size at birth. Whereas, the differences between mothers and their protein metabolism account for substantial amounts of the various in the size of one baby rather than another. And that is an unsurprising conclusion, because the idea that putting food into the mother's mouth will somehow do something for the baby directly is, of course, naive, because the mother breaks the food down and then resynthesizes the amino acids into proteins, and then once she resynthesizes the amino acids, they have to then be transported across the placenta, and that is a conflex.

One of the things that is my next slide is an embryo, and one of the things we have learned recently partly through assisted reproduction techniques is that very early embryo is extremely sensitive to its nutritional environment. Even as the fertilized egg goes down the Fallopian tube accompanied by its outriders, its nutritional cells, like the

president going through the capital city, even at that point the cells is sensitive to the mother's nutrients, and stem cells are allocated in response to the Fallopian nutritional content of the fluids that bathes the embryo.

So that is an important new thing for us to take on. Any kind of strategy which is based on once you're pregnant, eat the right thing, that is absolute history. That's been known across America since America began, because farmers all know it. You don't farm sheep by just putting a ram in and then worrying about the ewes that get pregnant. The ewes are nourished well long before they mate.

So let's move now to the placenta I'm sorry, I hope it isn't lunchtime. That's rather a shocking picture. But I just wanted make sure people understood what the placental surface looked like. That's the placental surface from the baby's side. It's an important new thing which came up last year, which was known long ago and has been forgotten, that the surface of the placenta is oval. And I'm not going to elaborate on this, but below that surface looks quite homogenous. It is not. There is a breadth and length, and the tissue along the length has different functions to the tissue along the width, and the tissue along the width is nutritionally responsive and may well be capable of being manipulated by variations in the mother's diet.

But I want to talk about three aspects of the placental programming of disease which seems to be a key. Now, I've got in front of me a slide that says mean systolic blood

pressure for men and women that I hope you have. And I'm going to dwell at some length on this.

This is a group of some 450 men and women who were born in the same hospital, one after the other, and followed up 50 years later, and their blood pressures were measured, and that is the figure in the middle of the table, the mean systolic blood pressure. And the men and the women are simply arranged by their birth weights and by the weight of the placenta in pounds, and there's no adjustment for anything.

So where is the good place to be? The good place to be is the bottom left, to be a baby who is relatively large and had a willful small placenta. Now, that's kind of intuitive. When a woman decides she wants to become pregnant, her intention is to have a baby rather than a placenta. So this is an efficient pregnancy; a lot of baby and not much placenta.

The next good place to be is the top left. The small placenta has not been able to deliver a big baby, it's been an inefficient placenta.

The worst place to be is the top right. A large placenta has failed to deliver a big baby as it should, because most big babies have big placentas. They go together. But in there you've got a big baby big placenta, I'm sorry, and a small baby. That is a catastrophic pregnancy.

And the bottom right is better, but it's still far from ideal, where a big placenta has produced a big baby.

So why would it be bad for a baby to be 7.5 pounds and bigger but have a big placenta? Well, firstly, for a lot of babies, a nice, big baby with a nice, big placenta is fine. But there's a subgroup of babies in whom a big placenta is a bad thing. And we know how this works.

In sheep farming, the strategy is to nourish the ewe well before pregnancy and then on the 30th day, or thereabouts, of the pregnancy, to transfer the ewe from good pasture into poor pasture, often by just grabbing the flock uphill. And then after 30 days, the ewes are returned to good pasture, and you get a bigger lamb than you would otherwise have got if you had kept the ewe in good pasture through the whole pregnancy.

Now, this has been standard practice in sheep farming for 200 years. It's only recently we've discovered how it works. How it works is that by making the fetus malnourished in the middle bit of pregnancy by putting the ewe on poor pasture, the fetus expands its placenta; it expands its attachment to the mother to extract more nutrients from her blood.

When the ewe is then returned to good pasture on the 60th day, there is a bigger placenta through which nutrition can come to the baby.

So that is fine in sheep farming. But there's now evidence that the same process happens in humans, but that it has massive long term costs, and the compensatory expansion of the placenta in mid pregnancy does produce a bigger baby, but it has high costs in terms of later cardiovascular disease and, we now know, some forms of cancer.

So this is new and exciting. You heard a message about children that said compensatory weight gain after the age of two has costs. And now we're seeing that compensatory placenta expansion has costs.

So why would this be a costly thing? Well, if a baby expands its placenta, it has to maintain that placenta, and the baby sheds its nutrition with its placenta, and in the hierarchy of pregnancy, a hierarchy in which the mother is top, the placenta is second and the baby is third. So at all costs, this bigger placenta has to be maintained. And if there isn't much nutrition around, then the baby will have to trade off its own development in order to keep the placenta.

It's kind of like a tree. If in drought a tree is forced to expand its root system, then it's going to have to maintain that root system, and it can only do so at the expense of its own growth, the growth of its trunk.

So what I want to do now, if I may, is show you the next slide, which is the progress of hypertension according to the area of placenta and the mother's heart. And I'm sorry if I'm going into areas of complexity, but that's how it is.

So on the bottom of this slide you have placental area. You have the area of the placenta, which I've just shown you, which was routinely recorded in the past in Helsinki. And I have spent a lot of time trying to find out why on earth you would want to measure the area of a placenta, its length and breadth, and this is completely unlearned. It just was standard practice in some European countries 60, 70 years ago, and it isn't standard practice anywhere today.

Anyway, we can relate the area of the attachment of men and women to their mothers when they were in the womb to their health today. And on the vertical axis you have the prevalence of hypertension.

Could I ask you to look at the yellow line. The yellow line shows simply that in this group of people whose mothers were short, they were below the median of 160, which is what the median happened to be, a small placenta is related to an increase in the risk of hypertension in later life.

Well, what does that mean? We know that women who are short are less capable of synthesizing proteins when they become pregnant. And that is because the ability to fashion proteins is learned at the time of life when one first encounters high protein

diets, which is not in breastfeeding, in the case of breastfeeding, breast milk has a lot of protein. It is the period after weaning when the child starts to live on protein diets.

And if the child has not been well nourished, if its had to divert a lot of its nutrition to combat interaction, it does not acquire the ability to synthesize amino acids to the extent that taller women who have had a more favorable early experience are able to do. So you can imagine the combination of a mother who's short and unable to synthesize a rich array of amino acids and the placenta that is small and unable to transfer those amino acids. That is a poor combination, and it is associated with an increased risk of hypertension in later life.

So now we look at the blue line. The blue line is about tall mothers. And there there's no relationship, no linear relationship, with placental area. In fact, there's a U shaped relationship.

We can disaggregate this. What I didn't tell you about the ewes and compensatory placental expansion is that it is only possible in ewes that are well-nourished at the time of conception. We don't know how that works. So is it possible that the blue line is U-shaped because there's a group of mothers in whom the placenta being small is a bad thing and another group in whom being tall is a bad thing, and is it possibly that it's tall, well nourished mothers in whom there's been compensatory placental expansion among a minority, but a significant minority, and that this is an association with later hypertension?

And, indeed, that is exactly how it works. If you just look at the mothers who are tall and middle class and were presumably the best nourished in fact, we know they were the best nourished then it isn't a small placenta that's related to hypertension, it is a high placental to birth weight ratio that's the top right hand group.

So this is a layer of complexity to maternal nutrition which is now surfacing that's broadly nice, big baby, nice, big placenta is good, but within that there's a subgroup in whom the placenta has been induced to expand to compensate for fetal malnutrition, and that has a very high cost.

There are two more complexities before I'm done with the placenta. But here is the next slide has conclusions written on it, and here is a conclusion. A small placental surface area is associated with later cardiovascular disease. In well nourished mothers, the placental surface can expand to compensate for fetal malnutrition, but this has long term costs that include cardiovascular disease and certain forms of cancer.

It should be note surprise that cancer is coming into the programming because cancer is merely uncontrolled growth, and in diseases like lung cancer, when they're initiated, developmental genes which should have been suppressed are turned back on, and you get uncontrolled growth.

The next slide is the one you've already seen. I'm just showing it to you again to make another point, a simple general point. You can't look at a placenta and say it has a surface area of whatever and therefore this offspring is going to get this disease or that. It doesn't work like that.

What you have to know is both the placental area and the mother; the mother's height, for some diseases, the mother's body mass index. It makes sense, because the baby's nutrition depends on the mother's body and it depends on the placenta, and knowing only one of those won't tell you the answer. You have to have both.

The next thing the final sort of complexity I want to throw at you is this, is we've always known that there are baby boys and baby girls and then there's the placenta, but it is now looking pretty clear that there are boy placentas and there are girl placentas and that they are very different.

The boy placenta seems to be more sensitive to the mother's diet in pregnancy, and the girl's placenta is reading the mother's metabolism, her lifestyle nutritional experiences.

In the Dutch famine, many fewer boys were born than girls. Why? Well, that is consistent with the fact that boys read the mother's current diet, which is a good strategy in enabling a boy to capitalize on improving food supplies but a dangerous strategy if the food runs out, which it did.

The girls have a conservative strategy. And there is a paper that's just been published in the American Journal of Human Biology called Boys Live Dangerously in the Womb. They grow faster, they invest less in the placenta and they depend more on the mother's diet during pregnancy. That is dangerous, although it has rewards potentially.

So when we think about maternal nutrition, we may be having to think about are we talking boys or girls here. So let me go to my final theme, which is the lifetime nutrition of girls.

In the next slide, which is called "Pelvic Diameters," you have on the right the front to back measurements of the female pelvis from the pubic bone to the spine and the lumbar vertebrae. And on the left, which is not what I meant to talk about, you have the transverse measurements. And these were routinely taken by using external calipers in pregnant women in the U.S. and in Europe 60, 70 years ago, because obstetricians needed to predict whether the baby would be born the normal way.

And the right hand measurement, which is called the external conjugate, is the measurement that is narrowed in a little girl who develops or a boy who develops rickets. Rickets, due to Vitamin D deficiency, starts to affect the structure of an infant's pelvis when he or she stands up for the first time, and it flattens, it narrows the front to back measurement because of the forces of the legs, the hip joint, on the softened bands of the pelvis.

And the obstetricians across the world use seven and a half inches as a magic measurement, below which the mother was immediately put into a high risk pregnancy category. Now, these measurements are taken routinely, and so they can be used as a way of relating the mother's infant experiences to her child's later health. So this is just the formal definition of the external conjugate diameter, and it says a diameter of less sorry, this is the next slide, called the "External Conjugate Diameter" a diameter of less than 18 centimeters was used as a marker of a flat pelvis.

And it was not just rickets, but it was of lesser degrees of malnutrition in early childhood. There were a lot of studies of this in the '30s and '40s and a famous study of nurses at Yale showing that they had round, less flat pelvises than their patients, who tended to be less affluent than the nurses. And so there's a big literature on how the environment of an infant girl leaves her with a pelvic shape which we know, of course, that the pelvis grows hugely between one and maturity nevertheless, it never reformulates, it never reshapes itself. It's a wonderful example of programming. An event happens, it leaves an imprint which never changes even though the body grows much larger.

So in the Helsinki Birth Cohort, 32 percent of the mothers my next slide 32 percent of mothers born during December and January had external conjugate diameters of less than 18 centimeters compared with 20 percent among mothers born in the

remaining months, which is exactly what you'd expect because, of course, there's not a lot of Vitamin D being made in Finland in the winter.

And here is, on the next slide, all the ratios for stroke and hypertension in the offspring. So you're relating the mother's external conjugate diameter when it's less or more than 18 centimeters, flat if less than 18, not flat if it's more than 19, 19 or more, it should be, and you can see that there's an increased risk of stroke and hypertension in the offspring.

So if you vaguely remember in the early bit of this talk, I showed you that people who later developed stroke as children, they didn't grow well, they didn't thrive. The origins of that are not in the placenta, they're in the mother's childhood, which left her and the next slide summarizes this left her with an inability sorry, the next slide simply shows that this relationship between the external conjugate and later hypertension or stroke is very specific. The mother's height doesn't tell it to you. Neither do the other pubic diameters.

And my final slide, this conclusion to this, is that malnutrition during infancy, including lack of Vitamin D, leads to specific changes in protein metabolism in the girl, in a young woman, which prejudices the early nutrition and growth of the next generation and therefore programs adversely their health in later life and leads to a [Inaudible] for getting lipid profile, hypertension and stroke.

So in a more stark and I'm winding up now more starkly, we have to live in the next slide with the fact that poor diets of girls and young woman are causing disease in the next generation, and these are helpful insights. Michael talked about health I think it was Michael talked about health disparities. And when you think of the map of the U.S. and think where you are this minute, you are reasonably close to the least healthy parts of America, which is the Deep South. And why South Carolina has more stroke than any other state in the U.S. has been the subject of investigation for more than 50 years and has produced only the realization that to be part of the high stroke rate in South Carolina, you have to have been born there.

Now, if you were born in South Carolina 60, 70 years ago, things were not all that good. There were still nutritional problems around. But if the key in the door is not where you were born but where your mother was born and grew up, that takes you back a hundred years, and that takes you back to a very different South Carolina, which was battling with all the problems, the social disruption that followed the Civil War.

So these realizations that the nutrition of girls knocks down through generations is, I think, a helpful one, and takes us to a place where we all want to be, which is my concluded slide called "Preventing Chronic Disease."

It's not new to say that chronic disease may be prevented in the next generation by improving children's growth. We don't know how to figure it out because we've let the

childhood obesity epidemic happen, but nevertheless, we're aware of it. We've known that there were issues about the mothers' diets before during pregnancy. Of course, that's been known a long time.

But the new things are that we've got to figure out the human placenta a whole lot better, and we have to understand that the key to health disparities could lie in the diets of girls.

So thank you very much for listening to me. Michael has asked me to respond to any questions there might be, and I'm very happy to do that, and thank you for listening.

[Applause].

WANDA BARFIELD: Thank you, Dr. Barker.

We'd like to now open the floor to questions. There are mics located in the aisleways, please come to the podium and introduce your name and your question.

FAY MENEKER: Good morning. My name is Fay Meneker [Phonetic], Dr. Barker, from the National Center For Health Statistics.

You spoke quite a bit about the importance of the placenta.

DAVID BARKER: Uh huh.

FAY MENEKER: And I'm wondering if you have an opinion or any data about the effect of more than one Cesarean delivery on the health of the baby since an initial Cesarean delivery produces a uterine scar, which, you know, causes placental problems for some women.

DAVID BARKER: Thank you very much for the question, which I actually can't answer. But before I try to, let me thank the audience for their applause. It's been a curious experience giving this lecture in my office, and there were times when I thought I was all on my own just talking to myself [Laughter]. And so it was nice to know that you were still out there [Laughter].

I think it's a very interesting question. And what is known about the general question of whether the implantation types of the human matters, there's just no literature on that at all. The study of the normal placenta people just don't study.
Placentologists study pathology, and these very important questions have yet to be addressed. There is a meeting in Cambridge this weekend, just a small meeting, and the reason it's a small meeting is, actually, there aren't more than 20 people in the world who could even vaguely begin to address the question that you've answered. Thank you for it.

I think ideas about implantation sites, is this why two sisters born one after the other look different, how important is exactly where the embryo implants. Great question.

FAY MENEKER: Thank you.

UNKNOWN SPEAKER: Hello, Dr. Barker. I'm from the University of South Carolina, a state can you hear me?

DAVID BARKER: Yes, I can.

UNKNOWN SPEAKER: yeah, a state which you used in your presentation of hypertension 70, 60 years ago. Right now in the United States the current association is overnutrition to pregnancy and overnutrition and excess weight among the children, you know, childhood obesity. So have you looked at evidence about overnutrition and its impact on mother and children's health?

DAVID BARKER: Well, obviously I accept very much the big problem of overnutrition. And what in my talk I pointed out that the effects of having a high body mass index in the child was conditioned by its experiences in utero, and that's how it works in adults. We all know that if you lined up a group of people with a BMI more than 30 that some would be fit and healthy, some would be diabetic and have gallstones and be unhealthy. And here, too, we've said, oh, well, that's just genes, because that's a kind

of idleness of thought to attribute it to some magic force. But we now know that the effects of obesity on metabolism are conditioned by both sides.

I understand that the concerns, of course, are about the overweight in mothers and the production of children at increased risk of diabetes, that that is a new scenario. Around the world, it not the important one, but it certainly is important [Inaudible]. I see it all the time.

So that doesn't answer your question, but I accept your point.

UNKNOWN SPEAKER: Thank you.

MANDY BELFORD: Hi, Dr. Barker. I'm Mandy Belford [Phonetic] from Children's Hospital in Boston.

My question is related to the last question. You say in your concluding slide that chronic disease may be prevented by improving children's growth. I'm specifically interested in how what your thoughts are on the strong association of rapid weight gain in infancy with obesity and related diseases and how we should be thinking about improving children's growth. Specifically in infancy, does that mean faster or slower?

DAVID BARKER: Well, thank you for the question. And I know that there are people in Boston who think about this a lot.

In the Helsinki data, it is quite clear that all weight gain between birth and two years is good. It only becomes problematic in terms of programming after the age of two. And so I need to be convinced that although there's some tracking in weight between six months and, say, seven years, that that actually is a harbinger of doom.

And I think it's a very good question to have raised, and people forget that fat is good, fat grows your brain. The brain is growing has a very critical period of growth in the first year after birth, and faced with a choice between a clever somewhat fat child and a stupid thin one, most parents would opt. And there may be some tradeoffs. That's my thought [Laughter].

MANDY BELFORD: Thank you.

RUSSELL KIRBY: Dr. Barker, this is Russell Kirby from the University of South Florida, and I wanted to kind of extend your discussion in a slightly different direction. And that is that many women have more than one pregnancy, and it occurs to me to wonder to what extent the you talked about the fetal programming, but to what extent is there also a uterine programming that potentially affects the outcomes of subsequent pregnancies and how it could interact with the fetal programming that you discussed.

DAVID BARKER: That's a wonderful question. I should say, first of all, the answer to every question you could ask me is I don't know [Laughter]. This is a new field, and it's just hurtling along.

But we've started off with fetal programming. We've now rediscovered placental programming. That's clearly important. I think that's just a really cool thing to suggest, and thank you for doing so.

LAUREN SMITH: Good morning. My name is Lauren Smith. I'm from the Massachusetts Department of Public Health.

I had a question about the diet of girls as they're growing and whether or not sort of all diets are created equal, and did you find anything or consider the quality of the diet? In other words, you can gain weight in various ways by eating high protein or high carbohydrates and the weight or the BMI's might be same, but the quality of the diet might be different.

DAVID BARKER: Well, I like your thought very much, and I can give you, yet again, a tangential answer.

There's been a lot of interest in what's called the French paradox, which is why places like Toulouse in South France have essentially low rates of heart disease given the fact that they smoke and drink like it was going out of fashion [Laughter].

And it's forgotten that in 1870 the French got interested in the well being of their mothers and babies because they were not pleased with the quality of their young men. It was about armies. And they set in place the protection of mothers and children that you can still in France today. And, of course, they made fruit available to women who were pregnant and so on and so on. And they were doing in the context of a very high quality diet. So given a half a chance, it was easy for children and mothers to have high quality diets, and that is the French diet is a high quality diet.

So even if you go to France this is way away from your question now today, a mother has to take her child to a clinic when it's nine months, when it's two years, when it's three years, when it's four years to have its weight measured and checked out. And if she doesn't do that, the French government will deny her state assistance, financial assistance, and she may have difficulty getting her child into a school. She's regarded as an irresponsible mother, because the French feel, which the audience may well not share, that a child has three parents: its mother, its father and the country of its origin. And so it's the duty of the country to play its role and the duty of the mother and father to see that the child has growth charts.

So I'm doing a study in Marseilles cause, because every pretty much every student at the University of Marseilles has a growth chart, which carries right through until puberty. So the French experience is very encouraging because it suggests that

coronary heart disease is not inevitable. There are ways of westernizing without running into a wall of coronary heart disease.

So thanks for your question.

LAUREN SMITH: Thank you.

MICHAEL KOEGAN: Dr. Wilcox?

ALAN WILCOX: David, this is Alan Wilcox. I have to compliment you for how well you did with well, the lecture was very effective.

DAVID BARKER: Thank you, Alan, very much.

ALAN WILCOX: You mentioned cancer in your lecture. That's the first time I recall your bringing that into the picture. And cancer, of course, is a very interesting issue because the associations of, for example, birth weight with lifetime adult cancer risks, and also childhood, go in the opposite direction to shows associations of cardiovascular disease. And I was wondering if you plan to do more to bring in that perspective into your hypothesis.

DAVID BARKER: Yes, we've spent a good many years trying to get access to the Finnish cancer registry, and so for the kind of bureaucratic reasons that many of the

people in the audience will be familiar with, it just took forever. But we've now done it, and this is how these things come forward.

And, I mean, the breast cancer story, which originated in Harvard many, many years ago saying, look, breast cancer is associated with early [Inaudible] so it must have its origins in early life. That was a paper 40 years ago by [Inaudible].

Then the next bit was and on the whole, people who have breast cancer tended to be big birth weight babies. That is kind of Michael's recent review.

And then more recently our data said, well, it is true that babies tend to be a little bit bigger, but actually you get a much bigger prediction if you look at length of gestation, because breast cancer seems to be associated with being born after term. And that makes a lot of sense, because if the root origin of breast cancer is exposure to the mother's hormones, as many people believe, then staying on in the uterus at a time when the placenta is literally dying and ceasing to be the barrier it once was between the mother and the baby, it makes a lot of sense.

So I think we can go beyond birth weight and cancer, and that's where the story will go. And, I mean, there's a paper which has been considered for publication now which takes it into another cancer I'm not really prepared to talk about it but, Alan, I think this is a story that's going to run.

Does that help?

ALAN WILCOX: Yes. Thank you.

UNKNOWN SPEAKER: Hi, Dr. Barker. This is [Inaudible] speaking. I'm a doctorate student in Bryant University. So actually I'm very interested in your in vitro programming hypothesis. I'm doing my thesis work related to your hypothesis.

So I have a question for you. You show the result for so you certified the people by the birth weight and the adult weight and kept their risk of [Inaudible].

DAVID BARKER: Yes.

UNKNOWN SPEAKER: So I have a question here. So do you think the adult weight or BMI is in fact [Inaudible]?

DAVID BARKER: Well, the slide thank you for the question the slide showed weight because, actually, it's both high BMI and tallness, which has been shown in other studies. It's kind of total amount of body.

I can't answer whether reduction in BMI would be beneficial because there isn't the literature. But I think it's highly likely. Because if you can reduce one component of

your body, its fatness, then there would be less bloodflow through the kidneys. So that's really my response.

UNKNOWN SPEAKER: The reason for me asking the question is that in the literature under association between birth weight and later blood pressure or hypertension is that so a lot of studies didn't found the significant association just between the birth weight and the blood pressure, but after they adjust to adult weight or BMI, those associations become inactive. So there is a great debate here whether the adult weight or BMI is an active confounder or something else.

DAVID BARKER: Well, it's not a confounder. I mean, in my view, that was never a starter as a debate because small birth weight is inversely related to later BMI. So in the simultaneous regression you're describing, what you're doing is pointing out that high BMI has a much greater effect on blood pressure if somebody was small at birth. That's really the message. And I don't think getting bogged down in that thing, I don't know, it was produced years ago that somehow that the birth weight thing isn't real because it's confounded by current body mass index, I'm afraid I don't see it as an intellectual proposition. And so many studies have shown links between birth weight and blood pressure and three year olds, ten year olds, 20 year olds. It's just come through. I mean, the number of studies show associations of the order of 150.

UNKNOWN SPEAKER: Thank you.

ITALIA ROLL: Hello, Dr. Barker. My name is Italia Roll [Phonetic]. I work with the field epidemiology training program in the African region with CDC. And I wanted to find out if you are aware of any research that's ongoing in the African region. Because we are seeing an increase in chronic disease such as heart disease, diabetes, stroke. Are you aware of anything going on in that area related to

DAVID BARKER: I only know about work in two places. One is in South Africa, where, of course, there is work, as you would know, and there are cohorts there that are part of this six country cohort study which has been published [Inaudible]. So that is active.

And the other African country is the Gambia, where there are deeply interesting studies of people who were in the womb during the dry season as opposed to the wet season, and there is a seasonal famine in parts of West Africa you would know better than me which is associated with the end of summer food is running out, the rains come, malaria comes, and women have to do heavy work in the fields. And people who were in the womb during the wet season, as adults as adults have high death rates from infection.

So that's I mean, that's tremendously interesting. And how that works, we don't know. There's talk about it may be the thymus of the baby is affected because the thymus is a low priority organ for the baby because the mother deals with the immune problems to an extent.

And I'm not aware of programs across Africa. I suspect you'd know better than me, really. It's very disappointing. There are programs across South America, there are programs in India, there are programs in China, but Africa as a whole I mean, nothing.

ITALIA ROLL: Thank you.

CELESTE PHILLIP: Hi, Dr. Barker. My name is Celeste Phillip. I'm with the Florida Department of Health.

We know that duration and amount of breastfeeding reduces risks for obesity and Type II diabetes and other conditions in children, and I was wondering if you looked at that in your study either in the children or the mothers to see if that may have some effect on the genetic programming.

DAVID BARKER: It's kind of disappointing. Firstly, 80 percent 90 percent, actually, of the Helsinki Birth Cohort were breastfed because they were born at such a time. But we know how long they were breastfed for, and I had kind of high hopes, and all that's come out of this and other studies in terms of programming long term is that prolonged breastfeeding beyond a year is associated with reprogrammed thyroid hormone production, which is associated with high cholesterol, which is associated with increased rates of heart disease. That's been shown twice now.

And when you think about it, the duration of breastfeeding beyond a certain point, the mother is exposing her fetus to her hormones which are secreted in breast milk, and it certainly seems that the thyroid hormone in breast milk beyond one year becomes adverse. It's not a field I know much about, actually.

CELESTE PHILLIP: Thank you.

DAVID BARKER: I mean, did I give a ride into that? We are profoundly ignorant about the human placenta, and we know less about the human placenta than we do about any other human organ, and also the placenta is the most variable of or mammalian organs. It's as though the placenta no species got it right. The monkey has two placentas and so on.

Now, one of the very interesting about breastfeeding that's been known a long time but forgotten is the that the breast the mammary gland ripens in late pregnancy. It is instructed by placental hormones which effectively say how big the baby is. And experimentally, if you reduce the size of the placenta, you'll residue the size of the breast tissue and you'll reduce the amount of milk and the quality of milk. That's been easy to show experimentally.

So, you know, we don't we think we know quite a lot about breastfeeding, but actually we don't. When you go back into the old literature, people like Peter [Inaudible] in the '60s were talking about this very important dialogue, because a

woman doesn't want to make huge surpluses of breast milk because that's wasteful, and in days gone by there were big issues about maternal survival.

So there's another simple example of something I don't suppose anybody in the audience knows anything about. And I certainly don't. But I just know that there's an agenda.

Thanks.

SHERI SPENCE: Hello. My name is Sheri Spence, I’m an epidemiology consultant from Colorado.

I have a two part question for you, going back to the comment about going beyond the weight. The first part is, thinking back to your comment about the sample you had and the fact well, going back to the picture of the children in London, the health of the mothers growing up in the country was, I think, maybe a combination of two things. One, a healthier diet, and another, a great deal more physical activity that allowed for a great deal more consumption of what we now think is an unhealthy diet.
So I'm wondering if that the physical activity

DAVID BARKER: Well, I think I think that's a very reasonable thing to suggest. We've done surveys, recall surveys, among elderly women of what life was like, and

the abundance of food was associated with a very they lived on farms. It was like America a hundred years ago. Most people lived on farms.

So I like the thought, yeah. They certainly the concrete marker of the well being of the baby's is that in London, the London described by Charles Dickens, neonatal mortality was the lowest of anywhere in the country. I mean, it's astonishing. Post neonatal mortality was sky high, of course. Infants died all the time. But not in the first month after they were born. And maternal mortality was exceptionally low.

CELESTE PHILLIP: Thank you.

And the second part of my question is, is have you thought about the going beyond [Inaudible] with respect to something, chronic disease other than cancer. I'm thinking specifically cardiovascular.

DAVID BARKER: I'm sorry? I haven't quite picked up on that.

CELESTE PHILLIP: Okay. You said in your last comment about going beyond obesity with respect to breast cancer.

DAVID BARKER: Oh, beyond birth weights, yes.

CELESTE PHILLIP: Beyond birth weight, I'm sorry.

DAVID BARKER: Yes. Well, I think where we're going to go is replacing birth weight with combinations of maternal body size and placental size. Because if you're given a choice in our data, would you like to know about the baby or would you like to know about the mother and the placenta? You're better off knowing about the mother and the placenta. And it's taken me 20 years to figure that out, but it's completely obvious that the baby is merely a display of the mother and the placenta.

There's a chapter and a paper called Beyond Birth Weight. They're both moving through I mean they've been accepted. They'll come out next year.

CELESTE PHILLIP: Thank you.

NICOLE RICHMOND: Hi, Dr. Barker. This is Nicole Richmond from Louisiana. And while you were speaking, I was kind of thinking of what is the common theme here, and it really has to do, in my humble or small opinion, with hormones and how it is part of growth. It's related to diet. Whether you're undernourished or overnourished, your hormone regulation is a little bit

DAVID BARKER: Sure.

NICOLE RICHMOND: And then we have the idea of a child that's born premature, they undergo catch up growth, they undergo puberty earth at an earlier than normal

age. And I'm wondering if you have looked at the role of the placenta and the output, because the placenta supports the continuation of the pregnancy, in terms of later cardiovascular disease or if there's a dose response effect.

DAVID BARKER: No. I mean, I like your question. I think hormones have to be very central in this. And to a and the placenta is, to an extent, a display of the mother's estrogen. And people forget that the estrogen in pregnancy goes up hundreds of times. I mean, it's way higher than it it's absolutely huge.

And so what estrogen does, and this is the discovery of Gene Orbeck in Maryland, I just think it's a completely brilliant thing to discover is that it is the mother's estrogen which limits the invasion of her uterine lining by the embryo. It stops the embryo getting into the spiral arteries too far. And faced with high maternal estrogen and this big inhibition, the placenta then has to spread out. So the shape of the placenta at birth is actually saying telling you about the mother's estrogen.

But, again, that's a recent discovery, and, you know, I don't suppose a lot of the people in the world know it. It is very brilliant because there has to be a mechanism to stop the embryo invading the uterus and going clean through and not coming out the other side. And Gene has discovered it. It's the estrogen, which in most respects is obvious, like all great discoveries. But that's he's done.

So I like the hormone thing will come and come. Mother's hormones have to be important because they affect placenta which necessarily affects its function, which necessarily affects programming of the baby.

WANDA BARFIELD: We'll take two more questions from the audience.

UNKNOWN SPEAKER: Hi. This is Laura [Inaudible] from Centers for Disease Control and Prevention. And I'm interested if you have thoughts on the impact and continued impact of the increasing use of assisted reproductive technologies which are associated with both multiple births, but also increasingly shown to be associated with smaller births and preterm births for singleton births, and also not just ART, but I've given some thought to the stead use of other infertility treatments that involve large doses of hormone in the preconception and early conception period and what impact that might be having on this.

DAVID BARKER: Well, that's a terrific question. And now we know that the early [Inaudible] is very sensitive to the fluid that bathes it. It makes it likely that taking eggs out and fertilizing them and then putting them back into the mother, it's almost unthinkable it wouldn't do nothing. So then the issue is, is it harmful? And I've seen a paper from Holland about adolescents who were conceived by assisted reproduction, and they were compared with there were two groups of mothers. They were all attending infertility clinics. One group of mothers conceived spontaneously and the others had assisted reproduction, and the two groups of offspring were compared.

But it's very difficult to know what that means, because women who eventually conceive spontaneously and those who don't are different in many ways. I think you've just voiced an area of huge of concern. Not huge concern, but of concern.

Thank you.

NICOLE RICHMOND: Thank you.

CINDY MOORE: Hi, Dr. Barker. I'm Cindy Moore from the Centers For Disease Control and Prevention. I have a question about sort of the other half of the parental unit, the father, effects of diet, especially early in childhood, imprinted genes and their effect on the placenta.

DAVID BARKER: Yeah, I love it. I think it's a great question. Like all the other questions, I don't know what the answer is, but, of course, it saddens me that the father's genes are more important in growing the placenta and the mother's genes are more important in growing the baby. I suppose there must be a story there we need to push on a bit. I mean, all these things that are being raised by the audience, they're things that could be researched, and ten years ago you wouldn't have got any money for looking at the normal placenta. But, I mean, somebody better start spending some money in this field.

I mean, I have a grant which is being considered by the National Institute of Aging, and it's very difficult for them. It's very difficult for one of their panels to consider an application which says, well, lifespan is likely to be linked to the placenta. I mean, most people around that table would not know what the placenta was [Laughter]. So the field has got a structural difficulty, because people who know about late life don't know about early life, and people who know about early life don't know about late life. And we kind of have got to bring things together, and I significantly failed to do that in 20 years and probably will continue to do so. But thanks.

MICHAEL KOGAN: Dr. Barker, this is Michael. I'd like to thank you very much for giving an excellent presentation under unusual circumstances, and I hope the audience will join me in thanking you very much.