

## Raising the Bar Sydney 2018

### Adrienne Gordon – Beyond the genetic code

Welcome to the podcast series "Raising the Bar: Sydney." Raising the Bar in 2018 saw 20 University of Sydney academics take their research out of the lecture theatre and into bars across Sydney, all on one night. In this podcast, you'll hear Adrienne Gordon's talk "Beyond the Genetic Code." Enjoy the talk.

[ Applause ]

All right. Hi, everybody. Thank you for coming. When I heard that this was my bar, I was slightly alarmed because I'd last been here 15 years ago, dancing on the 80s floor. So that will tell you how old I am. [laughter] So I'm going to talk to you today about the story of what happens before you are born and how what happens before you are born actually shapes the rest of your life, and not only your future, but your children, and actually, your grandchildren too. And hopefully, by the end of the talk, I will have convinced you that the key to actually solving some of the epidemics that we currently face is investing in life before birth.

So I'm going to start off in 1944 in the Netherlands. So in 1944 in the Netherlands, there was a railway strike. This is just near the end of World War II. And the Dutch railway workers went on strike to try and help the allied forces, help them avoid Nazi occupation. And essentially, this strike was a massive fail. The Nazis occupied a vast part of the western Netherlands and blockaded food into that area. So this tragic event happened from around the fall, sort of October, November of 1944 and lasted to spring of 1945. And during that time, which was known as the "hunger winter," people were actually reduced to eating less than 30% of their normal caloric intake. So at this time, people ate grass, they ate tulip bulbs. They ground that up into flour to make some form of bread. And people burned a lot of the wood and furniture in their homes because the winter was so cold, it was the only way that people could survive. [microphone feedback] So what happened, remarkably, was that this was actually a perfect scientific study population. So once World War II ended, food supplies were actually restored to normal really quite quickly. So this population had very well characterised timing. They all had energy restriction, which affected everybody in a defined area. And they had excellent record keepings in the Netherlands.

So they were able to follow up these people and what happened to them afterwards. So this is exactly the sort of experiment that if you're a basic scientist, which I'm not, you get to do on mice and on rats. And you can control everything and you can actually work out what happens. It's very unlikely that you would ever be able to experiment like this in humans. You would never get anything like this past an ethics committee. [laughter] So one of the first things that they did was they were able to look at the size of the babies born to the women who happened to be pregnant during the hunger winter. And some of the things that they found were really surprising.

So first of all, they realised that it wasn't just energy restriction that was important, it was timing. So if somebody had been very starved in the later part of their pregnancy only, but they'd been well-fed at the beginning, then those babies were small. And I guess that's hardly surprising, because we know that in the last part of pregnancy is usually when babies do most of their growing. So if people have been pregnant or they know somebody that's been pregnant, that's when the bump increases dramatically. That's when now everybody does their Instagram posts, and that's when people feel comfortable to say they're pregnant and they haven't eaten too many cakes. [laughter] So the fact that these babies were small was not

surprising. But what was really surprising was people who were really starved in the very beginning of the pregnancy, even if the food supplies had been restored so that in the later part of pregnancy they were okay, those babies weren't small. They caught up and they were born at a normal birth weight. And then the epidemiologists were able to follow these children through the next few decades. So the babies that were small, they stayed small throughout the whole of their life, despite for the next 40, 50 years having adequate food supply to whatever they wanted, they actually stayed small. So something happened that affected how they developed over time. The normal weight babies, and just remember, those mothers were starved very early in the pregnancy, they actually ended up having a much higher risk of chronic disease.

So by the time those children were in their middle age, they had higher triglycerides, higher cholesterol, higher rates of diabetes, and higher rates of obesity. And as they went into older age, they also had higher rates of early death, and they had higher rates of schizophrenia. So something has happened that is critically important to nutrition and pregnancy that has affected these children for decades. And even more interesting is the children of those children have some of those same effects. But some of them might not even have heard of the Dutch famine, never mind had any exposure to that sort of malnutrition. So this really means that timing is absolutely critical. It's also really important when we think about these effects before birth, we don't just blame all of this on women, particularly of this time of MeToo and Time'sUp, the time is definitely up for blaming these things on women.

And there are the same natural experiments in men. So if we think back to Scandinavia, in the very northern part of Sweden in an area called Overkalix, they have a real issue with weather and isolation and boom and bust types of harvests. And what scientists have discovered that the offspring, the grandchildren of men who were going through puberty in times of wildly varying harvests, they found that a single episode of overeating, so one good harvest in amongst several poor harvests, means that the grandchildren actually die on average 30 years earlier for people born in that part of northern Sweden. So they have a very small population and very well-characterised. So this really means that timing is critical and nutrition is critical. So how does this happen? How does something actually continue on for generations after generations? So how do we pass on our information to the next generation? So if I asked you that, probably people would say DNA. And for some things, you would definitely be right. But DNA, we understand now, is not just our destiny. And there are other things around how that works that we're really just learning about.

So we often think of DNA like a template. So if we think about something like a LEGO factory, and you might think about a mould, a plastic mould that molten plastic is poured into. And that machinery, unless something goes on, will spit out hundreds of thousands of millions of identical LEGO parts, unless something happens with the design. But in fact, DNA is not really like that. It's not really like a template. It's a little bit more like a script or a story that gets rewritten by your environment. So if we think about something like "The Great Gatsby" – we know there's a '20s novel by F. Scott Fitzgerald. There is a movie featuring Robert Redford in 1974. And then there's another movie by our own Australian, Baz Luhrmann, in 2013, and those movies, if people have seen them, are completely different. So they basically have the same script, but different productions. So the name for what this is when it affects your DNA is called epigenetics.

So I'm assuming that people that are here tonight might have heard of epigenetics. But if you haven't, learn that word, say it, epigenetics. Show it off at the bus stop, talk about it. [laughter] Talk about it to your friends at work. And this is a really very important thing, because it actually means that there are chemical signals which can change the way that your genes work. So if we think about DNA like the alphabet, the epigenetics is kind of like the punctuation or the grammar. So if your DNA was letters in a book, and epigenetic changes

meant you could staple some of those pages together, that might mean that you change the whole meaning of that book. You might not be able to read whole chapters or some sections of the book, and so the whole meaning of that would change. But every single letter in that book is identical. And what we know about epigenetics is that these changes can be seen in at least two generations. So they've been able to look at these chemical signals in the grandchildren of the Hunger Winter, and one of the things they particularly look at is methylation. And methylation means that you have a chemical tag on the DNA, which is really like a switch for turning genes on or off. And often, what it does is down regulate genes. So this means that really, we didn't start life where we started.

So if I think about myself, I was an egg inside my mother when she was a baby inside her mother, and she was born in 1944. A bit of a 1944 theme today. And my grandmother, who has now died of cardiovascular disease – I'll come back to that later – she would now be 92. So actually, my epigenetics and my DNA is actually 92 years old. So I think, you know, I'm looking pretty good in the pub at 92. [laughter] All right. So at this point, I'm going to tell you about a very important person in this whole story of life before birth. And that is somebody called David Barker. So David Barker, who died around five years ago, was a doctor and epidemiologist from England. He was the son of an engineer father and a concert cellist mother. So he already had probably pretty good DNA in there already. So he, at school, was very interested in natural history, and actually throughout school, had special access to the biology labs to try and understand some findings that he had done through his own research.

So obviously, a very keen interest in research at an early age. He did medicine in London, went to Africa for around a decade, and then came back to South Hampton in the south of England as professor of epidemiology. And at that time, he made a very simple but very seminal discovery around this area that we now call the developmental origins of health and disease. And what he saw was that the patterns of infant death and of cardiovascular death overlapped. And at that time, that was really done by putting a map on top of another map. There was no AI or anything to work out those initial correlations.

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And one of the – there were several papers around that time that were published in the late '80s. But one of the most important is the simple u-shaped graph – if I had a slide I would show you – that looks at the relationship of birth weight to later cardiovascular deaths. So what he found, secondary to an excellent midwife collecting really good birth records in Hertfordshire in the UK – go, midwives. They're very good at doing things like that. And they found that if your birth weight had been under five pounds, so in metric that's around two and a half kilos, you were three to five times more likely to die of cardiovascular death. And the other thing that was seen at that time very clearly on the graph, but actually less emphasised, was that there was an upturn of that graph for babies that were bigger at birth, as well.

And they had almost the same risks of later cardiovascular disease. And so babies that are small, this is relatively easy to understand potential risks. If you're born too small because of poor nutrition, like the offspring in the Hunger Winter, you actually have developed slightly differently. So really small babies have less heart cells, they have less filtering units in their kidney, and they really importantly have less islet cells in their pancreas. And those are really important because they help you produce insulin and that helps you manage your glucose, which helps you reduce your later life risk of diabetes. Babies who are born larger are usually born larger because of increased glucose in utero, and that can be from maternal diabetes or from just a general higher glucose, even if you haven't got to a diagnosis of diabetes. And those babies have a different mechanism for their risks.

They basically sense that there's extra sugar and they're not doing very much, just hanging around in utero, so they don't need to use that. So they actually just store that as fat. So the

underlying pathogenesis of the risks for the small and big babies is different. But it's very clear that how you grow before you were born matters for your health and for your offspring's health. And one of the other things around that whole hypothesis, which was originally called the foetal origins of adult disease, is that that programming in utero affects how you adapt to life. So if we think of that small baby, and initially David Barker called this the "thrifty phenotype hypothesis," that small baby had a lot of metabolic adaptations that would make that baby stay alive in utero. He or she wasn't getting the right nutrition, either because the mother was malnourished or because the placenta was not working. So the placenta delivers the nutrition to the baby, so you could have a well-nourished mum with very high blood pressure and preeclampsia and you'd still get the same problem. What actually happens is that then those metabolic changes, when you're born into this environment where you've got adequate supply of everything, you have poor nutrition, you have less physical activity, and you have a McDonald's down the road and you're struggling with screen time, then those metabolic adaptations aren't as helpful for you when you're born into that environment. And David Barker stated at this time that the foetal origins of adult disease will be more important than tobacco in the development of chronic disease. And at that time, when he said that, he was very much ridiculed. And there wasn't a lot of scientific clout behind some of these observational findings.

What we're now finding is that obesity and diabetes have overtaken smoking as the leading cause of premature death in this country and others like it. Okay. So now I'm going to tell you a little bit about why I even care about any of this and then why you should too. So I care about this because I'm a neonatologist. I spend my life looking after babies. So a neonatologist is a paediatrician or a kids' doctor who is specialised in looking after babies in the first months of life. And that is a great speciality. It's exciting. It combines intensive care with gadgets and technology and procedures and all of these exciting things that many people that go into medicine go into medicine to do. So if there's any potential students interested in medicine, we need more neonatologists. [laughter]

But one of the very interesting things that I have found over the last 22 years I've been doing this job is that what I do in that job has just become less and less. And that's not because I've become more senior and I'm in charge – well, it's a little bit of that. But it's because we've got much better understanding about how those early life exposures actually affect the outcome of those babies down the track. So we now know that some of the very things that we do to ensure survival, the painful procedures, the ventilation of the baby's lungs, the constantly checking, the doing the tests, we know that babies who've had more exposure to those things in utero are actually less resilient as adults and more likely to have neurobehavioral problems secondary to those advertisers events. And one of the amazing things that has happened in the last decade in neonatal care, which was much better done in the developing world, not in the places with the snazzy technology and the 400 gram babies, is something called "kangaroo care." And this is really revolutionising what we do and is potentially being – will affect our epigenetics for these babies. So kangaroo care was developed in Colombia out of necessity. So they had a real issue with early births. They had a problem with babies just not – them not having enough equipment to look after small babies. And they had a huge problem with babies actually being abandoned because the hospital couldn't look after them, the family couldn't afford to look after them.

And so what one of the paediatricians did there, out of total necessity, was use the mothers as incubators. And what they found is that the babies on the mothers who were skin-to-skin with their mums and weren't having all the snazzy technology, they found that those babies were far less likely to die than the baby next to them in the expensive cot or incubator. And so we now do this practice as standard care in pretty much every neonatal unit in the country. And we have some evidence already from places that started doing this earlier that if you had more skin-to-skin time with your mother, more kangaroo care, that as a ten-year-old and as a

teenager, your responses to stress are different and the methylation of the genes that code for your stress hormones are different. So I mean, that is amazing to me. We're actually just kind of going back to the future. And any of you who are basic scientists might say, well, we knew all of this. Like, we all knew all of this from rats and mice decades ago. And that is true. So the really early studies of epigenetics actually looked at the offspring of rats and mice and the way that they were licked and groomed by their mothers. And they found that the rats' offspring who were licked or groomed were far more resilient when they exposed them to stress. And they also had epigenetic changes on their glucocorticoid hormones. So this is why it's really important to have people in clinical practice and people in basic science thinking about questions at the same time.

Otherwise, these sorts of things take decades to actually turn up somewhere where they might actually affect human health. I also care about this story because I was a growth-restricted Scottish baby. So my birth weight was 2.4 kilos. I've already told you that my grandmother died an early cardiovascular death. My mother's been on high blood pressure medications since I was a medical student. And I don't have a BMI under 25. So I am currently probably thinking of going for a kind of rejuve [phonetic spelling] with my GEP when I'm doing all of this research. So why should you care? So you should care because this is so important for our current epidemics. So life expectancy in the current century has increased miraculously. In 1900, you could expect to live to the age of 50. By the time you got to the mid-90s, you could actually expect to live to about 75. And now the average life expectancy is about 85. So it's a huge increase in a really short space of time, if you think about centuries of evolution. But what we know at the moment is that the generation now, so the Generation X, the one I'm part of, the first generation that actually might not outlive their parents.

And we're also the first generation that represents three generations and if you think about those epigenetic things and the grandchildren, three generations of processed food and a life of plenty following World War II. So World War II is responsible for so many things in this whole area. And critics of epigenetics would say, particularly if they're interested in natural solution, would say that there are flaws in all of these natural experiments, and certainly that's true. These are not randomised control trials. There are obviously lots of other exposures that happen in life that actually might affect your behaviours, might affect your risks. But it's very clear now in different countries and also now backed up by the science that what happens before you're born in some way affects the next generation and also that those effects are modifiable and that DNA is not everything. So one example of DNA not being everything is identical twins. So I've looked after lots of identical twins. Lots of them are born early and end up in a newborn intensive care. And it's very clear that despite identical DNA, those twins are not the same. They don't end up with the same problems at school. They don't even end up with the same disease. Only about a third of identical twins get the same disease, and they very rarely die of the same thing. So that's one experiment that is very clear, that there's something as well as DNA that affects what happens to us.

So I would say, in finishing, that there are things that we can do. So this is not all a bad news story. This means that actually there is not nature or nurture. It means that we actually can nurture our nature. And we can test that by looking at epigenetics and looking at some of these chemical signals. And there are certain things through research that we know absolutely already do that. So things like sunlight, chemicals like bisphenols in plastics, nutrition, so particularly folates and B vitamins, social interaction, pollutants. We already know from many of these things that you can actually turn on or off these chemical signals. So what should we do? We should eat real food. We should not eat all the food with all the labels on it, even if we're busy. We should just try and eat the thing that it's trying to mimic, rather than the thing with the labels. We should get outside, we should be in the sunlight. We should teach our children to eat real food. We should go to the GEP for a rejuve [phonetic spelling] if you're in your middle age and you have the risk history that I have. And I think if we, as a population,

invest in health at the beginning of life, we have a far greater chance of changing the life trajectory than treating established disease. And the problem is our health set-up is all set up to treat established disease. But if we take a long view, I think we can nurture our nature and we can potentially prevent the epidemics of the next generation.

[ Applause ]

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