#255: Pregnancy 2.0: The lingering effects of modern reproduction

VOICEOVER
Welcome to Up Close, the research talk show from the University of Melbourne, Australia.

DYANI LEWIS
I'm Dyani Lewis. Thanks for joining us. For most people, the basics of starting a family are very much the same as they have always been. You find someone you like, have sex, and then nine months later you have a baby. But in many ways modern day pregnancy has also vastly changed. Incredible advances in assisted reproductive technologies have enabled thousands of couples who are unable to fall pregnant naturally, to have children. Even for those who do conceive naturally, there are pre-conception health checks, vitamin supplements, and self-imposed bans on soft cheeses, alcohol and spa baths. Pregnancy has become a time of caution as much as it is a time of excitement. My guest today on Up Close is a reproductive biologist who has been studying the precisely choreographed process of embryo development during early pregnancy. Garnering information from a range of different species, Dr Mark Green is looking at how hormonal, environmental and dietary factors can all have immediate, and sometimes lasting effects on the health of an embryo. Mark is from the Department of Zoology at the University of Melbourne. Welcome to Up Close, Mark.

MARK GREEN
Thanks Dyani.

DYANI LEWIS.
Mark, our knowledge of some of the most common risks during pregnancy has improved immensely over recent decades. Can you talk us through some of the more common and preventable exposures or deficiencies that we are aware of?

MARK GREEN
I think some of the most common ones that people don't understand is that they expect that their body is fully prepared when they go into, and want a child, or in terms of when they become pregnant. That's really not always the case. Our diets, our level of exercise, have probably not been what they should be. And so women
and males can do a lot in terms of supplementing their diet, and looking at proper nutrition around helping the reproductive process and to ensure the health of their offspring.

DYANI LEWIS
But things like folate or folic acid and alcohol consumption, we certainly know more about these than we used to.

MARK GREEN
Yeah I think recent studies have found more towards some of the more micro-nutrients as well as folate, which is obviously inherent to some of the neurotubal defects, and we know there's some very good evidence for that. There's now increasing evidence for some of the other issues that we can maybe mitigate through nutrition and supplements. There's selenium, zinc, some of the vitamin A, vitamin C, so antioxidants, high antioxidants. We know that diets - maternal diets are very high in high fats and we need to counteract some of those things through supplementation.

DYANI LEWIS
So in the very early stages of pregnancy, whereabouts is an embryo actually getting its nutrients from?

MARK GREEN
Okay, so it depends again on the species. I guess if we take human as our primary example, then obviously once fertilisation occurs, which is in the fallopian tube, that embryo then travels along and then enters the uterus a day after fertilisation. Before implantation, which in that case about day nine, ten, the embryo is just free-floating in the uterine fluid that is in the environment. So it's really getting its nutrition through a very small amount of fluid that's in the uterine environment. And those are principally derived from some of the proteins that come through from the blood as well as actual specific factors secreted by the uterus itself.

DYANI LEWIS
and then at what stage does the placenta form so that the embryo can get its nutrients from the umbilical cord?

MARK GREEN
Yeah, so as soon as it starts to invade and implant, it has an attachment. Then after that it then obviously makes it way to invading and to having nutrition exchange through the maternal system, and blood vessels. So in the first two or three weeks of pregnancy, it's then starting to do that transition. So quite early on, and usually before most people understand that they're pregnant. Then it's usually that first pang of worry when women find out there's a little blue line on the stick, and oh my goodness I went out drinking and I did some other things, and so if they're not actually actively seeking to become pregnant.

DYANI LEWIS
So by invading, this is actually the process of the embryo embedding itself into the uterine lining is it?

MARK GREEN
Yeah it depends on the species again, in terms of the severity of the embedding, or the invasion. Certain placental forms mean that there are more barriers between the foetus and the mother. In terms of the human, it's actually very invasive and a lot of the layers are actually lost completely. The blood is actually in full contact with some of the - so about one or two layers between the foetus and the mother. So yeah, it is a complete invasion of the system. That's how you regulate it, because obviously if it goes too far through, it can go out the other side of the endometrium and there are some pregnancy disorders that we need to be careful of, that women have issues with.

DYANI LEWIS
That sounds frightening.

MARK GREEN
It is. Yeah, it's under quite good control by the body and most of the time - majority of the time it works quite well.

DYANI LEWIS
You talked before about some of the micro-nutrients, but in terms of diet we often can't go past our expanding waistlines. Do we know much about what dietary excess, whether it be fat or sugar or just calories in general, how this affects embryo development?

MARK GREEN
Yeah, there's a number of studies from maybe animal species more, where we can obviously manipulate diet and have more control over the environment. We know that a high fat diet can change the composition of the oocyte and then of the surrounding membrane, and then of the embryo itself.

DYANI LEWIS
So the oocyte is the egg that get fertilised?

MARK GREEN
The egg. Yeah, the egg that's obviously in the ovary, before it's ovulated. So we can change the consistency and the types of fat that's in there. Then obviously once that egg has ovulated, fertilisation occurs and we know that we can alter the amount of glucose that can be seen by that embryo and uptaken. So if the maternal diet's quite high in glucose, or high in fat, then obviously that's going to feed through into the uterine environment, and that's what the embryo's seeing. So that's really the focus on the studies that I've been undertaking.

DYANI LEWIS
Yeah so you've looked at sheep. I imagine it would be fairly hard to enrol a whole lot
of women in to a study controlling diet [laughs].

MARK GREEN
Yeah, a few ethical questions there that we might want to not deal with, but yeah [laughs].

DYANI LEWIS
So what was the study that you did on sheep then?

MARK GREEN
So there's quite a bit of literature around sex-skewing, around diet and what we were principally looking at was whether the potential - the high-fat nature of the diet could have implications on whether you have male or female offspring. Most of the studies to the fact that an excess of nutrition, whether it be glucose, in a monogastric like humans, or fat for example, can then lead to boys. So what we did in a very controlled way is obviously keep the body weight of the animal the same, and to try and show a true nutrition effect of the diet. Then we had one control group that were on a low-fat diet, and one on a high-fat diet and specifically around poly-unsaturated fatty acids.

DYANI LEWIS
So what's the mechanism? Because this is actually even before the embryo exists, this is pre-fertilisation. So what's happening that would cause there to be more males or more females?

MARK GREEN
Again, lots of evidence and theories around this. And o we were feeding the diet probably three weeks before, during the whole cycle before ovulation, and then subsequently while the embryo's growing in that first couple of weeks. The levels of things that can be altered in terms of again the composition of the oocyte itself, or the egg before it's ovulated, and then the surrounding membrane of that egg can be changed. So that's made of fatty acid composition, and again if we alter that through maternal diet there is potential, in theory, that the sperm can have penetration in terms of whether it's a male or a female sperm that's penetrating. We could alter that. Probably most reliable, and more information's around the uterine environment, so obviously after an animal has had sex, then the sperm coming through the uterus and the uterine environment itself can be altered in terms of its viscosity, and the nutrients that are available for those sperm to swim towards the egg. If you're a very small sperm that's a long distance to go, and so they need nutrients and they need signals from the egg where to go. So we can preferentially skew whether it's a male or a female that are probably getting there faster. There is some anecdotal evidence, that obviously the Y sperm is slightly smaller than the eggs, so maybe they're faster swimmers, but who knows. So that's at that level, and then once there is obviously fertilisation it's whether there's selective loss in terms of male or female embryo within the uterine environment. That obviously is more apparent for animals that have litters rather than ourselves, but even with ourselves you can have early losses. So we know for example that in females where they have two X chromosomes, we
know early on that both of those X chromosomes are functional. It isn't until later in the first probably ten days after that, that one of the X chromosomes is turned off and therefore we've got one X - functional X chromosome in both the male and the female. So before that period, well we've got two X chromosomes. We know that a lot of the metabolic enzymes are actually based on those chromosomes, or expressed on those chromosomes.

DYANI LEWIS
So in the female embryos where you've, as you've said, two X chromosomes, one from the mother, one from the father, what determines which one gets inactivated? Is that a random process?

MARK GREEN
Good question. That's something that I don't think there's an awful lot of knowledge on. We're beginning to understand a bit more about that in terms of which specific genes are turned on and which are turned off. The timing of that isn't all at once, it's over a matter of a few days. So as I said some of the enzymes, to do with glucose metabolism, are actually located on those chromosomes. So that poor female embryo I guess, is technically seeing twice as much, or metabolising twice as much glucose. Although that sounds like a great thing, it obviously means through metabolism she's generating a reactive oxygen species that can be detrimental. So it's a double-edged sword.

DYANI LEWIS
So the female embryos are perhaps slightly more sensitive to the environment than?

MARK GREEN
Yep. So at that point, before the second X chromosome is turned off, then they are more sensitive in theory to the nutrition environment. We know that male embryos grow faster than female embryos, and that female embryos compensate in a different way by actually producing a stronger signal to the mother to let her know that she's pregnant. So even at that very early stage, there are differences between the sexes in the embryo and what they tend to see in terms of metabolism.

DYANI LEWIS
Now the study that you did in sheep, that's obviously a very different system.

MARK GREEN
Yep [laughs].

DYANI LEWIS
How much can we take what we know from sheep and other animals, and apply it to humans?

MARK GREEN
Yeah, we've done it in a number of species in terms of mice and sheep and wallabies. All sorts of animals that we've now looked at in terms of sex-skewing
mechanisms. Most of the literature sits not only around nutrition, but also of stress, and so it’s very important to understand the environment interaction. So we know in humans, there’s lots of anecdotal data and large studies that after quite acute events, such as war or famine, those chronic events, then we can skew the sex of the offspring towards male. We know that women who are diabetic and therefore have problems regulating their glucose can obviously have more males. Again with women who have binge eating disorders, again having more males. And controversy to that, is obviously, women who are anorexic tend to have more females. So there is quite a lot of data out there, in quite large numbers, from humans, the difficulty being of course we’re quite heterogeneous in different circumstances. So I guess we can take a large amount of information from the animal model into the human, and tease apart some of those finer questions.

DYANI LEWIS
It’s interesting that some of that anecdotal evidence exists, because I was going to ask you why, given the increase in obesity rates, do we not see a skew towards males? You’re saying that if you drill into some of the specific situations, you do see that skewing.

MARK GREEN
Yeah, but a lot of it depending on whether it’s paternal or maternal stress, or the timing of intercourse, or frequency of intercourse. There’s lots of other compounding factors in that as well. And social hierarchy as well, which obviously is very, very hard to put a finger on in human circumstances.

DYANI LEWIS
I’m Dyani Lewis and you’re listening to Up Close. In this episode we’re talking about embryo development in pregnancy, with reproductive biologist Dr Mark Green. Mark, we hear a lot about maternal age in the media, and today people are settling down and having children at a much older age, both men and women, than their parents or grandparents did. Why is age, particularly for the mother, a concern?

MARK GREEN
So historically there’s obviously been more research on the mum. We now are doing that on the dad. But really, it’s around the fact that from birth you’ve obviously got a limited number of eggs that sit in the ovary. Those are obviously activated after puberty. Every month you’re recruiting a number of eggs, only one of which will then ovulate. So you have a decreasing number of eggs that are over time being dwindled down. Then by the time that you get in your late 30s, if women are leaving it that late, then obviously they have a smaller pool to choose from. Also they’ve got a large amount of time for those eggs to be more susceptible to environment and nutritional differences. We know with aging that the hormone regulation of a woman becomes a less tight synchrony. That can have an effect on the oocyte or the egg quality in terms of how the cells divide once they are fertilised.

DYANI LEWIS
So it’s not just a matter of accumulating mutations?
MARK GREEN
No, not always. It's triggered by more relaxed hormone cyclicity and shorter cycles in women, and therefore mistiming sometimes the environment that the egg's released into. So obviously the hormones are fundamental in terms of controlling the uterine environment or the oviduct or in terms of the proteins that are produced. So there's a bit of that, but also as you mentioned there are a higher mutation rate obviously once those eggs are coming through as well; they have been sitting there for a long time, and when it's their time to then be ovulated then yes, we know that the non-disjuncture that occurs in oocytes can lead to a lot of chromosome abnormalities.

DYANI LEWIS
So non-disjuncture is just the process of pulling apart, separating the chromosomes.

MARK GREEN
Yeah, separating the chromosomes, yeah.

DYANI LEWIS
So what sort of results do we find from these older eggs then?

MARK GREEN
In terms of the outcomes for the children? We?

DYANI LEWIS
Yes that's right.

MARK GREEN
Yeah. I think there's been a number of studies looking at whether the growth rate of those children are altered, or whether they're initially - probably some of the things that we see is, are they born smaller or larger in terms of birth weight.

DYANI LEWIS
So with eggs that go through this abnormal non-disjunction process, what kind of consequences does that have for the embryo?

MARK GREEN
Well initially probably what you would see is a higher miscarriage rate. The body is very good at picking something that probably isn't going to be viable, early on. So we know that obviously women suffer from a higher miscarriage rate the older they get, potentially. Then we obviously have the incidence of Down's Syndrome is increased. That's why it's obviously very important to go along for your scans once you are pregnant, and especially to look at the nucal fold and look at your rates and chances of getting those kind of disorders.

DYANI LEWIS
So the nucal fold is an indicator of Down's Syndrome is it?

MARK GREEN
There are a number of indicators that the sonographer will look at when they woman goes to be scanned. The nucal fold is basically the amount of fluid at the back of the neck that they'll look at. Again with Down's Syndrome, there are other signs such as a flatter nose. A lot of Down's Syndrome babies can't actually, when they go for a later scan, they can't open or close their hands, in terms of they've got some different movements. So that's why when the sonographer's there she'll check all sorts of organs and functionality.

DYANI LEWIS
And what about the male contribution? You alluded to the fact that male nutrition and male age are now also being looked at. So what does male age do to the quality of sperm?

MARK GREEN
Yeah, I guess, we're 50 per cent of the equation, and we do have a role. So now we've understood that older males, so males probably above 35 and definitely above 40, we're seeing studies come out in terms of high instance of miscarriage in the partner, after conception, independent of whatever maternal conditions there are. And also a higher instance of autism in those children. There are neurological issues as well. So yeah, there's - just starting to look at that. That's something that we're focusing on in our lab, is looking at the difference between just paternal and maternal age, and the combination, and then on top of that the effects of maybe obesity on top. So it's a very complex process.

DYANI LEWIS
In the case of women, where the eggs are forming so much earlier than when they're actually being used, there's I guess a clear mechanism of how the eggs can actually age. But what's happening in men where spermatogenesis, the formation of sperm, actually only occurs at the time the time the sperm is needed?

MARK GREEN
A very good question. We know it takes - in humans it takes about 70 days from the start of a sperm cell being produced, to when it's actually ready for ejaculation. So - and there's obviously continual turnover from the different cells in the testes. So again we're very susceptible to environmental toxins, to nutrition impacts, even temperature. So it's well known whether people are wearing different sized pants, or hot baths, and - so I guess again there are other factors in terms of hormonal control underlying that, that as we age that those things are also being impacted. But that's something that's relatively new, and we need to look into further.

DYANI LEWIS
You mentioned that some of the consequences are an increased rate of autism for males who are over 40. So this is a population-based study of humans, rather than an animal study, I presume?

MARK GREEN
Yes. A lot of these have been follow-up studies in human cohorts, where they've
gone and looked at outcomes from large database studies. Especially some very good evidence in Scandinavia where they keep a lot of records, and it's very easy to then follow up those children.

DYANI LEWIS
Mark, I wanted to talk about assisted reproductive technologies, because they have changed the lives of many couples, for whom it would have been impossible without these technologies to fall pregnant. So what type of situations are the most common for couples to turn to? Reproductive technologies?

MARK GREEN
There's a - there's growing evidence, and I think we're getting better at diagnosing some of the, what were potentially unexplained infertility problems. So some of the things that we will see is polycystic ovarian syndrome, PCOS. We'll see endometriosis. Unfortunately that's coming to be a very high incidence now. Endometriosis is obviously where the uterine lining can grow outside of the uterus itself, and that causes unfortunate adhesions to surrounding tissues. Now it's very hard for women to understand how much pain they should go through, in terms of when they're having a period. That's often associated with a lot of intense cramping. And so women are now luckily going to their doctor and asking more about this. This underlying cause can be there for many years before it's actually detected, so - those are common ones that you'd often see.

DYANI LEWIS
So problem in either releasing the egg from the ovary, or then problems with the actual environment that the uterus is providing for the embryo?

MARK GREEN
Yeah and there's a number of other factors. Of course males, they're obviously going, it's not just the female. We're now seeing more 50 per cent of those treatments are for male factor infertility. So poor sperm counts, poor sperm motility, movement, morphology. So yeah it's an increase on both sides.

DYANI LEWIS
Mark, most people would be familiar with in vitro fertilisation, or IVF. Could you describe what the IVF process entails?

MARK GREEN
Yeah sure. So depending on the infertility diagnosis of the couple, will determine what treatment they have. So if it's not a male factor one, then it will be more of a female. And what will happen is the female will be given FSH in high dosages, much higher than she'd normally see. So follicle?
Follicle Stimulating Hormones. So they will try and recruit a large number of eggs rather than just the usual one that is ovulated. So they have more to then potentially fertilise. That can be quite a painful regime for those women to go through, with frequent daily injections over, well probably ten days. Then once the follicle which is surrounding the egg is large enough, then the woman will be given more hormone to trigger the ovulation. Just prior to that the clinician will come in and actually recover those eggs through surgical means. Those are then entered into the dish, and depending on whether there's a male factor infertility or not, then they'll be done to a standard IVF, which is just the addition of the sperm to the eggs in the dish. If there is a male factor infertility, then they'll actually use ICSI, Intracytoplasmic Sperm Injection. They take a single sperm and they'll inject that directly into the egg, so try and help that male factor a little bit more. Obviously after fertilisation, it will depend on the clinic and the diagnosis. But we usually culture either for two to three days and put the embryo back into the woman in that actual cycle, or they can develop onto a day five blastocyst, again going back into the woman. Or maybe the - all those eggs or embryos are frozen and then put back in a subsequent cycle. Obviously the preference in Australia and the UK, and many countries apart from the US, is for single embryo transfer. And the US tend to go for the whole octomom more bang for your buck thing, which has some severe consequences for the offspring and - in terms of multiples.

DYANI LEWIS
I'm Dyani Lewis, and my guest today is reproductive biologist Dr Mark Green. We're talking about how diet and lifestyle can affect embryo development, here on Up Close. Mark, given what we know about the importance of the early environment for the embryo, do we know if there are any lasting effects on the embryo, of being in this artificial growth medium? Even if it is just for a few days.

MARK GREEN
There are a number of studies looking at what specific components are in the medium. And that's just one of many factors that we know influence the offspring. We can see during that artificial environment that we're not getting things right. Usually that embryo is in the maternal environment, and it's a very dynamic environment in terms of the nutrition that's going across. And we've got it in a very static environment on a piece of plastic, in an incubator which isn't similar to the in vivo environment. So that's one thing. A lot of these patients are sub-fertile, so we are having an underlying probably expression of genes and things that probably aren't the same as a couple that are of sound fertility. Also the amount of hormone that the woman has been given can have an - a lasting environment effect on the uterus. So those hormones are given to stimulate the number of eggs, but obviously if that embryo that's subsequently produced is put back into that uterus, that uterus has also seen those hormones and so we know that in that case, as it's termed a fresh transfer, and we know that those offspring or those children are actually born lighter than the children where the embryo is put back in, in another cycle later. So yeah there - a number of studies have shown the differences in birth weight, and something that I've been looking at is longer term studies on these children. Yeah, been really interesting.
DYANI LEWIS
Yeah. So you looked at the health effects on children of a fairly low-tech reproductive technology which was just artificially inducing the ovulation. So could you describe what induced ovulation entails and then what you're looking at in the children?

MARK GREEN
Yeah sure. So we did two studies. The simpler one that you're talking about is a lot of women, when they first - or couples experience infertility, the doctor will often prescribe clomiphene which is oestrogen antagonist. So it's blocking the effects of oestrogen and basically it's helping ovulation or multiple ovulations in some cases. So that's really the first step on the ladder towards an IVF, and if that doesn't work the couple would then go back and maybe consider IVF. So really that's the first step, I guess, in infertility. A lot of couples are going through that. You usually get about seven per cent of children born in Western countries can be through assisted reproduction with a clomiphene rather than just IVF. So it's quite widespread. Yet again it's just a simple way of disrupting that oestrogen production, which causes more eggs to grow and to be ovulated.

DYANI LEWIS
Importantly the children that result from ovarian stimulation haven't seen the artificial environment of the IVF test tube I guess you could say, but they do still have lasting consequences.

MARK GREEN
Yeah, the study that - yes, the study we saw, the children had changes in their stature. So the things that we were following up were in pre-pubertal children. So we were looking at their growth, their height, their body weight, and the percentage of fat. And we were also looking at their basic endocrine profile in terms of glucose and insulin, and some of the lipids in their bloods. And we found that these children were shorter stature, and - than those of naturally conceived where there was no clomiphene given. And again, mechanisms, there are numerous. And they can include that clomiphene has a lasting effect on the uterus again, after it's been taken. So potentially it's changing the environment the embryo's entering, and therefore the amount of nutrients or the type of nutrients the embryo's seeing. So very subtle effects. We saw it more in male children than female children. Again that potentially is due to the number of women that were recruited, and offspring. So we - in larger studies which are definitely needed, we would see maybe in both males and female children being shorter.

DYANI LEWIS
So what kind of differences in stature are we talking about?

MARK GREEN
Okay, probably about one to two centimetres difference, at the age of about six or seven, we were looking at. So pre-pubertal. In the additional study that we did when we looked at the whole of the IVF process, and in terms of the outcome of those children we saw a two to three centimetre difference in height, and this time they
actually - the opposite in terms of them being taller, specifically the girls. As you pointed out, the difference between the two is that they're - the two different hormones have different actions. Then with the with IVF children you obviously have the process of the IVF itself, and being in the lab, and the media exposure and many other factors, explaining why generally we can see that perturbations around that time are quite critical in terms of the long term health and height of those children. Do we know whether they're going to go on and maintain that height? Potentially yes, but again we need some very large studies to carry on.

DYANI LEWIS
It is still quite incredible that an embryo in the first few days of its life, can have an environment that effects the health of the child many, many years later. How is that events that early on can have lasting effects?

MARK GREEN
It's all to do potentially around the epigenetics, and gene expression, and subtle changes on the DNA of the timing. If we upset the timing and then - and the type of genes that are being turned on, then that can have a long term influence on the organ development for example, or sensitivity to the environment. Obviously an embryo should be set to see a certain threshold of whatever environment that is, and nutrients, and if we change that in some way then once that child is born, then if their expecting to see if they - for example, if they've had low nutrition in utero for whatever reason, and they enter an environment where there's a lot of fast food and a lot of high nutrition, then obviously there's a mismatch in terms of what they expect, and that can obviously add to outcomes in terms of obesity and cardiac stress.

DYANI LEWIS
So the genetics of the embryo aren't changing. They may have the same genetics as their tall parents, but the subtle ways in which different genes are turned on and off, the epigenetics is what's being affected?

MARK GREEN
Yes. That's what we're mainly driving at. That's a very, very complicated process I guess, to understand. But yeah, we're making some inroads into that now.

DYANI LEWIS
Now in spite of all of these things that affect embryo development, the process must be fairly robust because there are certainly a lot of healthy babies around.

MARK GREEN
Yeah definitely. Yeah, we wouldn't be here right? Yes. I guess the difference is, the process can be successful, but - although saying that, obviously IVF itself is not that successful depending on the outcome and the prognosis of the disorder to start with, and with lots of room for improvement. Generally in a healthy fertile couple, you've got a one in four chance every month of conceiving. So we're pretty good at reproducing. So yeah, I guess the difference is what kind of outcome do we have for that child? So we might a child born, but how healthy could it have been, would it
have been, is it - in the long term, and that's the subtle differences in that system.

DYANI LEWIS
Presumably much more to find out about those subtle differences.

MARK GREEN.
Yeah. Unfortunately of course that takes a lifetime and [laughs] we have to wait for those children, in terms of IVF children, as the technology's only 30, 35 years old, to then obviously get to that stage in life, and where normally you'd see some of those outcomes in terms of cardiac risk and obesity in your 50s and your 60s. Obviously none of those children are really quite there yet, and the numbers of children haven't got to that age, so we need to wait.

DYANI LEWIS
Mark, thank you for being my guest on Up Close today and talking with us about reproductive biology and embryo development.

MARK GREEN
You're welcome, thank you.

DYANI LEWIS
Relevant links, a full transcript, and more info on this episode can be found on our website at upclose.unimelb.edu.au. Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 3 July 2013. Producers for this episode were Kelvin Param, Eric van Bemmel, and myself, Dr Dyani Lewis. Audio engineering by Gavin Nebauer. Up Close is created by Eric van Bemmel and Kelvin Param. Until next time, goodbye.

VOICEOVER
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