

## Thalidomide & Primodos in the 2020's: Drug Safety Research & Communication

**Voiceover:** [00:00:02] This podcast is brought to you by the University of Aberdeen. Thank you very much for joining us today and welcome to the Explorathon podcast, a chance for you to hear about some of the latest research projects coming from the University of Aberdeen. Explorathon 2021 is a programme of events, online content and activities brought to you by the University of Aberdeen and other Scottish universities as part of European Researchers' Night, which this year takes place on Friday, the 24th of September. European Researchers' Night is a Europe wide public festival, which brings researchers closer to the public. All events run as part of Explorathon 2021 can be found on the website at [www.explorathon.co.uk](http://www.explorathon.co.uk) and is funded by the European Union's Horizon 2020 Research and Innovation Programme under grant agreement 101036101.

[00:01:19] After listening today, please let us know any comments or feedback by tagging us on Twitter using the hashtag Explorathon21.

[00:01:28] most of us will be aware of instances over the years where drugs have had to be withdrawn over concerns about patient safety. Most of us will be aware of the thalidomide scandal of the 1960s. How do researchers identify potential side effects with drugs, identify other uses for those drugs with side effects? And what can they do to inform the public policy makers and other interested groups about that important work? I'm joined today by Professor Neil Vargesson, Chair in developmental biology at the University of Aberdeen School of Medicine, Medical Sciences and Nutrition. Professor Vargesson has led research investigating the side effects associated with the use of Thalidomide has is also conducting research into another drug used to detect pregnancy in the 1960s and 70s called Primados. Thank you for joining me, Neil.

**Neil Vargesson:** Thanks very much for having me.

**Voiceover:** [00:02:25] So can you tell me a bit about your research interests?

**Neil Vargesson:** [00:02:32]

I'm a developmental biologist, I've been all my life. I'm interested in how you go from a single cell to a fully formed organism with one head, two arms, two legs, five fingers on each hand and toes on each foot. And I'm particularly interested in why that goes wrong. And in and, you know, in three percent of all births around the world, they have some form of birth defects. I'm interested in how birth defects come about and what's normal and what's abnormal and how to treat that.

[00:02:55] And I'm particularly interested in medicines and drug safety. I'm interested in how drugs such as Thalidomide might can cause birth defect. And if you understand how they do that, then you can, one, make safer drugs and make sure that they don't

have side effects. And two, you can understand how birth defects come about in general and perhaps understand that mechanism and therefore come up with some therapeutic strategies. So that's in a nutshell what I'm interested in.

**Voiceover:** [00:03:21] And so you've done research into the side effects associated with Thalidomide. Can you tell me more about your work in that area?

**Neil Vargesson:** Yeah. So Thalidomide is a drug that's still used today, but it was infamous because between 1958 and 1962, it caused an epidemic of at least 10000 birth defects around the world. 10000 children were born with severe birth defects. And this drug was originally marketed to be a sedative that was supposed to be a non-barbiturate based sedative. And in those days, in the 50s and 60s, most sedatives that they are drugs that calm you down and put you to sleep. If you overdose, you could die. So the idea was to come up with a new sedative that if you overdosed, it didn't kill you.

[00:04:09] And thalidomide was invented and it was found to be extremely good as a sedative. And very quickly, it was found to be very, very effective at treating morning sickness and reducing the effects of morning sickness. And it caused, it took a few years, but it had all these kids being born with limb defects, such as Phocomelia, where you have you're missing the long bones of the arm and you have the fingers sticking out the shoulder blade, you know, serious birth defects, damage to the eyes, the internal organs, the face, the genitalia. And it was withdrawn in 1961 at the end of 1961.

[00:04:45] And it's actually 60 years since it was withdrawn. Coming up in December this year. But we don't know how it worked. And what's what's odd about it is the drug is now used again, even though it was withdrawn in 1961. It's now been shown to be really effective in the treatment of anti-inflammatory disorders such as leprosy, multiple myeloma. And it's very useful for cancer because it has this ability to destroy blood vessels. So it's now used again. And we now have a new population of Thalidomide damaged babies and children in Brazil because this drug is used to treat leprosy in Brazil. And unfortunately, they don't have the same strict measures that we have in Britain and Europe. And so you have a new generation of babies. So I was interested in trying to work out how then the drug causes birth defects, because that's what I'm interested in. And if you can understand how it does that, see if you can make forms of the drug that are still affected to treat the condition but don't cause birth defects. And that's what we've done. And we've shown a couple of years ago now that it's the action on the blood vessels that this drug has that destroys the tissue in the embryo. So I mentioned to you that this used it to treat cancer. That's because it destroys the blood vessels of the cancer.

[00:05:56] And so it stops a cancer growing. So in an adult, that's how it works. It destroys the vessels. That same action in the embryo is what causes the damage in the embryo. So that's why you had the limb defects in the tissue damage in the embryo, because the drug targets the blood vessels. So we've shown that. And then

recently we've made new versions of the drug called analogues there. So they're not Thalidomide anymore, that they're based on Thalidomide and they're not they don't affect the blood vessels. And the idea is, is that we hope that they don't cause birth defects. And that's what we're we're up to at the moment. That's really interesting. And we're also working on research related to another drug called Primodos.

**Voiceover:** [00:06:38] Could you tell me about that research? Yeah, Primodos, I got involved in this a couple of years ago. You may have gathered already that I'm a little bit OCD about Thalidomide, it is my focus in life, it's what drives my research interest. And I saw a newspaper headline called The Forgotten Thalidomide. And of course, instantly I'm interested in reading about this because I didn't know there was a forgotten Thalidomide. It's a drug called Primodos.

[00:07:03] And Primodos was a hormone pregnancy test and it was used between 1958 and 1978 before it was withdrawn because of the introduction of the urine based antibody tests that we still use today. Now, the hormone pregnancy test was invented because up until 1958, the way that a woman had confirmation that she was pregnant, we would give a urine sample to a doctor that that urine sample was injected into a female frog or toad and if she was pregnant, the frog or the toad would therefore ovulate eggs the next day. And that's because the hormone system that works in humans for pregnancy and is the same as in a frog and a toad. So that's how it's confirmed in the 50s. How you were pregnant was that you had this test. It's called the Hogben test. Well, of course, that's there's a problem with that because you killing lots of animals off. So there was this big move to move away from doing that. And it was expensive. And so the hormone pregnancy test was invented.

[00:08:05] And this is a basically where you have a manmade version of the two sex hormones in women. That's progesterone and oestrogen. And normally progesterone goes up when you're pregnant because progesterone is required to help maintain the pregnancy and if you're not pregnant, progesterone is low. And if you're in the menstrual cycle, what you'll see is the production goes up during the natural cycle and then as the menstrual cycle ends, is zero. And that's what causes the situation where the idea of the hormone pregnancy test was that you had these high levels of these manmade versions of progesterone and if you were pregnant, it was believed that these manmade versions would be equilibrated out with the natural hormones in the body.

[00:08:49] So if you didn't have a menstrual bleed after taking one of these tablets, they gave you a second one just to make sure that it was a real result. And if after two tablets you still didn't have a menstrual bleed, you were deemed pregnant, but if you had a menstrual bleed that was believed because you had low levels of natural progesterone, you then have this hormone pregnancy test, which gives you a high dose of a manmade version, it goes right down and then you have a menstrual. And so that's how it was supposed to work. And you can already tell it's very hit and miss. It's not the best assay. And there were some people that were not pregnant that were deemed pregnant and there was some people that were pregnant that were deemed not pregnant. But ultimately, there are thousands of people born in the UK and in

Germany and around the world that allege that their mothers' use of this form of pregnancy test led to birth defects. It's called the forgotten Thalidomide because the damage is similar.

[00:09:45] It's not as severe, but you have the limb defects, i.e. internal organs similar to Thalidomide but they're not as severe as thalidomide. So they allege that. Now the manufacturer and the government say it's perfectly safe. So we got involved because the last research done on this was in the 1970s using old fashioned methods. You give it to mice or rats and you can't you see what happens to the embryo. So we did the work in zebrafish embryos and we found with quite high doses that you do get problems.

[00:10:16] And then this this has led to government reviews. It's led to media, it's led to documentaries. And we've done some follow up work on it. And now with really low doses, actually lower than you would see physiologically, we still see damage. So we're still working on this. Our opinion is that this drug in fish at least is harmful. And now what we're trying to do is convert that to human cell lines to say, well, can it can it harms human cells? Because if it does, then it just adds as a bit more weight to the idea that this could have the potential to cause harm. We're still doing that research. And so you can see that the work that you're doing is critical in enhancing drug safety for patients.

**Voiceover:** [00:10:58] Can you talk a bit generally about the work research does to influence drug safety and what role research plays in ensuring drugs are safe?

**Neil Vargesson:** [00:11:07] Yeah, I mean, it goes without saying that most researchers are doing research that's valid to the public and to the community in general and to government policy. You might not think that it is, but it is. You wouldn't be if you didn't find it interesting, other people will find it interesting. Therefore, inherently, it's going to be of interest to some groups. With drug safety particularly, I mean, you're taking drugs that are either known to be teratogens or might be to teratogens or they might believe might be believed to be harmless.

[00:11:37] And what you're then doing is you're testing them in embryos; they're not human embryos, of course, but they're vertebrate embryos and they develop very similarly to humans. Then you're asking that question, what does it do? And so the impact of our research on Thalidomide has been invitations to advise governments around the world about what Thalidomide can do to the embryo, what type of damage patterns it can cause. Was it ever safe to take during pregnancy, that sort of thing, but also to educate professionals. And so our research has also led to requests to educate professionals as well as the public by setting up websites or giving talks or giving lectures to various groups of stakeholders and with Primodos particularly because of the nature of that drug, there's so many people that feel that they're unrecognised they are unrecognised. That has led to government policy changes and the formation of an independent review to look at our research as well as other people, to make a decision on whether there is something to go on with this. And while at the moment our research isn't conclusive, it doesn't say that humans could be damaged by it, the fact

that you've got the government thinking about it, tells you that the research is valid, that there is something the government is at least listening to the research that people are doing and then saying, well, let's have a look at this a bit more detail. So I think drugs,

[00:12:55] drug safety research particularly is very important because we all take drugs at some point in our lives and we all want to make sure that the drug we're taking is as safe as it practically can be. No drug can ever be 100 percent safe, of course, but you want to make sure it's it doesn't have any harmful side effects that are going to surprise us.

[00:13:11] So that's where my thalidomide and Primodos work. It's taken us in a different area than we imagined it would go. We were just doing the research, trying to find out what these drugs do, how they work, can you accept forms? And it's sort of also then moved into this drug regulation and policy research. And it's also led to documentaries. I mean, the Primodos work particularly was featured in two Sky documentaries about Primodos, which was great to do. But again, wasn't the reason why we did the work. But the work has led to those documentaries being produced. So it's quite exciting.

**Voiceover** [00:13:42] And how are you going about getting people interested in this work? Because by the sounds of it, particularly for the work on Primodos, that was done as a result of, you know, you seen a newspaper article and then secured funding. How did you raise the profile of that work and reach out to the key audiences to say we're doing this work, let us share the findings with you.

**Neil Vargesson:** [00:14:10] Yes, that's where social media comes in and networks like that. And you know, if you want to get your research out into the world, what you do is you contact stakeholders, the people that are affected by your drug or by your research or could be influenced by your research. Doesn't have to be a drug. It could be any research. But if you want to get more kudos or you want to get more input from from other people, go to stakeholders, go to the groups of people that are affected by the drug or the condition you're working on, tell them you're doing it. This is what I found. This is what I'm doing. And they will they'll do the rest. They'll go to social media, they're go to Facebook, the MPs, that sort of thing, and they'll get it out there. And that's the other thing I do. I if I feel that the research that we've got is valid to the community,

[00:14:52,780] I contact our local MPs and let them make them aware that we're doing this work and that there are people in our area that have been affected by Thalidomide so there's a relevance for that. And then it's a question of contacting groups like the local media, the local newspapers, writing articles for things like The Conversation.com dot online, which is an online academic news resource which academics write about academic matters for the public.

[00:15:20] And you'll be surprised at how many hits you suddenly find yourself getting and how many emails you get from other people asking what you're doing. It's

interesting research. Could you come and talk about it, to talk to our groups? And it all snowballs from there. And then then you get invitations to do Sky documentaries, or you might not, but that's where it leads to.

[00:15:37] And as a scientist, I think it's really important that scientists do talk to the media and do talk to the public. Don't hide away and just do your own thing. It's an easy thing to do. But why do you do what you do? You do what you do to understand things, and then you should be telling everybody about what you're doing, and so I'm very passionate about public engagement and I think it's very easy to get your work out there and to get people interested in it. You just have to keep going at it.

[00:16:04] And even if you think it's not having an influence, if you start looking at old metric scores of conversation.com, your papers that have been cited, you start looking at the old metrics, you'll see them starting to go up and up and up. And that says there's interest. And then if your work is like drug safety and you've got a drug that's currently happening, you may well get invitations to parliament. And once you've been to Parliament, you then get those networks. You can then email that same group of people to say, look, I'm doing some other stuff now. Are you interested in that? Would you like to know more about it? And then you get an invitation to talk about that as well.

[00:16:40] And that's that's how it's worked, really.

**Voiceover:** [00:16:45] So why do you consider it so important to communicate with the public about your research?

**Neil Vargesson:** [00:16:49] I think it's essential. I mean, I think scientists need to talk to the public about what they do, why they do what they do, why they're interested in it, and what the impact of their research has on them. Now, not everyone's research has a direct impact on the public, right? I get that, but there's a way that you can you can there's always a way that you can make it the interest of the public. And I think it's essential. We need to make sure the public are on board with what science is doing, that they understand what we're currently doing and why. And if it's things like drug research or it's animal research that they understand the reasons why we have to do what we do.

[00:17:24] And there are laws and there are ethical reasons for this, such as we can't work with human embryos or human tissues, so we have to work with animals. But I think it's absolutely essential that we tell the public and we communicate regularly with them. And you'll be surprised that the public are interested in what we do and they are interested in finding out more. And then not as some of the mainstream media sometimes portray the public very simply, they actually want to know and they ask really hard questions. So I think it is really important that we do that and engage with the public and make sure that we get the truth out there.

[00:18:02] And this thing we've heard recently about fake news, this is our opportunity to go out to the public and and explain, well, what we're doing isn't fake. It's real. This

is what we're doing. This is why we're doing it with, for example, Covid-19. You know, we are trying to repurpose some drugs such as Thalidomide, which is what's going on at the moment. And why are we doing it? Well, because these drugs are very good at down regulating the inflammatory response. And so people with Covid-19 have severe lung infections and inflammation of the lungs and Thalidomide could be used for that. So I think, you know, getting things like that out there and dispelling some of the myths is really important.

[00:18:43] But I think also we owe it to the public. I mean, a lot of our research is taxpayer funded. And so the public have a right to know what we're up to. But if you roll all that into one about, you know, being excited about your work, telling people about it, getting people interested, you never know where that's going to end up. And you might find that you're talking to someone that's got money that would like to fund your research or you might find a stakeholder that then all of a sudden says, well, actually, I know some people are affected by that or you end up getting some opportunities that way. So to me, it's essential.

Voiceover: [00:19:14] And so you touched on the Covid-19 pandemic. We've seen with the introduction of the Covid vaccines that many people have been concerned about short term and long term side effects and have alleged that it's not clear whether the vaccines may cause side effects in the long term. What role can research play in reassuring people that another scandal like Thalidomide doesn't happen again?

**Neil Vargesson:** [00:19:41] This is a good question and it's a fair one. I mean, the reason why we re-investigating Thalidomide and Primodos, is that these are drugs that we used a long, long time ago is because people raised concerns about their safety and the right thing was done. Research was done to check how they worked. In the case of Thalidomide, we knew it was bad and we are working out why it was bad. But I think it's absolutely imperative that if people have got concerns about covid vaccines, that those concerns are aired.

[00:20:10] But it needs to be also addressed quickly. And I think given the fact that the Covid-19 vaccines were produced so rapidly and on the market, perhaps it's the fastest I think any vaccine has been put on the market ever. But let me let me reassure you that all of the safety checks that were needed to be done were done and the covid is a fantastic example of science working together. Normally you get different groups working separately from each other. They don't communicate. And to get a medicine or a drug through takes forever because of that, because there's people working on their own individually and they go to the regulator and the regulator asks for more work to do it. This time with covid because you had a world united front and everyone around the world was trying to do the same thing.

[00:20:55] Everyone was talking to each other, communicating with each other, going to the regulators. The regulators were going out saying, we need this, we need this, we need this. Different groups did all this little bits, put it together, hey presto, it worked. So I think that's great.

[00:21:06] And I think that drug safety has become at the forefront of a lot of people's minds. I think the public now also asked more questions from their doctors who didn't used to in the 1950s and 60s. If doctors gave you a tablet or medicine, you just took it. You didn't ask why. Now, I think people do ask questions, but I can say from my own experience of drug safety and the way that medicines are regulated and particularly covid-19, the chances of another disaster like Thalidomide happening are very slim. It's not it's not impossible because sometimes drugs behave differently than you think they should. But we're doing everything we possibly can to make them as safe as possible. And I think covid is a great example of when science works together with the public and government, and they all work together, you can come up with vaccines that are very successful. We now have a vast majority of the UK population double vaccinated.

[00:21:57] This is a fantastic achievement.

**Voiceover:** And moving forward for your own research, what's the next steps?

**Neil Vargesson:** [00:22:07] Next steps for us? We're still working on Thalidomide and Primodos. With Thalidomide we've now got versions of the drug that we think are clinically still relevant but don't cause birth defects. And so we patented those which is which is great. And now we have to screen them in pre-clinical trials on other species, but also human cell lines. And then if they do what we think they do, which is they treat the condition, but they don't cause birth defects, hopefully get that on the market at some point.

[00:22:35] So that's my that's my goal for the next couple of years. And Primodos, we're trying to find the molecular targets of that drug to understand how it works and then to work out, to do more work to show one way or the other; did it cause damage to human embryos? And I think, you know, our evidence in the fish is that it can do in a fish. But fish isn't human. So we just need to do a bit more work on that. So that's why we're following those two up. And it's exciting times. I mean, I think we're in a good position, so hopefully, I'd like to say before I retire, although when I first started working with Thalidomide about 20 years ago, I thought we'd have this nailed in five years. I now have more questions today than I had when I started. So I still hope to get it done by the time I retire. But I'd like to know the molecular pathway. How does a drug actually then cause Phocomelia when you have two fingers coming out of the shoulder. How does it do that? What's the exact, I'd like to say to the public, it does this, it does this, does this, bang. And the same with Primodos. Primodos is no longer used,

[00:23:41] but the components of it still are today, particularly in oral contraceptive medicines, which is a bit ironic when you think that it's used today or components of it, it's still used today to stop pregnancies, but in the past it was used in higher doses to see if you were pregnant. But I'd like to know how that works as well.



[00:23:58] And I think if you understand how the drugs work molecularly, then not only can you understand how to make safer forms of the drugs, but you can also work out how drugs act in general and hopefully make safer drugs in the future.

**Voiceover:** [00:24:11] Thank you very much for joining me today.

**Neil Vargesson:** Thank you.

**Voiceover:** [00:24:16] We hope you find today's podcast interesting, but for now, thanks for joining us. And keep an eye out for our other Explorathon podcasts being launched in September. As I said at the beginning, we'd love to get your comments and feedback on today's podcast, so please use the hashtag Explorathon21 to tag us on social media.

[00:24:38] If you're interested in finding out more about the other events taking place as part of Explorathon 2021 then you can visit the website at [www.explorathon.co.uk](http://www.explorathon.co.uk) Bye for now. This podcast is brought to you by the University of Aberdeen.