From:
To: Community Affairs, Committee (SEN)
Subject: PLEASE USE THIS LETTER FOR THE COMMITTE... Re: Hansard corrections - Support for Australia's thalidomide survivors - 31 January Sydney
Date: Wednesday, 6 February 2019 10:34:43 AM

Following on from my teleconference appearance at the Committee discussing Support for Australia's thalidomide survivors on 31 January, 2019, I would like to clarify and further expand some of the points I raised at the Committee:

First, thalidomide has very many different actions – it has the ability to prevent new blood vessel formation (which is why the drug is used today to treat some cancers); it has the ability to block the inflammatory and immune systems (which is why the drug is used today to treat inflammatory disorders such as complications of leprosy). Long term use in adults can lead to neurotoxicity resulting in peripheral neuropathy.

Second, given these array of actions the drug possesses, thalidomide causes an incredible amount of damage in embryos, which varies in severity between individuals (likely due to differences in timing of exposure). No two thalidomide survivors are identical. Several mechanisms of action in the embryo have been proposed to explain how thalidomide causes damage and are widely accepted (and are not necessarily mutually exclusive – indeed they likely are all intertwined in causing the range of damage); these include the drug's ability to prevent and block blood vessel formation, its ability to induce the loss of cells and tissues as well as through recently identified molecular targets such as Cereblon and SALL4. Though just how these molecular targets result in the actual tissue damage seen in thalidomide survivors remains unknown. Thalidomide's action on nerves and neural crest has also been proposed to be a method of how thalidomide causes damage – however there are several studies indicating that loss of nerves in the chicken embryo does not result in damage similar to that seen in thalidomide survivors. I believe nerves which innervate embryonic tissues quite late in development, exacerbate damage already caused by the drug, making the damage even worse.

I am developmental biologist and I am particularly interested in how thalidomide affects embryos. This remains important to determine as thalidomide is now used successfully to treat a wide range of conditions including multiple myeloma and complications of leprosy. Sadly, there have been recent instances of children with thalidomide embryopathy being born in Brazil, where the drug is used to complications of leprosy. So, can we ever make forms of the drug that don't cause harm to the embryo but retain clinical benefits?. We have dissected the drug' structure to isolate versions of the drug that display each of its known actions and asked which of these known actions causes problems to the embryo. This information will help determine if can make forms of the drug that retain clinical benefits without causing birth defect. We discovered that only the drug's ability to prevent new blood vessel formation in the embryo results in tissue damage, indeed we can reciprocate a lot of the drug's known damage in chicken embryos, including a wide range of damage to the limbs. The other actions of the drug we tested did not cause damage to the embryos – and this indicates that a good starting point to making 'safer' versions of the drug should look at removing the ability to inhibit new blood vessel formation.

Thalidomide is widely believed to cause damage to the embryo in a small time period in early pregnancy – however, several groups have shown and suggested thalidomide might have the ability to damage embryos even in late development, specifically to internal organs. This would indicate there is no time in pregnancy that is safe from the effects of thalidomide. Also given the diagnostic criteria to identify thalidomide embryopathy was devised in the early 1960s and based on the severest cases of damage, it is also possible there maybe a population of people with other (non-classical) damage that are unrecognised. Identifying such people will be very difficult but perhaps revisiting original clinical reports from Britain, Germany and Japan could help, as could looking at the 1964 UK Government Inquiry Report which listed all known cases. The molecular actions of the drug are becoming clearer and these might also help ascertain other damage that might be seen by the drug.

With regards the early onset age related problems currently being seen in and suffered by thalidomide survivors, this is clearly a major issue and requires urgent attention. Survivors have had to use their bodies in ways that have led to increased 'wear and tear' resulting in early onset age related issues, which could include painful neuropathies caused by compression from bones and tissues and perhaps excerbated by the misinnervation of organs and tissues during development (see above).

We also do need to remember that as no two thalidomide survivors exhibit precisely the same damage and as there is variance in survivors needs, any treatment plans devised need to be individually based.

Thank you.

Neil Vargesson
