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Brief Report

'The Legacy of Thalidomide' - a multidisciplinary Meeting held at the University of York, UK on September 30, 2016.

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Abstract

Background
Between 1957-1962 thalidomide was used as a non-addictive, non-barbiturate sedative that also was successful in relieving the symptoms of morning sickness in early pregnancy. Infamously, thousands of babies were subsequently born with severe birth defects. The drug is used again, today, to successfully treat leprosy, and tragically, there is a new generation of thalidomide damaged children in Brazil. While the outward damage in babies has been documented, the effects of the damage upon the survivors as they grow up, the lifestyle changes and adaptations required to be made, as well as studies into ageing in survivors, has received little attention and remains understudied.

Methods/Results
A unique multidisciplinary meeting was organised at the University of York bringing together thalidomide survivors, clinicians, scientists, historians and social scientists to discuss the past, the current and the future implications of thalidomide.

Conclusions
There is still much to learn from thalidomide, from its complex history and ongoing impact on peoples' lives today, to understanding its mechanism/s to aid future drug safety, to help identify new drugs retaining clinical benefit without the risk of causing embryopathy. For thalidomide survivors, the original impairments caused by the drug are compounded by the consequences of a lifetime of living with a rare disability, and early on-set age related health problems. This has profound implications for their quality of life and need for health and social care services. It is vital that these issues are addressed in research, and in clinical practice if thalidomide survivors are to 'age well'.

Background

Landmark papers in The Lancet by Dr William McBride (McBride, 1961) and Dr Widikund Lenz (Lenz, 1962) first drew the medical world's attention to Thalidomide and the extensive damage the drug caused to babies when their mother took it to combat morning sickness in early pregnancy. In the immediate aftermath, much was written about the health of babies affected, the teratogenic effects of the drug and the scientific and legal implications of the 'Thalidomide disaster' (Smithells and Newman, 1992). Given the drug is now used around the world again to successfully treat conditions like leprosy in Brazil, in 2014 a World Health Organisation sponsored meeting of experts (World Health Organisation, 2014; www.who-umc.org/graphics/28280.pdf) reexamined the diagnostic criteria of Thalidomide embryopathy and the mechanisms of causation (Vargesson, 2015). This was in response to a new generation of thalidomide damaged children being seen in Brazil (Schuler-Facini et al., 2007; Vianna et al., 2011; Vargesson, 2013). Yet, the effects of the damage upon the survivors as they grow up, has only recently started to be studied. It is really in the past decade, as Thalidomide survivors reached their 50's, there has been renewed interest in their health and in particular the effects of ageing with Thalidomide embryopathy. In November 2015, a symposium organised by the University of Tokyo focused on clinicians conducting research into ageing and early onset age-related effects in people with Thalidomide embryopathy (Honoshita, 2015).

However, the issues, both practical and clinical, affecting the day-to-day life of Thalidomide survivors have rarely been discussed. In addition an understanding of the long-term consequences of thalidomide embryopathy in survivors remains understudied. A recent meeting in September 2016 organised by Ms Elizabeth Newbronner and Prof Karl Atkin (Department of Health Sciences, University of York) and held at the University of York aimed to start a dialogue to begin to address these issues. The Meeting was a truly interdisciplinary gathering exploring the broader legacy of Thalidomide. It brought together Thalidomide survivors, historians, scientists, clinicians and social scientists to explore what lessons can be learnt from the history and use of the drug, its impact and ongoing consequences today; and how this knowledge can benefit Thalidomide survivors and others with rare impairments.

Legacy of Thalidomide Meeting

The meeting had three sessions each highlighting different perspectives: historical, contemporary and personal. Professor Karl Atkin, Head of the Department of Health Sciences at the University of York, opened the day. He remarked on the importance of understanding the life course when making sense of long-term conditions and in particular, how ageing with a disability creates specific disadvantages which need to be addressed.

The historical perspectives session began with a joint presentation by Dr Ruth Blue, (Secretary of the Thalidomide Society and Curator at the Wellcome Library) and Mr Brian Payne (Trustee of the Thalidomide Society; http://www.thalidomidesociety.org/). In their talk - *The thalidomide story: archives and voices* - they outlined the history of the Thalidomide Society and gave an overview of the practical work they are doing to conserve the history and advise researchers and the media. They also highlighted the wealth of Thalidomide related reports, papers, photographs and films, held by the Wellcome Library

(http://wellcomelibrary.org/). The archive also holds oral history recordings from Thalidomide survivors and will soon hold recordings of parents who took the drug.

Dr Julie Parle, (Honorary Associate Professor in History, School of Social Sciences, University of KwaZulu-Natal, South Africa) a UK-born Thalidomide Survivor, gave a fascinating presentation on the research she and other historians have been doing on the 'hidden histories' of thalidomide's distribution, impact and use in African countries since the 1960s (Klausen and Parle, 2015). Her talk showed that Thalidomide has many 'shadow' histories around the world, even where it has not been proven to have directly affected mothers and babies, and how some Thalidomide survivors are themselves now piecing these histories together, bit by bit. She argued that more archives need to be opened to researchers in pursuit of such histories.

The session concluded with a presentation about *Historic photographs for engagement and outreach: experiences from the Global Health Histories project* by Dr Alex Medcalf (Outreach Historian. Centre for Global Health Histories, Department of History, University of York; www.york.ac.uk/history/global-health-histories/). This project involves using visual images to tell a historical story. He highlighted some of the challenges and complexities they have faced in the project, in particular, the ethics of displaying difficult and sensitive material, and the importance of using the images to assist the argument or provoke additional questions.

The contemporary perspective session was opened by Dr Neil Vargesson, (Senior Lecturer, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen). In his presentation -*Thalidomide: mechanisms of action and current challenges* – he gave an overview of current opinion on the drug's mechanisms, in embryos and in adults (Vargesson, 2015). The drugs action on blood vessel formation, its ability to induce cell death and interact with *Cereblon* are widely accepted as mechanisms of the drug's action. Indeed, he described how the drug's actions on blood vessels can result in a range of limb damage (Vargesson, 2009; Vargesson, 2015; Vargesson and Hootnick, In Press). He also described the advances his team has made in finding a 'safe' form of the drug, retaining the clinical benefits but without the side-effect of embryonic damage (Beedie et al., 2016; Beedie et al. In Press). This is extremely relevant today as sadly new generations of Thalidomide children have been born in recent decades in Brazil as the original drug is used to treat a form of Leprosy (Schuler-Faccini et al., 2007; Vargesson, 2013; Vianna et al., 2011).

The contemporary health of Thalidomide survivors in Sweden was discussed by Dr Shadi Ghassemi Jahani (Consultant Orthopaedic Surgeon, Institute of Clinical Sciences, University of Gothenburg, Sweden). Dr Ghassemi Jahani has been researching the orthopaedic problems experienced by Thalidomide survivors in Sweden as they age (Ghassami Jahani et al., 2014). She set out the findings from her work on osteoarthritis and cervical spine deterioration (Ghassami Jahani et al., 2016) and then went on to discuss her recent work on Health related quality of life. Her research showed that Thalidomide survivors have significantly lower physical health related quality of life compared with the general population.

Ms Liz Newbronner (PhD student, Department of Health Sciences, University of York) then described her research on the contemporary health of Thalidomide survivors in the UK. Despite the drug being distributed in 48 countries, little research into the health of

Thalidomide survivors as they age has been undertaken and the research that has been carried out is limited to just seven countries – Australia (Jankelowitz et al., 2013), Canada (Vermette and Benegabi, 2013), Germany (Peters et al., 2015), Ireland (O'Carroll et al., 2011), Japan (Shiga et al., 2015), Sweden (Ghassami Jahani et al., 2016) and the UK (Nicotra et al., 2016). Findings from a new national health and wellbeing survey of UK Thalidomide survivors (Newbronner and Baxter, 2016), undertaken for the Thalidomide Trust (http://www.thalidomidetrust.org/) were discussed. The data shows that the health of Thalidomide survivors is declining more rapidly than that of their peers in the general population. Whilst this experience is similar in many ways to other people with early onset disability, there are some distinctive aspects and pertinent wider lessons for health and care services. In particular, the complex nature of Thalidomide damage and the implications of comorbidities, both of which call for a strongly collaborative approach between clinicians and Thalidomide survivors.

In the final session of the day, three UK Thalidomide survivors gave their personal reflections on living and ageing with Thalidomide-induced damage. They highlighted the legacy of learning for Thalidomide survivors across the world, other people with rare impairments (especially limb difference), and the clinicians and services that support them. Geoff Adams-Spink (Deputy Chair, European Dysmelia Reference Information Centre; http://www.dysnet.org/), discussed the power of networking between Thalidomide survivors and others with limb difference. He emphasised the scope to use networking to address contemporary issues such as the need for peer support, the development of 'workarounds' to support everyday tasks, and improved access to specialist health services. Mr Rowland Bareham (Chairman, Thalidomide Trust National Advisory Council) focused on the experiences of Thalidomide survivors with hearing damage. Around a third of Thalidomide survivors have total or partial hearing loss and this 'hidden' group of survivors often experience higher levels of poorer mental wellbeing. The day was closed by Dr Craig Millward (Member, Thalidomide Trust National Advisory Council) who spoke movingly about finding out as a young adult that his disabilities had been caused by Thalidomide, and how health problems in middle age had lead him into greater involvement with the Thalidomide community.

Conclusions

The meeting showed that there is still much to learn from Thalidomide, both from its complex history and its impact on peoples' lives today. For Thalidomide survivors, the original impairments caused by the drug are being compounded by the consequences of a lifetime of living with a rare disability, and early on-set age related health problems. Their health and functioning is changing, and this has profound implications for their quality of life and need for health and social care services. Clinicians and healthcare services often fail to understand the complex nature of Thalidomide damage, nor do they always recognise the self-management knowledge Thalidomide survivors have. It is vital that both these issues are addressed in research, and in clinical practice if Thalidomide survivors are to 'age well'. Furthermore, the experience of Thalidomide survivors provides lessons for supporting other people with rare impairments. In particular, there is a need for a flexible response which recognises a person's active engagement with their condition and is sensitive to the consequences of the life course. Finally, the meeting was an important reminder of the continued need for research into drug safety and for pharmacovigilance.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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