Institution: University of Leeds		
Unit of Assessment: C24 Sports and Exercise Sciences, Leisure and Tourism		
Title of case study: Helping people with severe spinal injuries to walk and regain bodily functions: from animals to humans.		
Period when the underpinning research was undertaken: 2007 - 2008		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Dr RM Ichiyama	Associate Professor in Motor Control	06/09/2007 - present
Period when the claimed impact occurred: 01/08/2013-31/12/2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Functional recovery following paralysing severe spinal cord injuries (SCI) has eluded science and medicine for centuries. Research by **Ichiyama** and colleagues has underpinned trials in the USA in humans with severe SCI extending the impact reported in REF2014 (one individual) to several people and, importantly, to further functional recovery (actual walking). Specifically, **Ichiyama** and collaborators used a combination of epidural electrical stimulation of the spinal cord, pharmacological agents and rehabilitation training to enable animals with severe SCI to walk and this provided the essential foundation for translation to humans with severe SCI. These new results are unprecedented as this intervention is the first in medical history to restore walking ability to people with a paralysing complete SCI. In addition, the combination treatment has enabled these people to regain other bodily functions, including bowel and bladder function. This clinical impact has also generated further increased donations for charities and spurred commercial investments in this technology.

2. Underpinning research (indicative maximum 500 words)

The intervention pioneered by **Ichiyama** gains access to spinal circuits controlling locomotion and restores motor function to animals with a complete spinal cord injury (SCI). Following his appointment at the University of Leeds in 2007, **Ichiyama** led the development of a detailed rehabilitative strategy in animals **(R1, R2),** which involved the combination of three elements - epidural stimulation of the spinal cord, daily rehabilitation (locomotor training) and the administration of quipazine (a serotonin agonist). This work **(R1, R2)** was performed in collaboration with researchers at UCLA. This research, which was based on previous proof-of-principle experiments, addressed critical issues including whether epidural stimulation was safe, what the effects of different stimulation regimes were on the animals, and the specific combination of stimulation, drugs and rehabilitation training that delivered optimal results.

Ichiyama and collaborators reported **(R1, R2)** that the intervention allowed animals with a severed spine to take weight-supported steps. They found that epidural stimulation (50Hz) of lumbar segment L2 resulted in weight-supported coordinated plantar stepping in rats receiving a complete spinal transection at thoracic level T9-10; that intraperitoneal administration of serotonin agonist (quipazine) improved functional recovery **(R1, R2)**; and that epidural stimulation combined with serotonin agonists significantly improved weight-bearing stepping **(R1, R2)**. The research also demonstrated that walking ability improved markedly when stimulation was combined with a locomotor training regime **(R1)**. Daily training using these three interventions resulted in stable and consistent stepping patterns, with increased and coordinated muscle activity. Rats with a complete spinal cord transection trained to step under epidural stimulation and serotonergic agonists developed a movement pattern with a narrower base of support better adapted to cope with the lack of postural control **(R1)**. The experiments also demonstrated that applying epidural electrical stimulation daily to the lumbar segments was a safe procedure that could also have further benefits not directly investigated in those studies. For example, a much more efficient recovery of bladder reflexes in treated as compared to non-treated rats was observed.

3. References to the research (indicative maximum of six references)

Web of Science citations as of 13/01/2021. Scopus citations as of 13/01/2021

1. **Ichiyama**, RM, Courtine, G, Gerasimenko, YP. Yang, GJ, van den Brand, R, Lavrov, IA, Zhong, H, Roy, RR, Edgerton, VR. (2008) Step training reinforces specific spinal locomotor circuitry in adult spinal rats. *The Journal of Neuroscience* **28**:7370-7375 DOI:10.1523/JNEUROSCI.1881-1808.2008 [WoS citations: 117] [Scopus citations: 123]
2. **Ichiyama**, RM, Gerasimenko, Y, Jindrich, DL, Zhong, H, Roy, RR, Edgerton, VR. (2008) Dose dependence of the 5-HT agonist quipazine in facilitating spinal stepping in the rat with epidural stimulation. *Neuroscience letters* **438**:281-285 DOI: 10.1016/j.neulet.2008.04.080 [WoS citations: 41] [Scopus citations: 43]

Selected grants awarded to Ichiyama to evidence quality of research:

2018 – 2020 International Spinal Research Trust; Ichiyama (PI). Development of Epidural Electrical Simulation for Bladder Control: Animal Model - GBP193,374

2013 – 2016 Medical Research Council; Ichiyama (PI) - GBP346,736.83. Enhancing functional recovery after spinal cord injuries with combinatorial treatments

2012 – 2015 International Spinal Research Trust; Ichiyama (PI) - GBP91,101 (Natalie Rose Barr Ph.D. studentship). Maximizing activity-dependent plasticity for recovery of function after spinal cord injury

2011 – 2013 Internationale Stiftung für Forschung in Paraglegie; Ichiyama (PI) - CHF150,000. Can the combination of anti-Nogo-A antibody and locomotor training result in beneficial effects on functional recovery?

2011 - 2012 Royal Society; Ichiyama (PI) GBP15,000 (equipment grant). Understanding rehabilitation mechanisms to improve functional recovery after spinal cord injuries

2009 – 2011 International Spinal Research Trust; Ichiyama (PI) - GBP97,174. Locomotor Training in Chronic Adult Spinal Cord Injured Rats: Plasticity of Interneurons and Motoneurons

4. Details of the impact (indicative maximum 750 words)

In REF2014 we reported translation of Ichiyama's work to one person, who recovered ability to stand independently. Here (REF2021) we report substantial new impact: for the very first time in medical history, recovery of walking in people with a paralysing SCI was accomplished by using (implanted) epidural stimulation by two independent groups **[A]**. Another group also using epidural stimulation recently showed recovery of walking in incomplete injury **[B]**. No other forms of treatment have ever shown such level of recovery of walking in chronic completely paralysed people. This substantially furthers the impact reported in REF2014 where Ichiyama's work was translated to one person with severe SCI who recovered independent standing and the ability to voluntarily move the legs when laying down or sitting.

As reported in REF2014, **Ichiyama's** work provided the foundation for the development of the epidural electrical stimulation interventions that have been demonstrated to restore voluntary movement control in people paralyzed by SCI. Specifically, a detailed rehabilitative strategy developed at Leeds from 2007 (i) established the effectiveness and safety in animals of a particular regime of epidural stimulation, locomotor training and drugs and (ii) provided the necessary foundation and model for translation to humans. Professor V. R. Edgerton (UCLA) then took the leading role in translation of the work to humans and achieved the first recovery of standing and voluntary control of movement in a paralysed person using a rehabilitation strategy based on the Leeds' rehabilitation regime (Harkema et al., (2011) Lancet 377:1938-47). That article directly acknowledged the causal relationship between the animal studies (**R1**) and the later human work in its opening paragraph: "Adult spinally transected rats can step only with a combination of interventions of locomotor training, pharmacological intervention, and epidural stimulation (**Ichiyama** et al 2008 [ie **R1**]). This evidence led to the hypothesis that if similar spinal circuits exist in human beings, then electrically stimulating the lumbosacral spinal cord epidurally coupled with intense training could facilitate…"

The new impact reported for REF2021 (Fig.1), substantially extends the number of people who have been treated with this combination approach, and includes people with both complete and partial paralysis. Crucially, it has been shown that this approach furthers **both** the extent of functional recovery (paralyzed people are now walking and showing other improved bodily functions) **and** the number of different groups/universities worldwide now successfully using this intervention. The widely publicised success in the first paralysed person to receive this treatment (original REF2014 impact) has now been applied to at least 29 more people living with SCI with unprecedented further positive outcomes (i.e. restoration of walking), in research centres in the USA (Louisville, Rochester) [**A**] and Europe (Lausanne) [**B**].

In a significant step from the original 2011 Lancet paper, in 2018, Angeli et al reported that 4 people with SCI had been treated with the combination of locomotor training and epidural stimulation derived from **R1** and **R2** **[A1].** Two of these participants, who had motor complete injury and were completely paralysed from a cervical or high thoracic SCI, were able to recover independent overground walking (with only a frame for stability). The other two participants, also with motor complete types of SCI were also treated and showed recovery of independent standing and some treadmill stepping components (e.g., stepping with one leg). Independently, another group (Gill et al 2018) also reported recovery of independent walking ability in a completely paralysed person with epidural stimulation and locomotor training **[A2]**. Prior to this **no other intervention** had ever been able to successfully restore walking ability in people with complete paralysis after a severe SCI.

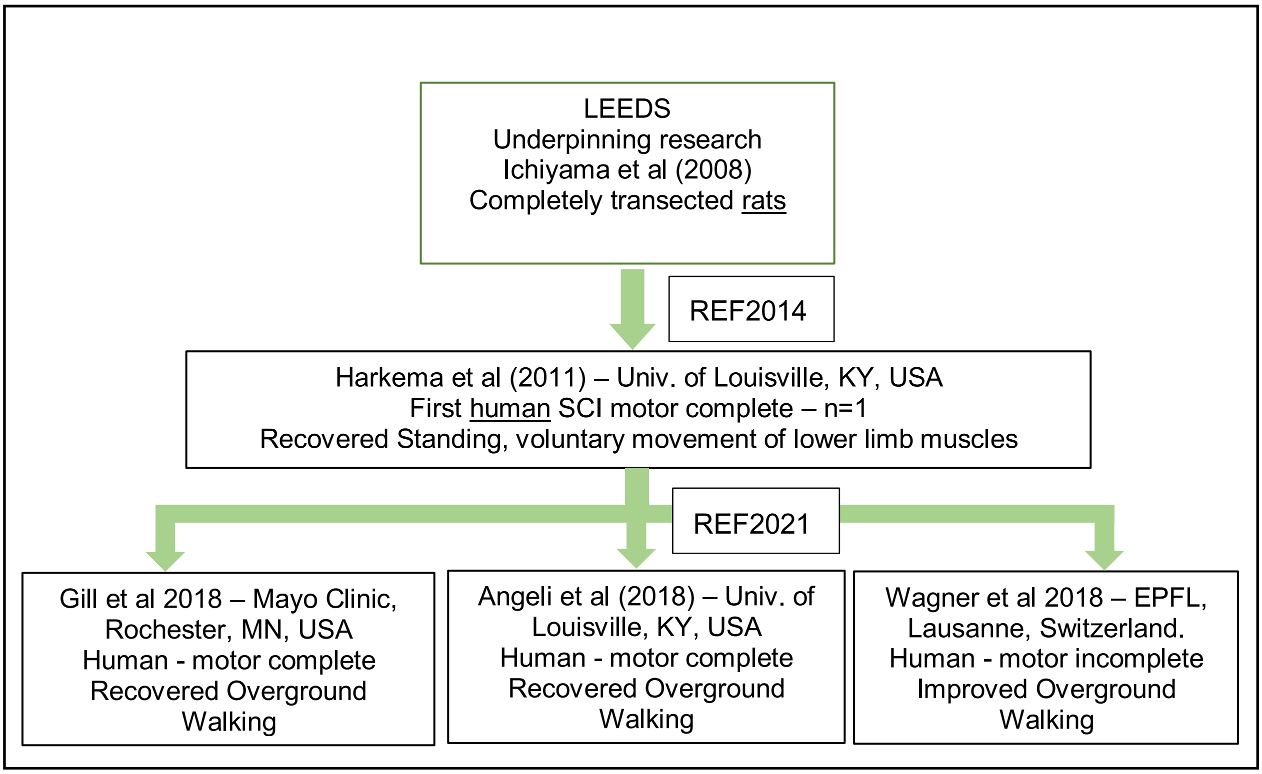

Figure 1. Impact map. The impact reported in REF2014 covered translation of Ichiyama's work to a Case Study reported in the Lancet with recovery of standing. This impact has extended substantially (REF2021) in both breadth and reach, with multiple centres now reporting recovery of actual walking.

Impact on people with SCI

The significance of the human intervention for people with severe SCI is profound. As reported in REF2014, the first person to benefit from the intervention, was a 25-year-old man who had been paralysed below the waist. The benefits to this individual have been long term: "*More than a decade on, he continues to strengthen and expand upon his recoveries*" **[I]**

Further to this original demonstration, other publications have repeated and extended those results **[C]** beyond the impact demonstrated in REF2014. Now, three independent laboratories (University of Louisville, USA; Mayo Clinic Rochester, USA and University of Lausanne, Switzerland) have independently reported recovery of walking ability in people with chronic complete and incomplete spinal cord injuries **[A, B].** The participant who has regained the most function can walk independently (2018) using a walker. She has stated: *"it makes me feel normal again. It makes me feel like I can be an active member of society. "* **[D]**

There is significant activity in the new field with several initiatives extending the reach (more participants) and breadth (investigating effects on other bodily functions). For example, the effects of epidural stimulation on bowel and bladder, sexual and cardiovascular functions have also been reported in USA, Canadian and European clinical settings **[E].** In these studies, a total of 29 people living with SCI are reported as being treated, all showed significant improvement and control of the specified function that was the focus of the studies, including cardiovascular, bowel, urinary, sexual and volitional control functions. In some individuals, improvements were found in more than one of these functions following the treatment. In one study, two participants both showed improvements after the treatment – which took place 5 and 10 years after the original injuries. The importance of these results to the individual participants is immense; in addition this approach to treating SCIs is of high value to healthcare practitioners, providing a new and improved way to treat people living with SCI.

The health and welfare impacts of Ichiyama's research have been of enormous significance to the people treated, and the reach of the research's impact is already developing beyond the immediate clinical setting, as demonstrated by the commercial and public/charitable impacts below.

Commercial Impact:

The commercial medical device sector is investing in technology to support the intervention including established companies in the field and newly created ones. Medtronic devices were used in the currently published reports but those devices were off-the-shelf implants specifically designed to treat chronic pain. Significantly, new companies such as Onward (originally GTX Medical (Netherlands) and NeuroRecovery Technologies (USA), prior to acquisition by Onward during 2020) have entered the market to produce new fit-for-purpose implantable electrode arrays **[F].** From 2014, at least 32 patents specifically covering epidural stimulation electrodes and technology have been filed by different groups, including GTX Medical, Medtronics and various clinical centres and institutes **[G]**.

Impact on the public and charitable organisations:

The breakthroughs based on **Ichiyama's** work have been widely reported in the academic, medical and mass media and have stimulated interest in the new field **[D, H]**. Charities focussed on SCI have reported that the successful outcomes have "further fueled ES research in laboratories and clinics around the globe" and "Donors, active and potential, are excited by the prospect of a therapy" **[I]**. This interest has directly affected the number of research grants funding investigations on epidural stimulation for recovery of function **[J].**

5. Sources to corroborate the impact (indicative maximum of 10 references)

A] First reports of recovery of stepping ability after severe SCI (motor complete):

1. Angeli, CA, et al. (2018) Recovery of Over-Ground Walking after Chronic Motor Complete Spinal Cord Injury. New England Journal Medicine **379**:1244-1250. DOI: 10.1056/NEJMoa1803588

2. Gill, ML, et al. (2018) Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nature Medicine (2018) Letter | Published: 24 September 2018. DOI: 10.1038/s41591-018-0175-7

[B] Report of recovery after partial SCI:

Wagner FB, et al., (2018). Targeted neurotechnology restores walking in humans with spinal cord injury. Nature. **563(7729)**:65-71. doi: 10.1038/s41586-018-0649-2.

[C] Studies extending and replicating the original effects (standing, voluntary control of lower limb muscles) reported in Harkema et al (2011):

1. Grahn PJ, et al. (2017) Enabling Task-Specific Volitional Motor Functions via Spinal Cord Neuromodulation in a Human With Paraplegia. Mayo Clin Proc. **92(4):**544-554. doi: 10.1016/j.mayocp.2017.02.014.

2. Rejc E, et al. (2017) Effects of Stand and Step Training with Epidural Stimulation on Motor Function for Standing in Chronic Complete Paraplegics.. J Neurotrauma. **34(9):**1787-1802. doi: 10.1089/neu.2016.4516.

3. Rejc E, Angeli C, Harkema S. (2015) Effects of Lumbosacral Spinal Cord Epidural Stimulation for Standing after Chronic Complete Paralysis in Humans. PLoS One **10(7)**:e0133998. doi: 10.1371/journal.pone.0133998. eCollection 2015.

4. Sayenko DG, et al. (2014) Neuromodulation of evoked muscle potentials induced by epidural spinal-cord stimulation in paralyzed individuals. J Neurophysiol. **111(5):**1088-99. doi: 10.1152/jn.00489.2013.

5. Angeli CA, et al. (2014) Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain. 2014 **137(5):**1394-409. doi: 10.1093/brain/awu038.

[D]: Examples of television coverage: Journalist CBS New York (2018), "Spinal Cord Study Offers New Hope for Paraglegics"*: https://www.youtube.com/watch?v=izFEOkmWDrM*. BBC News (2018) "Paralysed men walk again with spinal implants https://www.youtube.com/watch?v=iFJv78yGtNM.

[E] Publications on the use of epidural electrical stimulation for recovery of bladder, bowel, blood pressure and other autonomic functions after SCI were first reported in 2016/2017 (clinical data). Here are a few examples of such publications:

Harkema SJ, et al., (2018). Epidural Spinal Cord Stimulation Training and Sustained Recovery of Cardiovascular Function in Individuals With Chronic Cervical Spinal Cord Injury. JAMA Neurol. **1;75**(12):1569-1571. doi: 10.1001/jamaneurol.2018.2617.

Walter M, et al. (2018). Epidural Spinal Cord Stimulation Acutely Modulates Lower Urinary Tract and Bowel Function Following Spinal Cord Injury: A Case Report. Front Physiol. **9:**1816. doi: 10.3389/fphys.2018.01816. eCollection 20

Herrity AN, et al., (2018). Lumbosacral spinal cord epidural stimulation improves voiding function after human spinal cord injury. Sci Rep. **8**(1):8688. doi: 10.1038/s41598-018-26602-2.

Darrow D, et al., (2019). Epidural Spinal Cord Stimulation Facilitates Immediate Restoration of Dormant Motor and Autonomic Supraspinal Pathways after Chronic Neurologically Complete Spinal Cord Injury. J Neurotrauma. **36(15):**2325-2336. doi: 10.1089/neu.2018.6006.

Legg Ditterline BE, et al., (2020) Restoration of autonomic cardiovascular regulation in spinal cord injury with epidural stimulation: a case series. S.Clin Auton Res. 2020 May 13. doi: 10.1007/s10286-020-00693-2.

[F]: Onward https://www.onwd.com/ (originally GTX Medical (Netherlands) and NeuroRecovery Technologies (USA) prior to acquisition by Onward during 2020)

[G]: Selected examples of patents:

- Edgerton et al., University of California & Neurorecovery Technologies (2016) Epidural stimulation for facilitation of locomotion, posture, voluntary movement, and recovery of autonomic, sexual, vasomotor, and cognitive function after neurological injury. US 2016/0175586 A1
- Bradley et al. Boston Scientific Neuromodulation Corporation Valencia, CA (2014) Method for epidural stimulation of neural structures. US 8,923,988 B2
- Harris & Klein, Medtronic, Minneapolis MN (2017) Percutaneous flat lead introducer. US 2017 / 0354804 A1
- Howard et al. Direct Spinal Therapeutics Inc University of Iowa Research Foundation (2019) Transdural electrode device for stimulation of the spinal cord. WO 2019/232544 A1
- Courtine et al. Ecole Polytechnique Federale de Lausanne, Lausanne (2019) System to deliver adaptive epidural and/or subdural electrical spinal cord stimulation to facilitate and restore locomotion after a neuromotor impairment. US 10,265,525 B2

[H]: Example of newspaper coverage: Journalist: NBC News (24/09/18) Paralyzed patients walk again with help from pain stimulator. https://www.nbcnews.com/health/health-news/paralyzed-patients-are-walking-again-help-pain-stimulator-n912541.

Nature (31/07/19): "How a revolutionary technique got people with spinal cord injuries back on their feet." https://www.nature.com/articles/d41586-019-02306-z.

[I]: Letter (dated September 2019) from Christopher and Dana Reeve Foundation – increased interest, increased donations

[J]: Spreadsheet compiling grant information: In the USA, prior to 2013 the NIH had funded 1 grant (~US$ 1.5mi) focused on epidural electrical stimulation for functional recovery after SCI. From 2013, there were 11 grants totalling over US$11mi (not all values were reported, source: National Institutes of Health). Similarly, in the UK and Europe, Research Councils and Charities had funded 4 grants (£1.1mi) before 2013, with a total of 12 (at least £3.7mi; not all values reported) from 2013 (source: ERC, Wings for Life, ISRT, MRC).