**Institution:** University of Leeds

**Unit of Assessment:** UoA26 Sport and Exercise Sciences, Leisure and Tourism

**Title of case study:** Helping patients with severe spinal injuries to stand and step: from animals to humans.

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

Research by **Ichiyama** and colleagues has resulted in humans with severe spinal cord injury (SCI) recovering standing and stepping, combined with other major health benefits including restoration of urinary continence, bowel movements and sexual function. 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 spinal injuries to walk again. This work was the necessary foundation for translation to humans with severe spinal injuries. The publicity surrounding these landmark clinical studies stimulated charitable donations and commercial investment in this new field.

**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 **(1,2,3),** which combined epidural stimulation of the spinal cord with daily rehabilitation (locomotor training) and the administration of quipazine (a 5-HT agonist). This work **(1,2,3)** was performed in collaboration with researchers at UCLA resulting in publications in high impact factor peer-reviewed journals, two of which **(1,2)** have been entered as individual outputs for **Ichiyama** in REF2014. 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 **(1,2,3)** 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 agonists (quipazine, 8-OHDPAT) improved functional recovery **(1,2,3)**; and that epidural stimulation combined with serotonin agonists significantly improved weight-bearing stepping **(1,2,3)**. The research also demonstrated that stepping ability improved markedly when stimulation was combined with a locomotor training regime **(2)**. Daily training using these 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 **(1,2)**. 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 than non-treated rats was observed.

Researcher:
Dr Ronaldo **Ichiyama**, lead investigator, Associate Professor in Motor Control, University of Leeds (2007-present)

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

1. Courtine, G, Gerasimenko, Y, van den Brand, R , Yew, A, Musienko, P, Zhong, H, Song, B, Ao, Y, **Ichiyama**, RM, Lavrov, I, Roy, RR, Sofroniew, MV, Edgerton, VR. (2009) Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nature Neuroscience* **12**:1333-1342 DOI: 10.1038/nn.2401

2. **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

3. **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

Grants:
2013 – 2016 Medical Research Council; Ichiyama (PI) - £ 346,736.83. Enhancing functional recovery after spinal cord injuries with combinatorial treatments
2012 – 2015 International Spinal Research Trust; Ichiyama (PI) - £91,101 (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) - CHF 150,000. Can the combination of anti-Nogo-A antibody and locomotor training result in beneficial effects on functional recovery?
2011 - 2012 Royal Society; Ichiyama (PI) £15,000 (equipment grant). Understanding rehabilitation mechanisms to improve functional recovery after spinal cord injuries
2009 – 2011 International Spinal Research Trust; Ichiyama (PI) - £97,174. Locomotor Training in Chronic Adult Spinal Cord Injured Rats: Plasticity of Interneurons and Motoneurons

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

**Ichiyama's** work provided the foundation for the development of a clinical intervention that has been demonstrated to restore standing and stepping in paralysed patients. 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 stepping in a paralysed patient using a rehabilitation strategy based on the Leeds' rehabilitation regime **[A]**. The widely publicised success in the first paralysed patient to receive this treatment has since been applied to a group of four patients with the same positive outcomes (i.e. restoration of standing, stepping, bladder, bowel and sexual function).

The Lancet article in 2011 publishing the results of the first study of the intervention's effectiveness in humans directly acknowledged the causal relationship between the animal study (references **1** and **2**) and the later human work in its opening paragraph **[A]**.

> "Adult spinally transected rats can step only with a combination of interventions of locomotor training, pharmacological intervention, and epidural stimulation (**Ichiyama** *et al.,* 2008; Courtine *et al.,* 2009). 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…" **[A]**.

The methodology of the human work also grew out of the earlier animal research **[1, 2, 3]**, with **Ichiyama's** work providing the initial model for the location of electrodes (lumbar), the frequency of the regime of stimulation and the parameters of the training regime. The human study did not require the use of pharmacological agents because the initial human subject had not suffered a complete spinal cord injury and therefore had sufficient amounts of serotonin in the spinal cord, unlike the completely transected rats in the original studies **[1, 2, 3]**.

**Impact on people with SCI**

The significance of the human intervention for patients with severe spinal injuries is profound. The first patient to benefit from the intervention, a 25-year-old man who had been paralysed below the waist, said: "This procedure has completely changed my life. For someone who for four years was unable to even move a toe, to have the freedom and ability to stand on my own is the most amazing feeling." **[C]**. The consequences of severe spinal injuries reach far beyond mobility. Once stabilised, those with SCI face a series of obstacles including management of respiratory, genitourinary and dermatological problems. A loss of bladder and bowel control, as well as sexual function, also present severe psychological and physical challenges.

After two years of unsuccessful conventional rehabilitation, the 25-year-old patient had no bowel or bladder control and no sexual function. The treatment resulted in the restoration of voluntary standing and stepping under epidural stimulation **[A]**. This recovery of function only occurs at the time the epidural stimulation is being delivered, but the treatment has transformed the patient's everyday life because the stimulating equipment is fully portable. The patient also recovered urinary continence, bowel movements and is sexually potent **[A**, supplementary data section of paper**]**. Four people with SCI have since been implanted with similar stimulators. According to the leader of the study all four implanted people demonstrated similar outcomes to the first case study **[A]** recovering voluntary motor function and standing ability **[B]**.

**Increased charitable donations and commercial investment**

The health and welfare impacts of **Ichiyama's** research have been of enormous significance to the patients treated, and the reach of the research's impact is already developing beyond the immediate clinical setting. The breakthrough based on **Ichiyama's** work was widely reported in the academic, medical and mass media and has stimulated interest in the new field **[D,E]**. Charities focussed on spinal cord injury have reported increased interest in spinal cord injuries from the general public and a significant rise in donations **[F]**. There is significant academic activity in the new field and the commercial medical device sector is investing in technology to support the intervention.

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

**[A]**: Harkema, S. *et al*. (2011) Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study*. Lancet* **377**: 1938–47 DOI:10.1016/S0140-6736(11)60547-3 including the supplementary data

**[B]**: Letter (dated 12th June 2013) from the lead researcher on the first study in humans of the effectiveness of a regime combining epidural electrical stimulation and rehabilitation training. This researcher is also leader of a second study, paper in preparation, on four more patients.

**[C]**: Journalist "Paralyzed Man Shows Remarkable Recovery," *Science*, May 19, 2011. (http://news.sciencemag.org/sciencenow/2011/05/paralyzed-man-shows-remarkable.html) (accessed 23/09/2013)

**[D]**: Example of newspaper coverage: Journalist, "Small steps, giant leap for treating spinal cord injuries," *Los Angeles Times*, May 20, 2011. (http://articles.latimes.com/2011/may/20/health/la-he-spinal-cord-20110520) (accessed 23/09/2013)

**[E]**: Example of television coverage: Journalist "Paralyzed man stands up thanks to new therapy", CBS Evening News, May 19, 2011 (including video) (http://www.cbsnews.com/2100-18563_162-20064470.html ) (accessed 23/09/2013)

**[F]**: Letter (dated 12th June 2013) from Christopher and Dana Reeve Foundation – increased interest, increased donations