Institution: The University of Manchester

Unit of Assessment: 1

Title of case study:
Design and implementation of a new treatment for dysphagia after stroke

1. Summary of the impact

Dysphagia affects >50% of stroke patients with increased risk of aspiration and pneumonia, costing the NHS approximately £400m pa. Until recently there has been no effective treatment. Over the last 15 years, **Hamdy** has identified the mechanisms underlying dysphagia after stroke and demonstrated that electrostimulation delivered to the pharynx dramatically alters brain regions controlling swallowing beneficially. This work has gone through extensive clinical evaluation and forms the basis of a company, Phagenesis Ltd (~£10m VC funding), which has now commenced implementation of the technology (Phagenyx^{TM}), gained CE marking and has sold >£2.0m of product in the UK, Europe and the Middle East.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

Research activity was carried out from 1996 to the present. Key researchers at UoM:

- **David Thompson** (Professor of Gastroenterology, 1996-date)
- **Shaheen Hamdy** (MRC Clinician Scientist, 2000-2005; Professor of Neurogastroenterology, 2010-date)
- **Qasim Aziz** (Clinical Research Fellow, 1991-1994; Clinical Lecturer, 1994-1998; Clinical Research Fellow, 2000-2002; Senior Lecturer, 2002-2006; Honorary Professor, 2006-2009)

Details of the research innovation

Swallowing problems (dysphagia) after stroke result in major morbidity and mortality yet the treatments available are both disappointing in terms of efficacy and lacking in terms of scientific evidence. The research was developed to revolutionise the management of swallowing after dysphagic stroke. The initial phases of the research are described below:

1. **The cortical organisation of swallowing in health**
   This research demonstrated that the swallowing muscles are arranged in separate areas on the motor strip, with the oral muscles most lateral and the pharynx and oesophagus more medial. However, the most important finding was that in the majority of individuals, one or other hemispheres tended have dominant swallowing representation, independent of handedness (1).
2. **Mechanisms for dysphagia after stroke**
   This research showed that although activity in the stroke damaged hemisphere was reduced or absent in most stroke victims, activity in the undamaged hemisphere was greater in the non-dysphagic than in the dysphagic patients. Thus, the size of the hemispheric projection to swallowing muscles could determine the presence or absence of dysphagia, supporting the concept of cerebral dominance for swallowing (2).
3. **Mechanisms for swallowing recovery after brain injury**
   This research explored the mechanisms of recovery from dysphagia by mapping changes in swallowing representation in a large series of dysphagic stroke patients over several months. In those who recovered swallowing, the area of pharyngeal representation on the unaffected hemisphere increased markedly, suggesting that the recovery depends on the increasing activity in intact pathways in undamaged hemisphere (i.e. compensatory reorganisation) (3).
4. **Inducing reorganisation in swallowing motor cortex**
   This research examined the role of peripheral pharyngeal stimulation as a means of accelerating swallowing reorganisation and recovery. The work was able to show that prolonged electrical stimulation of the pharynx can induce immediate and sustained changes in cortical swallowing excitability (4).

5. Peripheral stimulation and plasticity associated with changes in swallowing behaviour
This research identified the parameters for optimal excitation of the cortical swallowing pathways (i.e. 10 minutes of 5Hz of pharyngeal electrical stimulation at 75% of that maximally tolerated). Critically, when applied to stroke patients, this was associated with an improvement in swallowing using objective measures. The implication from these results was that input to the human adult brain can be programmed to promote beneficial changes in plasticity that result in an improvement of function after stroke (5, 6).

3. References to the research

Below is a list in sequence of the 6 key references that have led to the implementation of pharyngeal stimulation in stroke patients.

1. **Hamdy S**, **Aziz Q**, Rothwell JC, Singh K, **Barlow J**, Hughes DG, Tallis RC, **Thompson DG**. The Cortical Topography of Human Swallowing Musculature in Health and Disease. *Nature Medicine.* 1996;2(11):1217-1224. DOI: 10.1038/nm1196-1217

2. **Hamdy S,** Aziz Q, Rothwell JC, **Crone R**, Hughes DG, **Tallis RC**, **Thompson DG**. Explaining Oro-pharyngeal Dysphagia after Unilateral Hemispheric Stroke. *Lancet.* 1997;350:686-692. DOI: 10.1016/S0140-6736(97)02068-0

3. **Hamdy S**, **Aziz Q**, Rothwell JC, **Power M**, Singh K, **Nicholson DA**, Tallis RC, **Thompson DG**. Recovery of Swallowing after Dysphagic Stroke Relates to Functional Reorganisation in Intact Motor Cortex. *Gastroenterology*. 1998;115:1104-1112. DOI: 10.1016/S0016-5085(98)70081-2

4. **Hamdy S,** Rothwell JC, **Aziz Q**, Singh K, **Thompson DG.** Long-Term Reorganisation of Human Motor Cortex Driven by Short-Term Sensory Stimulation. *Nature Neuroscience* 1998;1(1):64-68. DOI: 10.1038/264

5. **Fraser C**, **Hamdy S**, **Power M**, Rothwell JC, **Tyrell P, Hollander I, Hobday D**, **Williams S, Jackson A, Thompson DG**. Driving Plasticity in Adult Human Motor Cortex Improves Functional Performance after Cerebral Injury. *Neuron*. 2002;34:831-840. DOI: 10.1016/S0896-6273(02)00705-5

6. **Jayasekeran V**, **Singh S**, Rothwell JC, **Tyrrell P**, **Mistry S, Jefferson S**, **Michou E**, **Gamble E, Thompson DG, Hamdy S**. Adjunctive functional pharyngeal electrical stimulation reverses swallowing disability following brain lesions. *Gastroenterology*. 2010;138:1737–1746. DOI: 10.1053/j.gastro.2010.01.052

Key Grants

1. Studies of dysphagia following hemispheric stroke using transcranial magnetic stimulation: assessment of pathophysiology, mechanisms of recovery and outcome. Stroke Association. 1994-1996. £150k. Awarded to **David Thompson**, UoM.
2. Exploring mechanisms of dysphagia in brain injury. MRC. 1996-1999. £280k. Awarded to **David Thompson**, UoM.
3. Characterisation, modulation and therapeutic application of neuroplasticity within human cerebral cortex in health and after brain injury. MRC Clinician Scientist Fellowship. 2000-2004. £600k. Awarded to **Shaheen Hamdy**, UoM.
4. Exploring the functional, behavioural and neurochemical correlates of stimulus-induced cortical plasticity in health and stroke. MRC. 2004-2006. £220k. Awarded to **Shaheen Hamdy**, UoM.
5. Imaging the neuroanatomical, functional and behavioural substrates of cortical swallowing organization. Wellcome Trust. 2007-2010.£260k. Awarded to **Shaheen Hamdy,** UoM.
6. A randomised controlled trial of pharyngeal electrical stimulation in the treatment of dysphagia

after brain injury. NIHR Research for Patient Benefit Scheme. 2009-2013. £265k. Awarded to **Shaheen Hamdy,** UoM.

7. Design and implementation of electrical pharyngeal stimulation in chronic dysphagic stroke. Wellcome Trust. 2011-2014. £990k. Awarded to Daniel Green, CEO of Phagenesis.

4. Details of the impact

See section 5 for corroborating sources S1-S7.

Context

Dysphagia after stroke affects at least 40,000 patients annually in the UK alone, increases mortality (x2.7 relative risk of death) and prolongs hospital bed stay by 10 days. The consequence is that dysphagia in stroke has an estimated £400m cost burden to the NHS each year. Despite this, the treatment of swallowing problems remains difficult, with very few treatments being shown to have any major effect on swallowing disability (S1).

The general goals in dysphagia therapy are to reduce the morbidity and mortality associated with aspiration and chest infections (6% of all strokes), improve nutritional status and return patients to a normal diet with resultant reductions in complications and improvement of quality of life. This is recognised in the UK *National Stroke Strategy* (2007), in which the aim of 'the life after stroke' strategy section is for patients to 'achieve a good quality of life and maximise independence, well-being and choices' (S2). The report goes on to identify seven target outcomes that contribute to achieving this goal. Restoration of swallowing function has the highest impact in almost all of the seven outcomes identified.

Pathways to impact

From these observations, the innovation was created and has progressed to an automated bedside, patient-friendly, battery operated intra-luminal throat (pharyngeal) stimulator for use in patients.

Two patent applications for the UK and Europe have been approved. Through a spin out company (Phagenesis Ltd – see below), the innovation has started to lead to improved patient outcome, shorter hospital stays, and significant financial savings for the NHS. An analysis of phase 2 study data shows that pharyngeal stimulation produces a 25% reduction in aspiration compared with standard therapy and that catheters are well tolerated by patients and are easily operated by carers.

Reach and significance of the impact

Research at UoM funded by MRC and then NIHR RfPB has led to new evidence that pharyngeal stimulation is an effective treatment in stroke. Over the last 7 years, in collaboration with the University of Manchester Intellectual Property Ltd, **Hamdy** has become the clinical scientific officer of a UMIP spin out company, Phagenesis Ltd (S3).

Funded initially by £220,000 of pump priming venture capital money from UMIP and The Liverpool Seed Fund, Merseyside Investment Group, Phagenesis Limited is now managing and leading the programme of work in the area. As industry lead, Phagenesis is now managing and delivering the commercial business based on the technology. Indeed, the company entered into an exclusive funding round arrangement with Angloscientific in 2010, a technology based investment company, and has secured 2 tranches of finance.

Phagenesis Ltd, having successfully raised ~£10m in VC funding, has now commenced implementation of the technology (Phagenyx^{TM}), gained CE marking in 2012 (S4), has been awarded the BioNow healthcare product of the year 2012 and is achieving sales in the UK, Europe and the Middle East. The medical technologies panel of NICE and Health Horizons are currently looking at the product with a view to providing the NHS with clinical recommendations (S5-7). Over 100 patients have now been treated. Sales are now estimated at £2m with orders from the Middle East (£1.5m), UK Hospitals (£0.25m), RoI (£0.3m) and Germany (£0.1m).

5. Sources to corroborate the impact

S1. Geeganage C, Beavan J, Ellender S, Bath Philip MW. Interventions for dysphagia and nutritional support in acute and subacute stroke. *Cochrane Database of Systematic Reviews*. 2012; (10). DOI: 10.1002/14651858.CD000323.pub2

S2. Department of Health. *National Stroke Strategy*. 2007 (p. 34) Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_081059.pdf

S3. http://www.phagenesis.com/

S4. CE marking certificate, awarded July 2012.

S5. Reuters, Electric stimulation may help stroke victims swallow, 24 Feb 2010 http://www.reuters.com/article/2010/02/24/us-electric-stimulation-idUSTRE61N5X320100224?feedType=RSS&feedName=healthNews&utm_source=twitterfeed&utm_medium=twitter&utm_campaign=Feed%3A+reuters%2FhealthNews+%28News+%2F+US+%2F+Health+News%29&utm_content=Twitter

S6. Letter from Professor of Stroke Medicine, King's College London.

S7. Letter from Professor of Stroke Medicine, University of Edinburgh.