

Impact case study (REF3b)

<p>Institution: University of Hull</p>
<p>Unit of Assessment: A3: Allied Health Professions, Dentistry, Nursing and Pharmacy</p>
<p>Title of case study: Changing the paradigm of Chronic Cough – the Cough Hypersensitivity Syndrome</p>
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Research at Hull into hypersensitivity of the airways has provided novel insights into the epidemiology and causes of cough, and its burden on patients. This was achieved by the development of novel methodologies that allow the rigorous and objective testing of new and existing drugs. Patients benefit through the online provision of a diagnostic tool, and Proctor & Gamble have successfully exploited the cloned cell receptors in their drug development programme resulting in a new range of pharmaceuticals for cough. The work has underpinned the standardisation of cough challenge methodology through incorporation in national and international healthcare guidelines leading to a widespread improvement in patient treatment.</p> <p>2. Underpinning research (indicative maximum 500 words)</p> <p>The underpinning research was carried out by Professor Alyn H Morice (Professor of Respiratory Medicine at the University of Hull and Hull York Medical School, from his appointment in 1998 to present), Dr Laura Sadofsky (Post-Doctoral Research Assistant 2006 to 2011; Lecturer 2011 to present), Dr Shoaib Faruqi (Lecturer 2007 to 2009; Consultant Respiratory Physician (2011 to present) Professor Martin Bland (Professor of Medical Statistics, University of York 2009 to present).</p> <p>In 2006 a group led by Prof Morice demonstrated the true prevalence of chronic cough; one in ten of 50 year olds and pointed by its association to the underlying aetiology of a form of reflux (1). Previously cough was neglected despite impacting significantly on patients' quality of life. In a postal survey of patients requesting information following a Radio 4 Case Notes programme on chronic cough, over 800 respondents indicated that they had seen an average of 6 different practitioners without successful diagnosis or treatment of their cough (2).</p> <p>The underpinning research has provided unique insights into the problem of chronic cough as an important component of many common respiratory ailments, proving that novel cough receptors underlie the hypersensitivity seen in patients - for example demonstrating the polymodal TRPA1 nociceptor as an important cough receptor in humans (3). Collaborative work in Yorkshire has shown that approximately 12% of the general population suffer from chronic cough and 7% feel that this interferes with activities of daily living (1). Unsurprisingly, this high incidence leads to a considerable workload in both primary and secondary care. Recently similar findings have been reported in an ERS funded study of 10,000 patients from three continents (presented at 1st International Cough Conference (ICC), 8th November, Guangzhou, China).</p> <p>In order to quantify morbidity caused by chronic cough and to allow interventions to be assessed an objective measure was developed. The Hull Automated Cough Counter (HACC) measures the degree and pattern of coughing both in a clinical and clinical trial environment. The work of the Hull Cough Clinic also developed the international standardisation of cough challenge methodology allowing for the objective quantification of cough reflex sensitivity. These methodologies were standardised in the report of the European Respiratory Society Taskforce (4). With this platform in place we have tested both new (TRPA1 antagonists) and existing (opiate) drugs in an objective fashion. New cough challenge agonists such as cinnamaldehyde have been developed and novel cough receptors described in humans as a result (3).</p> <p>Research undertaken by the Hull Cough Clinic has successfully challenged previous dogma that there were various conditions causing cough and the clinician should identify each cause and treat accordingly. We showed gaseous non-acid airway reflux (as opposed to acid gastro-oesophageal reflux) was the precipitating feature that sensitises the upper airway leading to cough. Through an iterative process relying on extensive patient involvement coupled with repeated refinement in the</p>

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clinic a validated questionnaire was developed, which identifies the distinguishing features of a single overarching diagnosis, the Cough Hypersensitivity Syndrome (5). Validity and sensitivity to treatment effects has been demonstrated in controlled clinical trials.

The consequences of airway reflux include the previously unrecognised worsening of a number of established conditions, such as treatment-resistant asthma, exacerbations of COPD, idiopathic pulmonary fibrosis and cystic fibrosis. The research has provided a paradigm shift in our understanding of the aetiology of these conditions through the clinical recognition of airways reflux and consequent nociceptor hyper-responsiveness.

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

1. Ford AC, Forman D, Moayyedi P, Morice AH. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax* 2006; 61:975-979.
2. Everett CF, Kastelik JA, Thompson RH, Morice AH. Chronic persistent cough in the community: A questionnaire survey. *Cough* 2007; 3(1):5.
3. Birrell MA, Belvisi MG, Grace M, Sadofsky L, Faruqi S, Hele DJ, Maher SA, Freund-Michel V, Morice AH. TRPA1 Agonists Evoke Coughing in Guinea-pig and Human Volunteers. *Am J Respir Crit Care Med* 2009.
4. Morice AH, Fontana GA, Belvisi MG, Biring SS, Chung KF, Dicpinigaitis PV, Kastelik JA, McGarvey LP, Smith JA, Tatar M, Widdicombe J. ERS guidelines on the assessment of cough. *Eur Respir J* 2007; 29(6):1256-1276.
5. Morice AH, Faruqi S, Wright CE, Thompson R, Bland JM. Cough hypersensitivity syndrome: a distinct clinical entity. *Lung* 2011; 189(1):73-79.
6. Dettmar PW, Strugala V, Fathi H, Dettmar HJ, Wright C, Morice AH. The online Cough Clinic: developing guideline-based diagnosis and advice. *Eur Respir J* 2009; 34(4):819-824.

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

The research's identification of the typical clinical characteristics of chronic cough pointed directly to gaseous non-acid airway reflux as the precipitating feature which sensitises the upper airway. This pioneered a markedly different approach to chronic cough aetiology and therapy based on the diagnosis and treatment of reflux and enshrined in the national guidelines. The proof that up-regulation of cough receptors underlies the airway hypersensitivity seen in patients suffering from a range of respiratory disease pointed the way to new therapeutic avenues such as the now widespread use of pro motility agents. The up-regulation of these nociceptors (demonstrated in Ref 3) underpins the hypersensitivity hypothesis and is now a major target for therapy e.g. TRPA1 antagonists such as GRC 17536.

The research has dramatically transformed the view of cough as evidenced by the ERS and European Lung Foundation surveys (2013 Congress) of doctor and patient attitudes. Changing this common symptom from intractable heart-sink into a distinct clinical entity allowing novel treatments greatly impacts on a patient's quality of life.

Specific impacts which have occurred since January 2008 to present include:

- A company and website (see Ref 6) www.selfnostics.com offers online cough diagnosis for patients worldwide, with further advice available at a charge. Since its launch on 1st March 2012 to 31st July 2013 there have been 9,845 page views (Google analytics account).
- Development of the Hull Automated Cough Counter to measure the impact of cough on patients' lives objectively. It is in clinical use in 3 national cough centres (Belfast – testimonial from Senior Lecturer in Medicine; Birmingham and Hull) in the UK and was chosen by the sponsors of 5 clinical studies (including Schering Plough, Philips and Proctor & Gamble) in over 250 patients to objectively measure anti-tussive activity.
- Standardisation of cough challenge methodology and adoption into the international guidelines, allowing for drugs to be tested in an objective fashion and for new agonists to be identified. The

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production of the British Thoracic Society and European Thoracic Society guidelines on chronic cough and European Respiratory Society guidelines on cough methodology. Professor Morice was the Chair and first author on all of these guideline documents. More recently, guidelines on the management of cough in lung cancer have also been produced. The effects of such national guidelines are difficult to quantify, but the websites of the British Thoracic Society and European Thoracic Society indicate a total of over 10,000 downloads of the guidelines demonstrating both the degree of the problem and the success in providing information to address it.

- Clinical studies have been informed by rational clinical practice. Cough is a difficult therapeutic area and most recent studies have failed to show effects greater than placebo. The resulting economic benefits are therefore difficult to quantify since drug development is often halted. However patients are now spared the promotion of drugs that are without an adequately proven evidence base. For example the data from the University of Hull cough clinics demonstrated an insignificant effect of SCH169734 in chronic cough allowing Merck Schering Plough to halt product development. Testimonial – Chief Clinical Scientist, Merck Schering Plough.
- Similarly, butamirate (Novartis Consumer Health) had no activity against challenge whereas the positive licensed control dextromethorphan was shown to be a potent antitussive agent. Unfortunately the latter product continues to be marketed in Europe, but the British consumer has been protected. Testimonial – Respiratory Products, Novartis Consumer Health.
- The underpinning research has also led to nociceptors being cloned and expressed within human cells (funded by Proctor & Gamble) and used in house by the company to test the effectiveness of potential cough products. Clinical research work has supported development of the “Vics First Defence” product range by Proctor & Gamble by demonstrating product efficacy sufficient to obtain licensing authorisation. Continued collaboration between the University of Hull and the Company is seen as mutually beneficial; highly productive in terms of clinical product development and further basic science research. Testimonial – Section Head Life Sciences, Proctor & Gamble.

Media coverage – the underpinning research has been given extensive international media and press coverage including BBC Radio 4 Case Notes and Inside Health, BBC News website, The Daily Mail and The Telegraph (Audience figures are 1.2 million for both Case Notes and Inside Health, verified by Paula McGrath, Producer, BBC Science Radio Unit).

Parts of the underpinning research were undertaken in collaboration with other HEIs as follows:

Ref 1 - Researchers at the University of Leeds co-ordinated the distribution of a questionnaire which gathered survey data for Professor Morice’s research.

Ref 2 - The panel which developed the guidelines was organised and chaired by Professor Morice, and included members from Imperial College London, King’s College London, the University of Florence and Einstein College New York. Professor Morice was lead author on the guidelines.

Ref 3 - The research on human volunteers and human cells was undertaken at Hull, and the research on guinea pigs at Imperial College London.

Ref 5 - The research was predominantly undertaken by Hull researchers, with statistical analysis by the University of York.

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

Website www.selfnostics.com – corroborating that the company and website have been established. Financial information for www.selfnostics.com (available confidentially on request) – corroborating the revenues from the website.

Senior Lecturer in Medicine, Belfast Cough Clinic – testimonial corroborating the value of the HACC in clinical assessments.

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British Thoracic Society cough guidelines (available online at <http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/coughguidelinesaugust06.pdf>) – demonstrating the contribution of the research to altering British guidelines.

European Thoracic Society guidelines (available online at <http://www.ers-education.org/pages/default.aspx?id=2005>) – demonstrating the contribution of the research to altering European guidelines.

Web management data from the websites of the British Thoracic Society and European Thoracic Society – corroborating 22,510 hits on the chronic cough guidelines.

Chief Clinical Scientist, Merck Schering Plough – testimonial corroborating the economic benefits of not pursuing the development of SCH169734 following use of the HACC.

Respiratory Products, Novartis Consumer Health - testimonial corroborating the economic benefits of not pursuing the development of butamirate following use of the cough challenge methodology.

Section Head Life Sciences, Proctor & Gamble - testimonial corroborating the economic benefits of launching the “First Defence” product range following use of the cloned cell nociceptors.