

Institution: University of Oxford
Unit of Assessment: UOA5
Title of case study: <p style="text-align: center;">Nitric oxide: a new first-line treatment for the common and painful condition of anal fissure</p>
1. Summary of the impact <p>Collaboration between Professor Alison Brading at the University of Oxford and her clinical colleague, Professor Neil Mortensen, translated her pioneering research on the ability of nitric oxide to act as a neurotransmitter in smooth muscle into a new treatment for the common, painful, condition of anal fissure. For many years the principal treatment was elective surgery, which carries a risk of faecal incontinence. Nitric oxide donors are now used routinely to limit and resolve the development of anal fissure, improving the lifestyle of sufferers and reducing the economic costs associated with time off work and surgical intervention. The treatment has been in existence since 2000, but since 2008 it has repeatedly been confirmed as the most effective non-surgical intervention.</p>
2. Underpinning research <p>Anal fissure (a split in the lining of the anal canal) is very common. It occurs mostly between age 20 and 50; the life-long incidence in the general population is at least 11% and may be higher owing to under-reporting of symptoms. Sufferers experience intense pain during and after defecation, frequently accompanied by rectal bleeding. The condition often becomes chronic, and in the past this has routinely been managed surgically by lateral sphincterotomy. However, this is an expensive intervention that is associated with a significant long-term risk of faecal incontinence. There has therefore been a need to develop alternative treatments for anal fissure, either as a bridge to surgery, as an adjunct, or ideally as a replacement.</p> <p>In 1993 Professor Alison Brading at the Department of Pharmacology and colleagues including Professor Neil Mortensen, Consultant Colorectal surgeon at Oxford's John Radcliffe Hospital, discovered strong evidence to suggest that nitric oxide (NO) acts as a neurotransmitter in the human anal sphincter. They showed that sodium nitroprusside, which is a NO donor, caused potent relaxation <i>in vitro</i> in isolated muscle strips from the human anal sphincter, and that stimulating the nerves to the anal sphincter caused a relaxation that depended on the release and action of NO¹. It was immediately clear to Brading that it might prove possible to manipulate NO neuro-transmission pharmacologically, and that this could have important therapeutic implications in the management of disordered anorectal function.</p> <p>Brading and colleagues went on to develop these observations in studies that characterised the endogenous pathways that link rectal stretch (following filling) with anal dilation, a key requirement for successful defecation. In the first of these studies, <i>in vivo</i> research was conducted on 12 patients undergoing rectal surgery. NO is synthesised in neurons which contain the enzyme nitric oxide synthase, and this study enabled the structure and distribution of these neurons in the anorectum to be determined. The distribution of NO-producing nerves was found to be consistent with the role of NO in mediating the relaxation of the internal anal sphincter². This research provided compelling evidence that NO was the neurotransmitter that mediates anal sphincter relaxation, but did not directly demonstrate the existence of a nitergic neuronal pathway which could mediate the reflex. However, in a study using a neuronal tracing technique in a guinea-pig model, Brading and colleagues provided direct anatomical evidence of this neuronal pathway in the anal sphincter, including additional evidence that the pathway is responsible for relaxation of the sphincter when the rectum is filled³. A further study in 1996 demonstrated that human rectal circular smooth muscle also receives an inhibitory innervation, which is mediated by NO⁴.</p>

Impact case study (REF3b)

In 2003 Brading and colleagues made some of the earliest observations using neuronal nitric oxide knockout mice, a model that ultimately proved to be of limited use in the study of normal sphincter relaxation. Although in the normal mouse NO is an inhibitory neurotransmitter in the internal sphincter, there are other inhibitory neurotransmitters which appear to compensate for the absence of nitric oxide synthase in knockout mice so that approximately normal function is maintained⁵.

During the period from 1993 onwards, Brading's research in this field provided very strong evidence of the role of NO in the relaxation of the anal sphincter, thus suggesting that NO donors could provide an effective treatment for anal fissure. Initially it was thought that anal fissure was caused by increased anal pressure resulting from the passage of a hard stool, but more recently it was proposed that the pressure relates to the restriction of blood flow, and that successful healing results from treatments targeted at reducing resting anal pressure and increasing blood flow. NO donors have subsequently been used routinely for this purpose (see section 4). Most importantly, recent research demonstrated that the intervention does not affect the adjacent urogenital tract⁶.

3. References to the research

1. O'Kelly T, Brading A, Mortensen N. (1993) Nerve mediated relaxation of the human internal anal sphincter: the role of nitric oxide. *Gut* 34: 689-693. doi: 10.1136/gut.34.5.689 **The first demonstration in vitro of a functionally important nitroergic relaxation in the human anal sphincter.**
2. O'Kelly TJ, Davies JR, Brading AF, Mortensen NJ. (1994) Distribution of nitric oxide synthase containing neurons in the rectal myenteric plexus and anal canal: Morphologic evidence that nitric oxide mediates the rectoanal inhibitory reflex. *Dis Colon Rectum* 37: 350-357. doi: 10.1007/BF02053596 **Together with reference 3 below, this paper provided the first demonstration of signalling between rectum and anal sphincter involving nitroergic innervation. The studies showed how this pathway can link rectal filling to anal sphincter relaxation.**
3. Stebbing JF, Brading AF, Mortensen NJ. (1996) Nitric oxide and the rectoanal inhibitory reflex: retrograde neuronal tracing reveals a descending nitroergic rectoanal pathway in a guinea-pig model. *Br J Surg* 83: 493-498. doi: 10.1002/bjs.1800830417 **See paper 2 above.**
4. Stebbing JF, Brading AF, Mortensen NJ. (1996) Nitroergic innervation and relaxant response of rectal circular smooth muscle. *Dis Colon Rectum* 39: 294-299. doi: 10.1007/BF02049471 **Paper demonstrating a rectal nitroergic innervation in humans.**
5. Jones OM, Brading AF, Mortensen NJ. (2003) Role of nitric oxide in anorectal function of normal and neuronal nitric oxide synthase knockout mice: a novel approach to anorectal disease. *Dis Colon Rectum* 46: 963-970. doi: 10.1007/s10350-004-6694-y **The first use of nNOS knockout mice to explore anorectal signalling with a view to translation.**
6. Ramalingam T, Durlu-Kandilci NT, Brading AF. (2010) A comparison of the contractile properties of smooth muscle from pig urethra and internal anal sphincter. *Neurourology and Urodynamics* 29: 1326-1331. doi:10.1002/nau.20863 **The first demonstration that targeting nitroergic neurotransmission in the anal sphincter does not impair urogenital function.**

Funding for research: This work was funded between 1993-2004 by grants of ~£1.2M from the British Heart Foundation, GlaxoSmithKline, Pfizer and the Wellcome Trust.

4. Details of the impact

Professor Brading and colleagues' research has led directly to the development of new NO-based treatments for anal fissure. NO donor treatments were available before the start of the impact period, but since 2008 they have repeatedly been confirmed as the most effective non-surgical treatment available by leading bodies including the NHS and British Medical Journal (BMJ).

Route to impact

Dissemination of the original research results, through publications in peer-reviewed literature, and through the clinical contacts of Professor Mortensen, gave the impetus needed for a move to clinical trials of NO donors such as glyceryl trinitrate (GTN) for the topical treatment of anal fissure. These included the first randomised controlled trials of GTN from 1994-99. The results were extremely encouraging; Lund & Scholefield, for example, showed that two-thirds of patients treated with topical GTN avoided surgery that would otherwise have been required for fissure healing. They suggested that GTN should become the first-line treatment for anal fissures, with surgery reserved for those not responding to pharmacological treatment⁷. An independent study in 2004 provided evidence that the pain associated with anal fissure can affect health-related quality of life, and confirmed that successful non-surgical interventions such as GTN treatment can lead to a lessening of pain and improvements in vitality, physical functioning and general health⁸.

In addition to the investigation of nitric oxide donors, in 2001 Brading and Mortensen were also responsible for early characterisation of another set of agents that they showed could potentially relax the anal sphincter, including botulinum toxin and calcium channel blockers⁹. However, they found that nitric oxide donors were the pharmacological treatment for which there was most evidence of effectiveness. Subsequent clinical trials have largely confirmed that other agents are less effective than the nitric oxide donors.

Impact since 2008

The fundamental research of Brading and Mortensen means that nitric oxide donors are now in routine clinical use as a principal first-line treatment for anal fissure, and remain the best available medical therapy apart from surgery. Use is by topical application to the anus 3-4 times a day for a period of several weeks, which removes or delays the need for surgical intervention. Nitric oxide donors (in particular GTN) offer an effective and inexpensive (off patent and cheap to produce) therapy compared with the medical and surgical alternatives. The BMJ's Best Practice site currently recommends GTN as an initial treatment for anal fissure¹⁰, as does the NHS Choices website¹¹, demonstrating that NO donor treatment has become standard in the UK. In 2012, a Cochrane systematic review on the treatment of anal fissure identified nitric oxide donors as the only effective non-surgical treatment¹², indicating the lasting and effective clinical translation that has arisen from the pioneering work of Brading and Mortensen on the role of nitric oxide in the human anal sphincter. A BMJ review in 2009 drew similar conclusions; of the available non-surgical treatments, only nitric oxide donors were deemed 'likely to be beneficial'¹³. Since 2008, the increasing use of GTN in developing countries as a cheap and effective alternative to surgery is evidenced by papers such as those published by researchers at the Suez Canal Hospital in Egypt¹⁴ and in India¹⁵, both of which recommend that GTN be used as a first-line treatment.

The impact of these therapies is particularly important as a bridge to surgery and in developing countries where access to surgical treatment is limited. In the UK, with a hospitalisation rate of 1.56 per 10,000 inhabitants per year, surgical intervention for anal fissure represents a significant financial burden, so the provision of medical alternatives has significant financial advantages. The age profile of the patients with anal fissures overlaps with their period of strong economic activity, so time missed from work owing to surgery is a significant consideration, and thus there is also a strong economic impact of treatment.

5. Sources to corroborate the impact

7. Lund JN, Scholefield JH. (1997) A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in treatment of anal fissure. *Lancet* 349: 11-14. doi: 10.1016/S0140-6736(96)06090-4 ***Clinical trial demonstrating the effectiveness of nitric oxide donors in the treatment of anal fissure.***
8. Griffin N, Acheson AG, Tung P, Sheard C, Glazebrook C, Scholefield JH. (2004) Quality of life in

- patients with chronic anal fissure. *Colorectal Disease* 6: 39-44. doi: 10.1111/j.1463-1318.2004.00576.x **Study demonstrating significantly improved quality of life results for patients with anal fissure who receive non-surgical treatments such as GTN.**
9. Cook TA, Brading AF, Mortensen NJ. (2001) The pharmacology of the internal anal sphincter and new treatments of ano-rectal disorders. *Aliment Pharmacol Ther* 15: 887-898. doi: 10.1046/j.1365-2036.2001.00995.x **A review of available non-surgical treatments for anal fissure and their effectiveness, confirming nitric oxide donors as the most reliable option.**
 10. Best Practice. Anal fissure. BMJ Publishing; 25 Mar 2013. Available from: <http://bestpractice.bmj.com/best-practice/monograph/563.html> **Outlines best practice advice for the treatment of anal fissure, provided by BMJ Best Practice; GTN is recommended as an appropriate initial treatment.**
 11. NHS Choices. Anal Fissure - Treatment. Department of Health; 23 May 2012. Available from: <http://www.nhs.uk/Conditions/Anal-fissure/Pages/Treatment.aspx> **Official NHS advice for patients outlining treatment options for anal fissure; GTN is again recommended.**
 12. Nelson RL, Thomas K, Morgan J, Jones A. (2012) Non-surgical therapy for anal fissure. *Cochrane Database Syst Rev* 2: CD003431. doi: 10.1002/14651858 **2012 review concluding that although surgery remains overall the most effective treatment for anal fissure, nitric oxide donors represent the most effective non-surgical treatment.**
 13. Nelson R. (2010) Anal fissure (chronic). *Clinical Evidence*. BMJ publishing; Mar 2010. Available from: <http://clinicalevidence.bmj.com/x/pdf/clinical-evidence/en-gb/systematic-review/0407.pdf> **BMJ Clinical Evidence review of the effectiveness of available treatments for anal fissure, concluding that nitric oxide donors are the only non-surgical treatment likely to be beneficial.**
 14. Ellabban G, Elkazaz G, Hokam E. (2010) Local glyceryl trinitrate versus lateral internal sphincterotomy in management of anal fissure. *World J of Colorectal Surgery* 2: Available from: <http://services.bepress.com/wjcs/vol2/iss1/art12> **Paper by researchers at the Suez Canal Hospital, Egypt, recommending the use of GTN as a first-line treatment for anal fissure.**
 15. Medhi B, Rao RS, Prakash A, Prakash O, Kaman L, Pandhi P. (2008) Recent advances in the pharmacotherapy of chronic anal fissure: An update. *Asian Journal of Surgery* 31: 154-163. doi: 10.1016/S1015-9584(08)60078-0 **Paper by researchers in Chandigarh, India, recommending the use of GTN as a first-line treatment for anal fissure.**