

Institution: The University of Liverpool		
Unit of Assessment: A6 Agriculture, Veterinary and Food Science		
Title of case study: Equine laminitis - changing practice for diagnosis, management, treatment and prevention by understanding the role of endocrine disease		
Period when the underpinning research was undertaken: October 2008 to present		
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:
Professor Cathy McGowan	Professor of Equine Internal Medicine	October 2008 – current
Dr Gina Pinchbeck	Reader in Veterinary Epidemiology	May 2004 – current
Dr Ellen Singer	Senior lecturer in equine surgery	August 1995 – July 2015
Harry Carslake	Senior Lecturer in Equine Internal Medicine (PhD candidate)	December 2012 – current
Period when the claimed impact occurred: 1 st August 2013 to 31 st July 2020		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact <p>Equine laminitis is a highly prevalent, painful, debilitating equine hoof condition, affecting one in ten horses/ponies annually. University of Liverpool research systematically proved the importance of the endocrine disorders that cause laminitis. This research transformed veterinary and equestrian industries' understanding of laminitis, leading to profound change in veterinary practice, nationally and internationally. Instead of solely addressing the resulting laminitis, diagnosis of underlying endocrine disease is now widely utilised, enabling appropriate treatment and informing owners on effective horse management, with improved outcomes. This research has had a major impact on the equine pharmaceutical industry, informing laminitis awareness initiatives and development of novel therapeutics.</p>		
2. Underpinning research <p>In 2007, Professor McGowan pioneered the experimental hyperinsulinaemic model of laminitis, proving her clinical suspicions of the link between insulin dysregulation (which causes hyperinsulinaemia) and laminitis. However, it required systematic epidemiological and clinical research at the University of Liverpool (UoL; 2008-present) to change industry practice. UoL research revealed the high prevalence and importance of the underlying endocrine diseases, pituitary <i>pars intermedia</i> dysfunction (PPID; formerly known as Cushing's disease) and equine metabolic syndrome (EMS) that cause insulin dysregulation and the vast majority of naturally occurring laminitis.</p> <p>UoL research provided the first robust prevalence estimates for veterinary-diagnosed PPID and EMS in field settings [3.1;3.6]. Both conditions showed a very high prevalence in susceptible populations; 21.2% of horses/ponies aged ≥15 years were diagnosed with PPID [3.1] and 23.3% of ponies and cobs, without PPID, had confirmed EMS [3.6].</p> <p>Diagnosis of PPID had been fraught with confusion and complexity, and in order to really effect change in the industry, a simple reliable diagnostic test needed validation. PPID is caused by an age-related degenerative disease resulting in overproduction of several pituitary hormones including adrenocorticotrophic hormone (ACTH). By analysing ACTH against a clinical reference standard, using advanced medical diagnostic statistics, the UoL team determined seasonal diagnostic cut-off values [3.2]. UoL research confirming the very high prevalence</p>		

of both PPID and EMS and ACTH validation research underpinned an international drug company campaign for diagnosis of PPID and prevention of resultant laminitis.

UoL-led histological research overturned the historical view that laminitis was a discrete disease. Laminitis was previously considered primarily linked with severe sepsis or systemic inflammation, and experimental models were based on gastrointestinal perturbations. Detailed histological examination of both experimental [3.3] and naturally occurring endocrine laminitis [3.4;3.5] were required to prove that this form of laminitis was distinct. **This underpinning research led to vets changing practice to seek a diagnosis for the cause of laminitis, and focus diagnosis and management recommendations on the cause rather than simply treating the resultant hoof changes.**

UoL histological research confirmed insulin dysregulation was consistent in naturally occurring laminitis cases, proving the endocrine causal role [3.4]. Amongst PPID cases, laminitis lesions only occurred when horses had insulin dysregulation [3.5], **refocusing endocrine diagnostic testing to include insulin, allowing more effective management in horses with PPID and insulin dysregulation.**

UoL histological research also showed subclinical disease could provide a vital window of opportunity to recognise preclinical laminitis and apply interventions before painful laminitis occurs [3.4]. The research demonstrated that lamellar epithelial cell stretching is the earliest structural event [3.3] rather than previously proposed basement membrane damage. Importantly, the lesion of cellular stretch translated to externally identifiable divergent 'hoof rings'. Historically these easily recognisable rings had been assumed to represent previous episodes of laminitis, whereas our histological research documented that the appearance of these rings frequently preceded lameness [3.4]. **Identification of this subclinical phase means hoof rings are now a key to laminitis prevention, representing a step change in equine welfare by management of the causal endocrine disease before the pain of laminitis.**

3. References to the research

- 3.1 McGowan, T.W., **Pinchbeck, G.L., McGowan, C.M.** (2013) Prevalence, risk factors and clinical signs predictive for equine pituitary pars intermedia dysfunction in aged horses. *Equine Veterinary Journal* **45**, 74-79. <https://doi.org/10.1111/j.2042-3306.2012.00578.x>
- 3.2 McGowan, T.W., **Pinchbeck, G.L., McGowan, C.M.** (2013) Evaluation of basal plasma alpha MSH and ACTH concentrations for the diagnosis of pituitary pars intermedia dysfunction from a population of aged horses *Equine Veterinary Journal* **45**, 66-73. <https://doi.org/10.1111/j.2042-3306.2012.00575.x>
- 3.3 Karikoski, N.P., Patterson-Kane, J.C., Asplin, K.E., McGowan, T.W., McNutt, M., **Singer, E.R., McGowan, C.M.** (2014) Morphological and cellular changes in secondary epidermal laminae in an equine model of insulin-induced laminitis. *American Journal of Veterinary Research* **75**, 161-168. <https://doi.org/10.2460/ajvr.75.2.161>
- 3.4 Karikoski, N.P., **McGowan, C.M., Singer, E.R.**, Asplin, K.E., Tulamo, R.M., Patterson-Kane, J.C. (2015) Pathology of natural cases of equine endocrinopathic laminitis associated with hyperinsulinaemia. *Veterinary Pathology* **52**, 945-956. <https://doi.org/10.1177/0300985814549212>
- 3.5 Karikoski, N.P., Patterson-Kane, J.C., **Singer, E.R.**, McFarlane, D., **McGowan, C.M.** (2016) Lamellar pathology in horses with pituitary *pars intermedia* dysfunction. *Equine Veterinary Journal* **48**, 472-478. <https://doi.org/10.1111/evj.12450>
- 3.6 **Carslake, H.B., Pinchbeck G.L., McGowan, C.M.** (2020) Equine metabolic syndrome is highly prevalent in UK native ponies and cobs with modifiable risk factors *Equine Veterinary Journal*. 30 October 2020 <https://doi.org/10.1111/evj.13378>

4. Details of the impact

Laminitis is a painful condition of the lamellae within the equine hoof, which affects up to a third of equids during their lifetime. For example, in the UK, an estimated 96,000 horses/ponies develop laminitis annually (based on an equine population of 1,000,000 with an incidence of 9.6 'new' laminitis cases per 100 horse-years-at-risk)¹. The prevailing approach to laminitis by simply managing hoof damage has been overturned by UoL's demonstration of endocrine disease as a distinct, and most prevalent cause of laminitis.

Consequently, the management of laminitis has been re-directed to investigating and treating the underlying cause starting with the diagnosis of endocrine disease using simple and well validated testing. Combined with the demonstration that divergent hoof rings could be used for early detection of laminitis, this has enabled intervention even before the onset of lameness. Re-focusing management is reported by veterinary surgeons to have improved laminitis outcomes, nationally and internationally [5.1;5.2].

Change in veterinary practice: Diagnosis and treatment of endocrine disease in horses presenting with laminitis

UoL epidemiological research demonstrated that both pituitary *pars intermedia* dysfunction (PPID; formerly known as Cushing's disease) and equine metabolic syndrome (EMS) are highly prevalent, highlighting the considerable proportion of the equine population that are at risk of developing laminitis. Moreover, insulin dysregulation, which is associated with these two endocrine diseases, was identified as the cause of laminitis in the vast majority of cases. Consequently, diagnosis of the underlying cause of laminitis is now considered to be vitally important for informing the treatment, prognosis and long-term management of affected animals, evidenced through surveying veterinary surgeons [5.1;5.2] and data from laboratory testing [5.3;5.4; Figure 1].

In a 2017 survey of UK veterinary surgeons, 84% reported that their diagnostic approach to laminitis cases had changed since they graduated, with increased use of endocrine testing being the most frequently reported change (89%) [5.1]. Overall, 99% of UK vets reported undertaking endocrine testing for laminitis cases at their initial and/or subsequent examinations [5.1]. The same questionnaire was also used to survey North American veterinarians, with similar results [5.2].

The survey results are supported by data from Boehringer Ingelheim Animal Health (BI), the pharmaceutical company that took on the marketing of the only licensed pharmaceutical for treating PPID (Prascend) and have financed diagnostic testing as part of their veterinary support package, with 90,000 tests since 2013. Currently 547 UK veterinary practices participate in their "Talk about Laminitis" (TAL) scheme [5.3] with additional international participants. BI represents only part of the diagnostic testing performed for endocrine disease annually internationally, and figures from three UK laboratories show that the numbers are much higher with around 40,000 horses tested every year since 2016 [5.4; Figure 1].

¹Pollard, D., Wylie, C.E., Newton, J.R., & Verheyen, K.L.P. (2019). Incidence and clinical signs of owner-reported equine laminitis in a cohort of horses and ponies in Great Britain. *Equine Veterinary Journal*. **51**, 587-594.

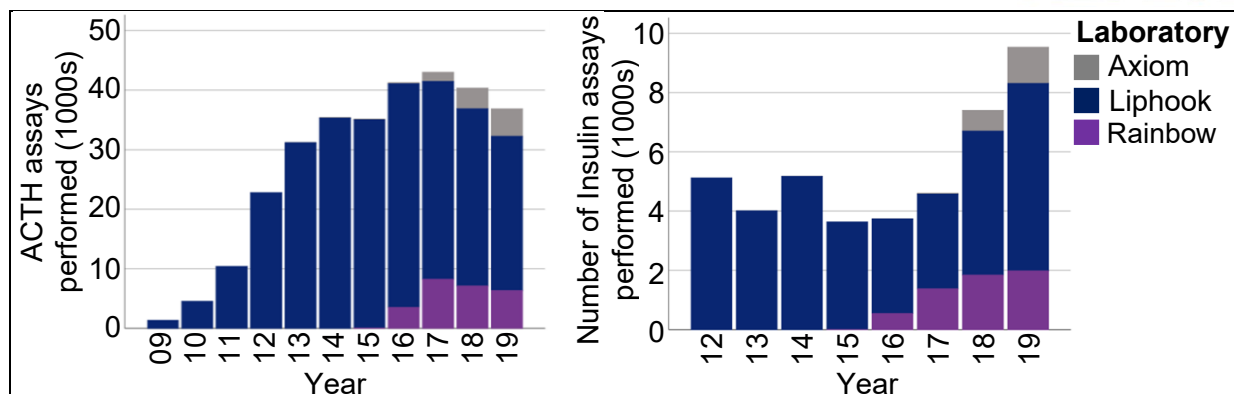


Figure 1: Bar charts showing number of ACTH (for PPID; left) and insulin (for EMS; right) assays performed annually at three major UK equine diagnostic laboratories.

Previously, treatment of laminitis by simply managing lameness often led to recurrent or chronic laminitis and was associated with increased risk of mortality. Increased awareness of the underlying endocrine cause has enabled effective interventions, with PPID treated medically using a dopamine agonist, pergolide (Prascend), while EMS is managed principally by a programme of dietary modification and exercise [5.8]. The impact is evidenced by the investment in, launch and sales of Prascend by BI, where the likelihood of diagnosis and treatment of this condition in the UK has increased from 1% of horses presenting with laminitis in 2000 to 94% in 2019 [5.3]. Approximately 19,000 horses were being treated with Prascend in 2019 (compared to 10,800 in 2013). This represents an estimated retail value of approximately GBP7,500,000. For EMS, BI have invested in development of a nutraceutical and pharmaceutical (SGLT2 inhibitor) [5.3].

In a further survey of UK vets in 2019, 88% of respondents considered that diagnosing an endocrine disorder improved laminitis case outcome [5.1]. Approximately 90% of UK vets [5.1] and 99% of US vets [5.2] considered that treatment of EMS or PPID is effective in preventing further laminitis episodes.

Detection of laminitis can be performed earlier with recognition of divergent hoof rings

This key finding has been picked up by the industry, as evidenced by “Study: Laminitis May Leave A Calling Card Before It Strikes” on The Paulick Report, North America's leading independent Thoroughbred racing website; and shared sites, e.g. the American Farrier's Journal [5.5].

Change in industry practice: Increase in horse owner and equine industry awareness of the role of endocrine disease in laminitis

In 2011, BI surveyed horse owners and reported that only 10% correctly identified that access to lush pasture on its own is unlikely to cause laminitis, without the presence of an underlying endocrine disorder. Addressing this knowledge gap, UoL published an open access review article entitled ‘Paradigm shifts in understanding equine laminitis’, which has been widely adopted within both veterinary and horse owner educational resources [5.6] and attracted unsolicited accolade from a USA based group representing thousands of horse owners [5.7]. Horse owners are now aware of the relationships between endocrine disease and laminitis, evidenced by owners presenting their animals for veterinary care for endocrine disease (see published case series from veterinary hospitals [5.8] and industry press [5.9]). Prof. McGowan was recognised for her “lifetime hoof-care accomplishments” by being inducted into the American Farrier's Journal Hall of Fame in January 2020 [5.10].

Key publications from UoL's underpinning research have been utilised in BI's continuing veterinary and horse owner disease awareness initiatives, which aim to raise awareness of

the underlying endocrine causes of laminitis, with the UK launch of “Talk about Cushing’s” in 2011 and its replacement with “Talk about Laminitis” (TAL) from 2012 onwards [5.3;5.6]. The increasing numbers of laminitis cases tested for endocrine disease each year following the TAL scheme demonstrates increasing owner awareness.

In conclusion, our research - discovering the importance of endocrine disorders in causing laminitis combined with new knowledge of laminitis pathology, highlighting a vital window of opportunity to recognise preclinical laminitis and apply therapeutic interventions before painful laminitis occurs - has led to a profound change in management of horses with laminitis. Redirecting management of laminitis from the lameness itself to the underlying endocrine disease has empowered veterinarians and owners to seek a diagnosis of endocrine disease and use that to improve treatment of animals affected by laminitis as well as implement prevention strategies minimising recurrence for the benefit equine health and welfare, nationally and internationally.

5. Sources to corroborate the impact

- 5.1 Translating research into practice: adoption of endocrine diagnostic testing in cases of equine laminitis. *Vet J.*, in press (March 2021). (Results of UK based 2017 & 2019 vet surveys.)
- 5.2 Survey of Perspectives on Veterinary Diagnosis and Management of Laminitis in the Field: USA Survey (same questionnaire as 5.1, with 99% US vets considered that treatment of EMS or PPID is highly effective in preventing further laminitis episodes).
- 5.3 A letter, from Boehringer Ingelheim Animal Health Head of Business UK, including numbers of endocrine samples tested and participating veterinary practices in their PPID awareness initiative, pharmaceutical treatment data, details of their investment in developing novel laminitis therapeutics, patents, underpinned by Professor McGowan’s research and contribution as a key opinion leader.
- 5.4 Spreadsheet of annual numbers of laboratory submissions for measurement of ACTH and insulin in laminitis cases between August 2013 and July 2020 (Liphook Equine Laboratory, Axiom Laboratory and Rainbow Equine Laboratory).
- 5.5 Detection of laminitis can be performed earlier with recognition of divergent hoof rings. “Laminitis leaves a calling card before it strikes” – the Paulick report (and shared sites).
- 5.6 ‘Paradigm shifts in understanding equine laminitis’ A key secondary output from the underpinning UoL research. Publication of this open access review article has been widely adopted within both veterinary and horse owner educational resources, including the Talk about Laminitis website (screenshots attached).
- 5.7 Letter from Equine Cushing’s and Insulin Resistance Group Inc. represents an unsolicited accolade following publication of the review [5.6] from a USA based group representing thousands of horse owners.
- 5.8 “Treatment of equine metabolic syndrome: A clinical case series” demonstrating increased owner awareness of the role of endocrine disease in laminitis by presenting their horses for veterinary treatment and USA based “The Horse industry” article based around the publication.
- 5.9 “Stamping Out Laminitis” An equine sanctuary has eradicated cases of laminitis through a blood (endocrine) testing programme. Horse Magazine – demonstrating increased owner awareness of the role of endocrine disease in laminitis with industry press information on the topic.
- 5.10 Farriers hall of fame: Professor McGowan was recognised by Farriers and Vets by a USA based “Farrier’s Journal” industry publication award for her “lifetime hoof-care accomplishments”. The nomination was based on her work on endocrine laminitis.