PART 1

Overview: From Basic Research to Caring for the Laminitis Patient
CHAPTER 1

Historical Perspective on Equine Laminitis

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Historical records reveal considerable well-documented evidence of Equine Laminitis as mankind has used horses throughout history. An excellent review of the entire history of laminitis was published by Wagner and Heymering in 1999 [1], and it is the purpose of this discussion to examine the history of Equine Laminitis as seen in the veterinary medical literature from 1800 to the present day.

Mention of laminitis associated with pasture exposure is conspicuously absent from the veterinary literature before approximately 1940. Absent also is reference to any particular breed predisposition to laminitis, or of obesity leading to the disease. Hormone-related endocrinopathic laminitis, the most common form of the disease today, is a relatively recently described veterinary diagnosis [2] and follows closely the first description of human metabolic syndrome in 1988 [3]. In industrialized countries during the 1900s, large numbers of horses were in daily use, and observations regarding the perceived primary causes of laminitis and response to treatments are recorded in detail [4].

In 1906, an observation was recorded that “…laminitis has been described as occurring when the animal is at grass, and when all causes – at any rate, active ones – have appeared to be absent.” H. Caulton Reeks was a Fellow of the Royal College of Veterinary Surgeons and, quoting a case history attributed to W. Stanley Carless (Veterinary Journal, vol. ix, p. 176) in his classic 1906 “Diseases of the Horse’s Foot” [5], he describes an obese mare developing severe laminitis on pasture:

“On July 3 an interesting case of laminitis came under my notice. The subject was a mare, eight years old, which had been running on the common here for some months, and was taken up on the night of July 2 by a boy, who did not observe anything amiss with her. The following morning, on the owner going to the stable, he found the animal in great pain, and when all causes – at any rate, active ones – have appeared to be absent.”

This may be the first recorded reference to pasture-associated laminitis (and laminitis associated with obesity). Relatively rare 110 years ago, this classic association between clinical laminitis and horses and ponies grazing pasture was not generally made until recently. Many causes are listed pre-1940, but not pasture.

By 1800, the terms ‘founder’ and ‘laminitis’ were both used in the literature. While the exact mechanism(s) resulting in laminitis were not understood, the conditions associated with it were well documented [6]. One of the primary causes listed was excessive concussion to the feet of exhausted horses. What seemed perplexing was that an animal doing the same work and receiving the same care and feed as other horses could develop the disease while others did not. It was thought by some authors that an unknown ‘excitatory factor’ must have affected the animal’s physiology, such as a core temperature change brought on by drinking cold water while very hot, or a cold draft that cooled a hot, standing horse too quickly [7].

The earliest reports of adverse effects from a particular feed are attributed to the Hittites in 1350 BC, where feeding barley was observed to result in ‘foot problems’ [8]. It was later established that feeding excessive barley, wheat, or corn could cause laminitis. Early authors also recognized that fever from infections could bring on the disease, and that laminitis was seen often seen after a horse had a severe illness resulting in diarrhea or pneumonia. This was commonly referred to as ‘metastatic laminitis.’ The use of cathartic medication was also reported to result in laminitis, as well as retained placental membranes in mares [9]. Additionally, it was well known that a horse with a severe injury to a limb could develop laminitis in the foot of the opposite limb if a sling was not used for support of the animal during recovery [4].

In 1915, the population of horses, ponies and mules in the United States peaked at 26.5 million [10]. This equated to one equid for every three people in the nation. With the advent of mechanized farming and the introduction of the automobile, the horse rapidly became functionally redundant. No longer needed for their role in war and as a ‘beast of burden’ in agriculture, the horse population declined dramatically and breeds of working horses virtually disappeared.

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Following World War II, horses became ‘leisure animals,’ relegated principally to sport and recreational purposes. In the USDA Yearbook of Agriculture (1942), mention is made of laminitis being caused by over-feeding, chiefly on grains but also green plants or any palatable feed consumed to excess [11]. A lifestyle lacking routine strenuous exercise along with ready access to abundant feed was imposed on a population of horses and ponies genetically predisposed to be ‘easy keepers,’ ones that required less food than others to maintain and exceed their optimum weight. No longer ‘working horses,’ these animals were now susceptible to a new form of laminitis linked to obesity and insulin resistance [12].

Equine Laminitis Treatments from the 1800s to the Present Day

Treatments for laminitis described throughout the nineteenth century cited bleeding via jugular, toe, or coronary band phlebotomy in volumes of up to 6–8 quarts (ca. 7–9 liters) as absolutely essential [13]. Some practitioners monitored the digital pulse in the foot and bled the animal until the pulse was no longer palpable over the palmar digital artery. It was believed that if bleeding was performed sooner rather than later, less damage would occur within the foot. Even after 1900, when the practice of bleeding was for the most part abandoned by veterinarians, some still insisted it was indicated for acute laminitis [14]. The stated purpose was to lower blood pressure in the extremity, which then reduced the pressure inside the hoof capsule.

Other early practices to treat acute laminitis were to dose orally with diuretics such as potassium nitrate in the water three times a day [15]. Salt petre was also used as a diuretic aimed at lowering blood pressure. Removing all cereal grain from the diet and feeding only forage was a recommended treatment [16]. If the case involved over-consumption of grain, a cathartic such as tartar emetic was given or a bran mash fed to evacuate the bowel. Caution was recommended, however, as excessive use of cathartics was suggested to actually cause laminitis in horses [4].

Treatment of the feet during a bout of laminitis usually included the removal of shoes when possible. Most early authors advocated using cold water on the feet [11]. It was suggested that this could be accomplished by standing the horse in a tub with ice, if available. Some described using warm water for 20 minutes, then switching to cold. Early in the twentieth century, the US Calvary used ice if available up to the knees and hocks [16]. When the affected horse was not standing in cold water, it was encouraged to lie down by providing it with a well-bedded stall. Bran or linseed oil poultices and ointments such as arnica were applied to the feet to soften them and reduce inflammation [4, 14].

Pain control was of great interest to early health providers working with laminitic horses. Many authors stated that the pain of laminitis was greatly relieved by the horse lying down [15]. To help control pain, Dadd recommended using hops or poppy heads (opium) [17]. Youatt recommended using digitalis as a sedative and nitre (potassium nitrite) to cool the feet in acute laminitis [13]. The 1918 U.S. Manual for Stable Sergeants recommends administering an oral tincture of Cannabis indica for the control of excessive pain. Interestingly, it was also the drug of choice for the control of colic pain in cavalry horses [16].

Exercise was then, as it is today, a controversial issue. By the early 1900s exercise was encouraged after recovery had started and the horse was willing to move on its own. It was then recommended that the exercise be gradually increased until soundness returned [4, 16].

From 1800 to 1920, the main cause of laminitis cited in the literature was that due to excessive concussion to the feet. Horses worked long hours pounding their feet on very hard surfaces, unlike our sport horses today, which perform on very controlled surfaces to protect their limbs. It is interesting to note that horsemen believed it to be important to condition horses’ feet before working them intensely to prevent this form of the disease. They knew that exercise made the foot stronger and the lamellae less likely to be injured by concussive impact. Perhaps coincidentally, the only reference to obesity found in this 1800–1920 literature was advice to “…not work a plethoric horse hard before the feet are in condition” [18]. Plethoric means ‘large or excessive,’ so this statement is assumed to refer to a horse that was heavy and out of condition and therefore without feet in good condition for work [4]. Authors also cautioned against over-working a green horse until its feet were conditioned to hard work. This concept that exercise strengthens the foot seems to have been lost on many horsemen today, who often allow animals to largely stand idle in stalls. From 1920–1940, little new information about laminitis is found in the literature. The sections on acute laminitis and its treatment in the USDA Diseases of the Horse are virtually identical in the 1911, 1928, and 1942 editions.

Changes in Pasture from 1920 to the Present Day

The first reference to pasture as a suspected cause of laminitis was published in the Yearbook of Agriculture 1942. In fact, pasture was cited in that reference as the most frequent cause of the disease: “Overeating and consumption of green plants…is the most common cause…” [11]. This seems to signal the start of an era in which the most common form of laminitis is what we now call the ‘pasture-associated laminitis’ form of endocrinopathic laminitis.

The factors that increased either the incidence and/or the reporting of cases of pasture-associated laminitis after 1942 are unclear, but the following factors may have played a role. Widespread pasture improvement in the United States through advances in agronomy practices may have increased exposure of horses to pastures that were primarily meant to provide forage for production animals (especially cattle). These pastures...
frequently contain cultivars of grass species that have been selected for higher levels of nonstructural carbohydrates than native grasses. Elevation in the nonstructural carbohydrate content of these grasses is observed primarily in the spring and the fall seasons, which is the same pattern of seasonality that is noted in pasture-associated laminitis in horses and ponies.

Another major change that occurred was to the horse itself. No longer a work animal, horses began to lead a more sedentary lifestyle. The greatly reduced workload, along with an increase in caloric intake from abundant rich grass, may have contributed to the burgeoning rate of equine obesity. Overweight horses are prone to develop insulin resistance and laminitis when grazing spring and fall grasses. Thus, horses may have been put at risk for laminitis from eating heavily improved grass by way of a newly described pathway referred to as endocrinopathic laminitis. This form of the disease is associated with elevated blood insulin levels; laminitis can occur repeatedly, eventually crippling the horse [19]. By the 1960s, the literature commonly lists grass as a cause of laminitis [20]. It is interesting to note that feral horses living on unimproved pastureland in the west seem to be spared this form of laminitis (D. Hyde, personal communication to D. Walsh).

It appears that this form of laminitis could be a man-made problem, one which science should be able to correct using responsible agricultural husbandry practices. Research to understand the pathophysiology of equine metabolic syndrome (EMS) and pituitary pars intermedia dysfunction (PPID) – both disorders that result in endocrinopathic laminitis – is ongoing and described in detail in the following chapters.

Modern Advances in Equine Laminitis Research: Development of Experimental Models

Equine Laminitis has been described since antiquity as an often fatal and therapeutically intractable disease of the equine foot [21, 22]. For several hundred years, information about Equine Laminitis has been gleaned from the observation and treatment of naturally occurring cases (as described above); advances in knowledge of the disease via this mechanism were painstakingly slow and yielded little conclusive information about how laminitis developed or how the condition could be effectively treated.

It was not until the development of several experimental models of laminitis over the past 40 years that major insights have been gained into the pathophysiology of the condition [23–26]. Reliable, consistent induction of laminitis in a controlled fashion has allowed modern researchers not only to investigate the mechanisms and pathways by which laminitis develops but also to evaluate the efficacy of various treatment modalities that have been suggested to be effective for the condition. In fact, one model in particular – the alimentary carbohydrate overload model (discussed further below [23]) – has been instrumental in this regard, as this model has been used to document the efficacy of one of the only consistently effective strategies for the treatment and prevention of sepsis-related laminitis, distal limb cryotherapy [27–29].

With the development of experimental laminitis models and the observation of pathophysiological differences between them, laminitis is now understood to be a heterogeneous condition, with structural failure of the digital lamellae as a ‘final common pathway’ that can result from diverse inciting etiologies. When comparing the current literature on experimental sepsis-related laminitis and that induced by hyperinsulinemia (as described elsewhere in this text), it appears that these two manifestations of laminitis are quite different. Future studies using these established models of disease are anticipated to exploit these differences to develop novel therapies for the two – now separate – diseases.

Models of Sepsis-Related Laminitis

Laminitis is most classically associated with sepsis and endotoxemia in adult horses, often observed as a complication of diseases such as gastrointestinal strangulation, colitis, pleuropneumonia, and septic metritis [30]. In 1975, Garner and colleagues published a protocol for the reliable experimental induction of laminitis with enteral starch overload [23], and, with this paper, modern laminitis research began to accelerate. This model involves a single-bolus intragastric administration of a mixture of 85% cornstarch and 15% wood flour (17.6 g kg⁻¹ body weight); treated horses were observed to become lami nitic (Obel grade 3) within 32–48 h, as well as febrile and endotoxemic. Approximately 20–30% of horses dosed according to this model would fail to develop laminitis, which over time became to be seen as a major limitation of the model [31]. That said, an entirely new line of inquiry was opened when some investigators became interested in looking at these ‘non-responders’ to identify factors that conferred protection [32]. A more consistent and possibly clinically relevant model of alimentary carbohydrate overload has been developed recently [26], involving the administration of a single intragastric dose of 10 g kg⁻¹ body weight of oligofructose. Using this model, laminitis can be consistently induced in dosed horses, mitigating the question of how to best deal with non-responding horses. Both models appear to induce disease which closely approximates the sepsis-related laminitis observed clinically in adult horses. Therefore, using these models, several research groups have investigated the roles of inflammation, the digital vasculature, metabolic pathways, and weight bearing on the pathophysiology of sepsis-associated laminitis. Krueger and colleagues [33] noted that acute enteral carbohydrate overload was associated with severe typhlitis/typhlocolitis and mucosal disruption, potentially leading to exposure of the systemic circulation of the affected horse to luminal contents that might predispose to laminitis. Additional studies later documented significant alterations in cecal and colonic microflora and pH
associated with this model – changes which were suggested to increase the transmural absorption of several postulated laminitis ‘trigger factors,’ including bacterial endotoxin and vasoactive amines [31, 34–39]. Later attempts were made at modifying the oligofructose model in an attempt to replicate a suspected ‘two-hit’ model of end-organ damage in sepsis (in which an initial sublethal ‘priming’ insult, such as hemorrhage or infection, alters immune responsiveness and is followed quickly by a second – often lethal – insult that induces inappropriate inflammatory responsiveness and organ dysfunction). These modifications did not enhance the severity of disease in experimental horses [40], and the original grain starch and oligofructose models remain the best experimental models of clinical sepsis-associated laminitis that are available to investigators today.

Black Walnut Extract Model

Historical and modern anecdotal observations of laminitis developing in horses bedded on wood shavings containing black walnut tree heartwood (Juglans nigra) led to the development of another experimental model of sepsis-associated laminitis [24]. Indeed, concerns about the inconsistency of the enteral carbohydrate overload models, along with the severe pain and systemic illness that they induced, led many investigators to pursue studies involving the black walnut heartwood extract (BWHE) model from 1990–2010. In this model, an extract made from soaking approximately 1 kg of black walnut heartwood overnight in 5 liters of deionized water is filtered and administered via a nasogastric tube to the horse. This model is considered to more closely approximate a single intravenous bolus of endotoxin [41], as horses can be observed to become febrile and leukopenic within 4 h of dosing, and mildly laminitic (Obel grade 1) within 12 h; if no additional doses of BWHE are administered, horses typically recover fully without sustaining significant structural damage to their feet. Critics of this model rightly state that laminitis induced by BWHE does not accurately mimic naturally occurring sepsis-associated disease for this reason. However, this model has contributed greatly to the current understanding of the early pathophysiologic events occurring in sepsis-associated laminitis, including the documentation of lamellar inflammation [42–48].

Models of Endocrinopathic Laminitis

Laminitis occurring secondary to EMS/insulin resistance (IR), PPID, or exogenous corticosteroid administration has collectively been referred to as endocrinopathic laminitis in horses and ponies. This category of laminitis, which is the most common form afflicting equids currently, has been long assumed to share pathophysiologic characteristics with other forms of laminitis (notably, sepsis-associated disease). However, with the recent discovery that iatrogenic hyperinsulinemia for a period of days can precipitate laminitis [25], studies of this form of laminitis have suggested that it may differ from other forms of the disease. The hyperinsulinemic–euglycemic clamp technique used by Asplin and colleagues has been used as an experimental model of equine metabolic syndrome–associated laminitis (EMASAL) [25, 49, 50]; however, consistent models of laminitis associated with PPID or exogenous corticosteroid administration remain to be described (attempts to experimentally induce laminitis in normal horses with exogenous steroid administration have been unsuccessful). Knowledge of whether these forms of endocrinopathic laminitis are pathophysiologically similar will depend on the development of consistent, repeatable models of the respective diseases, as has been done for sepsis-related laminitis.

Supporting Limb Laminitis

Laminitis is known to be a significant complication of prolonged unilateral weight-bearing in adult horses, and the few publications that exist in the scientific literature regarding supporting limb laminitis are epidemiologic or descriptive in nature [51–53]; however, very little information is currently available regarding the underlying pathophysiologic mechanisms that lead to this condition. Current attempts to develop a consistent experimental model of the disease will hopefully close this knowledge gap, as this is a problem currently receiving attention from the laminitis research community.

Pathophysiology Elucidated Through Study of Experimental Models: Shifting Hypotheses

Equine Laminitis – be it associated with sepsis, endocrine disease, or unilateral lameness – is unlikely to be caused by a single, linear exposure or molecular event. Rather, the pathogenesis of laminitis is likely to be complex, and moreover, it is likely to vary among the clinical circumstances in which the disease is most frequently encountered. The investigation of several hypothetrical mechanisms thought to be involved in the development of laminitis over the past 40 years has resulted in shifting attitudes regarding their relative importance; current research strategies favor an integration of many of these mechanisms.

One of the first mechanisms to receive vigorous research attention was that of altered vasomotor tone and resultant ischemia. During the 1970s, Garner and colleagues evaluated the role of hypertension in Equine Laminitis [54]; this same group was also one of the first to describe the angiographic appearance of the laminitic equine foot [55]. Hood et al. [22] likened Equine Laminitis to Raynaud’s phenomenon (a recurrent ischemic condition of the human digit); later investigations have evaluated the role of thrombosis [56, 57], the role of the veins/venules in lamellar vascular dysfunction [58–62], and the role of insulin [63, 64] on vascular dysfunction and lamellar ischemia in the
setting of laminitis. Current investigations of vascular pathophysiology are moving away from simple lamellar ischemia and substrate deprivation toward endothelial dysfunction (as might be associated with insulin resistance).

During the 1990s, the results of several investigations into the role of altered lamellar enzymatic activity were published, and this led to intense interest in the potential therapeutic utility of this mechanism. Pollitt and colleagues, through their studies with gelatin zymography, suggested that the activation of several matrix metalloproteinases (most notably MMP-2 and MMP-9) might result in the degradation of lamellar extracellular matrix components and the attachment of the lamellar basal epithelial cell to its basement membrane, thereby contributing to the structural changes within the hoof capsule that commonly occur in laminitis [65–67]. Later studies by Black and colleagues emphasized the role of other lamellar proteases [68–72]; the majority of work has applied to sepsis-related laminitis, and the role of MMP activation in endocrinopathic laminitis appears insignificant [73]. Additionally, while MMP activation in laminitis has been documented, the cause(s) of this activation remain elusive. As these enzymes can be inhibited pharmacologically in many cases, this mechanistic category remains an attractive therapeutic target for laminitic equids; additional information regarding target and timing, however, is required before widely recommending their use.

During the early to mid-2000s, lamellar inflammation in sepsis-associated laminitis was described comprehensively for the first time by Belknap and colleagues [45, 74]. Several studies were subsequently reported describing the presence of infiltrative leukocytes and elevated concentrations of several pro-inflammatory cytokines and chemokines in the digital lamellae of horses subjected to both BWE and carbohydrate-overload models of laminitis [42–44, 47, 75–77]; these changes were also shown to affect the fore and hind feet of experimental animals [32]. In spite of strong experimental evidence for lamellar inflammation in sepsis-related laminitis, systemic anti-inflammatory therapy has been somewhat disappointing in its attenuation of inflammation associated with laminitis [78]. The only therapy found to effectively block lamellar inflammatory signaling is cryotherapy, with little apparent effect of nonsteroidal anti-inflammatory drugs (NSAIDs) at this point in time [79].

Most recently, investigations of metabolic changes in the digital lamellae, particularly related to glucose and insulin dysregulation, have attracted intense attention. Insulin resistance has been identified as a risk factor for Equine Laminitis, and effects on lamellar metabolism were thought to be involved. Early work focused on the effects of substrate (especially glucose) deprivation, which was shown to encourage the detachment of lamellar basal epithelial cells (LBECs) from their basement membrane in vitro [65]; subsequent studies performed by this same group and others showed that glucose uptake by the digital lamellae was insulin-independent, suggesting that glucose deprivation was not a primary mechanism involved in EMSAL [80, 81]. The effects of systemic metabolic dysfunction on both vascular supply to the digit and the LBECs themselves is a primary focus of laminitis research currently, and will likely remain so in the near future, as EMSAL is the most common form of the disease observed clinically.

The advent of the molecular era has resulted in a rapid expansion of knowledge of the pathophysiology of laminitis. Most research groups acknowledge that laminitis likely represents a heterogeneous group of disease states (or a common end result of such states), and there is unlikely to be a singular inciting cause or pathophysiologic mechanism. Rather, the disease is complex and multifactorial, a fact which has been established over the past 40 years of modern laminitis research. The laminitis research community is well-positioned to make rapid advances in knowledge of this disease; the equine genome is published and available, as are rapid molecular screening techniques (such as transcriptome and kinome analyses). Finally, cohesion and cooperation between laminitis research laboratories internationally, including the formation of a laminitis tissue bank [82] and the wide sharing of tissues from animals subjected to experimental models, has advanced – and will continue to advance – the knowledge of this disease and the ability to treat affected animals in the future.

**Equine Laminitis Farriery from 1800 to the Present Day**

The literature of the 1800s and early 1900s offers very little description of special shoeing techniques for either acute or chronic stages of Equine Laminitis. A common treatment at the sudden onset of the disease advocated removing the shoes if possible, bandaging the feet, and applying cold water to the bandages. The cold was meant to reduce inflammation, and it was also thought that water would soften the horn of the hoof in order to allow the foot to expand (reducing pressure within the hoof capsule).

During recovery from acute (and flares of chronic) laminitis, when the affected horse started to move again, the farrier would attempt to provide support to the foot with a bar shoe, with the bar applied at the heel [5]. The horse with chronic laminitis presented a ‘pumiced foot’ (a dropped sole and dished anterior hoof wall). Horses with the chronic form, which could be the result of incomplete recovery from the initial attack or from gradual insults to the foot over time, were shod with a thicker bar shoe for support. Acute and chronic cases were also shod in wide-web shoes, with the area over the sole beveled to reduce pressure on the dropped sole. The frustration in trying to help animals with chronic laminitis (similar to today’s frustration with shoeing the laminitic horse) can be appreciated by the following description:

“All that can be done in the way of palliation is by shoeing. Nothing must press on the projecting and pumiced part. If the projection be not great, a thick bar shoe is the best thing that can be applied, but should the sole have much descended, a shoe with a wide web,
beveled off so as not to press on the part, may be used. These means of relief, however, are only temporary, the disease will proceed; and, at no great distance of time, the horse will be useless." [6]

By the early 1900s it was recommended that, by 10 days to three weeks after the onset of laminitis, the hoof wall at the toe should be shortened, the sole trimmed if necessary, flat shoes rolled at the toe placed on the feet, and the animal allowed to exercise for a short time daily [5]. Authors recognized that the foot grew rapidly and required trimming and the shoes be reset every three weeks. "The wall at the toe should be short, but excessive thinning of the sole should be avoided" [83]. It seemed to be generally understood that the success of the treatment and recovery was directly related to how much damage had occurred during the acute phase of laminitis.

Modern podiatric treatment of laminic horses remains in many ways very similar to that described over the past two hundred years. Many of the principles described over 100 years ago are still used today (i.e. heel elevation and increasing ease of breakover), but the mechanics of how these goals are accomplished have evolved over time, with many prefabricated shoeing systems available commercially for use by farriers and equine veterinarians who treat these patients. Popular devices include the NARIC Ultimate cuff, the Equine Digital Support System/Four-Point Rail Shoe, and the Steward Clog, the use of all of which has anecdotally increased in recent years. However, clinical trial data describing the relative efficacy of these devices is virtually absent currently and sorely needed in order to guide the effective treatment of laminic horses.

Regarding medical treatment and farriery, both early and modern-day horsemen recognize that preventing laminitis from occurring is far better than attempting to treat the disease once it occurs. The end results of laminitis are too often still ruinous to the horse, a situation that will hopefully be improved in the future through both basic research and well-controlled clinical trials.

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