# Laminitis in Horses: Through the Lens of Systems Theory

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## Abstract

Systems theory is a way of describing complex and dynamic relationships. We applied systems theory to the structure and function of the equine foot in an effort to better understand laminitis and, in so doing, reconcile the various theories of its etiopathogenesis and find more universally effective preventive and therapeutic strategies. The foot is described as an open system, and its inherent vulnerabilities are explored. Cascade failure is discussed as a potentially unifying theory of laminitis. The fundamental failure in laminitis is failure of the lamellar dermal-epidermal bond, but that endpoint can be reached via vascular, enzymatic, inflammatory, or mechanical mechanisms, or any combination thereof. Inflammation is discussed as a common denominator, making anti-inflammatory therapy of greater importance than just pain management. Multimodal anti-inflammatory therapy is discussed, including selective COX-2 inhibitors, heparin, nutraceuticals, and inhibitors of MMPs. Multimodal analgesic therapy also is important and may include NSAIDs, opiates, epidural analgesics, physical therapy, relief of weight bearing, diligent nursing care, deep digital flexor tenotomy, and case-appropriate trimming and shoeing. Preventing laminitis still comes down to risk management: knowing the risk factors applicable to an individual horse and adjusting the management accordingly. Examples include weight management and control of carbohydrate intake in overweight horses and ponies, the use of pergolide in patients with PPID, and distal limb cryotherapy in high-risk patients. It is anticipated that application of molecular biological techniques will further advance treatment and prevention of laminitis.

## INTRODUCTION

In November 2008, researchers, practicing veterinarians, and farriers came together for the inaugural Laminitis West Seminar. Looking back, we've come a long way in our understanding of laminitis since the first International Laminitis Conference in 2001. But as is all too clear to those "in the trenches," we still have a long way to go in both preventing and treating this often devastating disease. In this journal article we'll review some of the advances of the past 7 years through the lens of systems theory, and we'll take a fresh look at how they have changed the big picture.

## PUTTING SYSTEMS THEORY TO WORK

Systems theory originated in the 1920s as biologists struggled to find a means of explaining the interrelatedness of organisms in ecosystems. In essence, systems theory is simply a way of describing complex and dynamic relationships. It has now become a truly interdisciplinary field, applied in such varied areas as biology, sociology, and computer science [1]. We decided to see if systems theory, when applied to the structure and function of the equine foot, could help us better understand laminitis and, in so doing, reconcile the seemingly disparate theories of its etiopathogenesis and point us toward more universally effective preventive and therapeutic strategies.

### The foot as a system

A system can be defined as a collection of components or elements that are related in some way [1]. The equine foot is a collection of different tissue types (bone, connective tissue, blood vessels, nerves, dermis, epidermis, horn, etc.) that are related both structurally and functionally. These various components are united in the common function of supporting the horse's body, facilitating locomotion, and attenuating the forces of weight bearing and ground impact.

Complexity is a characteristic of a system that comprises a large number of densely connected parts and multiple levels of embeddedness and entanglement [2]. Embeddedness is a state in which one system is nested in another system [2]. For example, the cells of the equine foot are embedded in an extracellular matrix—or is it that the extracellular matrix is embedded in the cellular system which creates and maintains it? The cells and extracellular matrix are embedded in a vascular network; or is it the other way around? The distal phalanx is embedded in a connective tissue network that includes the lamellar dermal-epidermal bond, the deep digital flexor tendon, the common or long digital extensor tendon, and other connective tissues of the digit. The distal phalanx is also embedded in an extensive vascular network which thoroughly suffuses this honeycomb of bone and surrounds it within the hoof capsule, thereby creating what amounts to a fluid-filled boot. And then there is the neural network of sensory and vasomotor neurons which is embedded through all digital tissues except the horn [3].

Entanglement is a state in which the manner of being, or form of existence, of one system is inextricably tied to that of another system or set of systems [2]. This characteristic is of particular importance when discussing the equine foot and laminitis. The cells of the lamellar dermal-epidermal bond are structurally and functionally entangled with the digital vasculature. But while the lamellar blood vessels exist to supply the cells of the lamellar dermis and epidermis, there is

no hierarchy here. In fact, systems theory provides us with yet another useful term: heterarchy, defined as an ordering of things in which there is no single peak or leading element; which element is dominant at a given time depends on the situation [2]. Interruption of its blood supply for any reason can lead to failure of the dermal-epidermal bond. By the same token, failure of the dermal-epidermal bond for any reason can cause the release of inflammatory cytokines and other vasoactive elements and also precipitate biomechanical events which can cause dysfunction and even outright destruction of the digital vasculature [4].

Panning out to the larger view, the foot is embedded in and entangled with the rest of the body. It has been said "no foot, no horse"; but the reverse is also true: "no horse, no foot." The foot is inextricably tied to, and entirely dependent upon the rest of the body. The foot and all its component parts cannot be healthy if the body, the larger system of which it is part and on which it depends, is not healthy.

**The foot as an open system**

An open system is one in which the system continuously interacts with its environment; it maintains its integrity as a system, yet interacts with elements outside itself (Fig. 1) [5]. While the equine foot is a distinct and definable structure, a system, it relies on the rest of the body for its continued viability, and it is subject to influences from outside the body and from within (Fig. 2). It is the "open" nature of the equine foot as a system that we want to explore, because herein lies both its strength and its vulnerability.

With regard to laminitis, two critical elements of the equine foot are the lamellar dermal-epidermal bond and the digital vasculature. Both of these components have a certain inherent resilience of structure and function, but also some inherent vulnerabilities.

The lamellar dermal-epidermal bond is a remarkable structure. This simple cellular bond is robust enough to maintain its integrity despite the intense forces experienced during such activities as galloping and jumping. In fact, part of its function may even be to attenuate some of these forces, thereby protecting the lattice-like bone of the distal phalanx it suspends, a relatively flimsy structure that could easily be fractured under such loads. At the same time, this bond is dynamic enough to allow continuous hoof wall growth, a necessary requirement of hoof wall integrity as it replaces the horn lost through wear at the ground surface [3].

This ability to allow the ever-renewing hoof wall to slide earthward over the surface of the distal phalanx is achieved through a tightly regulated coupling–uncoupling cycle between the lamellar dermal and epidermal cells [3]. This process is mediated primarily by matrix metalloproteinases (MMPs), which are a group of enzymes that degrade specific components of the extracellular matrix, and their counterbalancing tissue inhibitors of matrix metalloproteinases (TIMPs) [3,6]. With the lamellar dermal-epidermal bond, the pair primarily involved are MMP-2 and TIMP-2 [3]. Recent research indicates that MMP-14 is also involved in this normal renewal process [7]. Working in balance, these substances allow the orderly coupling–uncoupling of the dermal-epidermal bond necessary for hoof wall growth, while still maintaining the structural and functional integrity of the bond.

Thus, it seems a cruel irony that the very feature which allows the lamellar dermal-epidermal

bond to maintain its integrity as part of a continuously changing system is also the feature that renders it vulnerable to destruction. Unregulated activation of MMPs, chiefly MMP-2, -9, and probably -14, leads to destruction of the basement membrane, the extracellular matrix component which adheres the lamellar epidermal cells to their underlying dermis [4,6-8]. When this bond is destroyed, the distal phalanx and hoof wall are free to separate under the force of the loads normally experienced by the foot even at rest.

Destructive overactivity of these MMPs can be triggered locally by local events. But because the foot is an open system, with the digital vasculature open to the systemic circulation, the lamellar bond is also susceptible to hematogenous delivery of preformed MMPs or their various trigger factors from distant sites such as the gut, the pleural or peritoneal cavity, or the endometrium [4,6,8].

The lamellar dermal-epidermal bond, being a bond between living cells, requires a continuous energy source for its maintenance. Part of the inherent resilience of this bond may lie in the fact that, while the cells of the lamellar dermis and epidermis rely on glucose as their primary energy source, and in fact have a high demand for glucose [9], they are not dependent upon insulin for their glucose uptake [10]. In this way, the dermal-epidermal bond probably is rendered less vulnerable to fluxes in food supply, such as would naturally occur over the course of a year. However, its high demand for glucose renders the dermal-epidermal bond vulnerable to interruptions in glucose supply, such as might occur during prolonged periods of ischemia either within the foot itself or more proximally in the limb.

A third “open system” aspect that is relevant here is the vulnerability of the lamellar dermal-epidermal bond to the influence of the deep digital flexor tendon (DDFT) and its governing myofascial connections. Supporting limb laminitis is believed to be primarily an ischemic event, wherein the constant pull of the DDFT on the distal phalanx is transmitted across the dorsal lamellar bond to the dorsal hoof wall for as long as the limb remains fully loaded. Digital venography performed while the healthy foot is fully loaded shows a reduction or even absence of filling in the dorsal lamellar vasculature and a resumption of normal vascular fill when the foot is unloaded [11]. In some cases of supporting limb laminitis, systemic factors may also be involved, such as the stress associated with severe injury and hospitalization, and a defective gut barrier associated with medications the horse may be receiving for its primary condition.

The digital vasculature is of course an essential component of the equine foot as an open system. Through the digital arteries, the cells of the foot are supplied with nutrients, oxygen, water, protective and reparative elements of the immune system, and other regulatory substances from the rest of the body; and through the digital veins byproducts of cell metabolism are removed from the digit. However, some of its unique structural and functional features, as well as its openness to the larger system, render the digital vasculature all too vulnerable to dysfunction and even destruction.

There is an extensive complex of arteriovenous anastomoses (AVAs) within the digital vasculature [3]. This network of AVAs creates numerous possible avenues for blood flow which probably serves a protective function during intense exercise, when pressures within the hoof capsule are intermittently high. Also, the AVAs are important in thermoregulation. For example,

in subfreezing conditions, periodic opening of the AVAs within the digit allows blood flow to be controlled such that cell viability is preserved while heat loss across the hoof capsule is minimized [3,12].

However, opening of the AVAs in the lamellar dermis shunts blood away from the capillary beds in the dermal lamellae, so when the AVAs open inappropriately, ischemia can result and compromise the viability of the dermal-epidermal bond, particularly at the tips of the lamellae. Reperfusion injury once blood flow is restored can further contribute to breakdown of this vital bond [4]. Much research attention has been focused on various vasoactive substances and their putative effects on the digital vasculature. The one that is perhaps of most practical concern is insulin.

Insulin toxicity, unrelated to blood glucose concentration, has recently been proposed as the mechanism by which hyperinsulinemia increases the risk for laminitis. In a group of healthy, lean ponies, laminitis was induced in all treated ponies simply by infusing insulin at a rate sufficient to cause persistent hyperinsulinemia, while maintaining the blood glucose concentration within the normal range [13]. In other species insulin causes vasodilation and thus increases blood flow to muscle and other tissues. However, despite an overall increase in blood flow, hypoperfusion and thus hypoxia and ischemic injury can occur in peripheral tissues (including nerves) because AVAs are dilated, shunting blood away from capillary beds. This is the mechanism by which diabetic neuropathy occurs and causes circulatory disorder and ulceration of the feet in humans. Incidentally, MMP-2 and MMP-9 are activated in response to oxidative stress, peripheral hypoperfusion, and increased local and systemic levels of pro-inflammatory cytokines, which may be another means by which hyperinsulinemia precipitates laminitis [6,13].

A second feature of the equine digital vasculature that may be important here is the relatively greater responsiveness of the digital veins to vasoconstrictive agents compared with the digital arteries [14]. The reason for this disparity remains a bit of a mystery, but perhaps it is to compensate for the fact that the digital veins are valveless and the digital vasculature is subjected to some intense variations in pressure (e.g. the hoof loading-unloading cycle during the gallop) which may necessitate some particular protective mechanisms. Regardless of the reason, disproportionate digital venoconstriction, triggered by locally derived or circulating vasoconstrictors, would quickly lead to engorgement of the digital vascular beds and consequent lamellar edema, microvascular thrombosis, and ischemia [4,14,15].

A third feature is that the arterial supply to the entire foot is dependent upon a single pair of palmar or plantar arteries which are superficially situated. Outflow is similarly limited to a pair of superficially located digital veins [3]. Once again, while this system evidently makes biological or evolutionary sense in some respects (e.g. economy of finite resources), it seems set up to fail in others.

So, the openness of the foot as a system exposes the tissues within to hematogenous distribution of substances that can directly or indirectly affect the dermal-epidermal bond, the digital vasculature, or both. The list of individual biochemicals is long and seems to grow longer by the year. It includes, but is not limited to, endotoxin (lipopolysaccharide), bacterial exotoxins such as

thermolysin and probably others, MMPs upregulated elsewhere such as the gut, tumor necrosis factor, various pro-inflammatory interleukins, prostaglandins, thromboxanes, cyclooxygenase type 2 (COX-2), serotonin (5-hydroxytryptamine), endothelin-1, protein kinase C, platelet activating factor, myeloperoxidase (MPO), various reactive oxygen species, inhibitors of nitric oxide synthase, gut-derived vasoactive amines (tryptamine, phenylethylamine, etc.), leptin and other adipokines, cortisol, and insulin [4,13-24].

Suffice it to say that the basic mechanisms by which laminitis may be precipitated can be categorized as inflammatory, vasoactive (particularly that which leads to ischemia-reperfusion injury), enzymatic (specifically, unregulated MMP activation), and mechanical overload. The clinical conditions or circumstances involving these mechanisms are summarized in Table 1.

**Individual response**

One intriguing and inadequately studied aspect of laminitis is its spectrum of clinical severity. Certainly in an experimental setting, laminitis can reliably be induced in all study horses or ponies with either the carbohydrate-overload model or the black-walnut model. However, the severity of clinical signs and histopathological changes can vary among individuals even in a single study. In the real world, not all horses and ponies subjected to the same conditions develop laminitis or, in those that do, develop laminitis to the same degree. Why?

What we have established up to this point is that the cells of the foot rely on the rest of the body for their health. While certain of their functions are relatively autonomous, it is a matter of "autonomy within community," which is another way of saying that the foot is an open system, embedded in and entangled with the larger body system. The foot relies on the rest of the system for its nutrients and waste management, and it is affected by what happens in the rest of the body. "Distress signals" from a distant tissue or the system as a whole inevitably reach the foot. It seems self-evident that whether or not the digital tissues are perturbed, and if so to what extent, depends on the strength of the signal but also on the resilience of the digital tissues to the perturbation. In other words, it largely depends on the health of the tissues and the system as a whole when the crisis occurs.

Psychologist William James coined the term "white crows" for the things in life that don't fit what we expect, and throughout his career he studied his "white crows" with great interest. A corollary here is to study the healthy, the robust, the resilient individuals, in addition to the diseased, to truly understand a disease. It would be useful for us to study these more robust horses with as much interest and urgency as we are studying those who succumb readily to laminitis, because then we would have a better idea of how to prevent this disease in all.

## CASCADE FAILURE AS A UNIFYING THEORY

In systems theory, cascade failure is failure in a system of interconnected parts, where the service provided depends on the operation of a preceding part, and the failure of a preceding part can trigger the failure of successive parts [2]. This aspect of systems theory may get us the closest yet to the Holy Grail of laminitis research: a unifying theory. There remains in laminitis research a schism between those who favor the vascular theory (it all starts with ischemia-reperfusion

injury) and those who favor the biochemical theory (it all starts with enzymatic destruction of the basement membrane) [4]. And now recent research into the developmental or prodromal phase of laminitis suggests that, at least in the carbohydrate-overload [23] and black-walnut models [18], it all starts with up regulation of genes that code for inflammatory cytokines and chemokines. Supporting limb laminitis further suggests that mechanical overload may play a pivotal role in some situations [11]. In addition, *in vitro* studies have shown that the lamellar bond can fail even in the absence of basement membrane pathology when the glucose supply is inadequate [24]. Although *in vivo,* such a profound glucose-deficient state may not occur; at least, not without some other pathological mechanism such as ischemia.

In effect, cascade failure means that the system can fail at any one of a number of points, for any one of a number of reasons, and the end result—collapse of the entire system—is the same, regardless of where the failure originated or what triggered it. That certainly fits the kaleidoscopic clinical picture of laminitis. Separate inciting events or mechanisms, same common endpoint, because everything in the system is interconnected in some way and thus dependent on every other part for its optimal function. It is agreed that the fundamental failure in laminitis is failure of the lamellar dermal-epidermal bond. But as Table 1 illustrates, that endpoint can be reached via vascular mechanisms, enzymatic mechanisms, inflammatory mechanisms, mechanical overload, or any combination thereof.

**Is inflammation the first domino?**

Inflammation is a particularly interesting mechanism and may well prove to be the common denominator in all cases of laminitis, perhaps, as recent research indicates [18,23], even the first domino to fall in this schema of cascade failure. Inflammation is a universal and somewhat scripted defensive mechanism used by the body whenever and wherever cell or tissue damage occurs for any reason. However, in prioritizing the destruction of pathogens, whether animate (e.g. bacteria) or inanimate (e.g. toxins), collateral damage can be severe. In that light, laminitis is simply collateral damage, the severity of which probably depends both on the intensity of the inflammatory process and on the anti-inflammatory resources available to the hoof tissues at the time. To illustrate the central role inflammation may play, let's look at two common causes of laminitis: endotoxemia and exposure to black walnut heartwood.

As inflammation has received greater research and clinical attention in human medicine, some classical concepts of disease have been rewritten. For example, sepsis is now seen as a systemic inflammatory response syndrome (SIRS) [22]. Laminitis in horses is a well-established sequela to various conditions involving gram-negative sepsis, such as pleuropneumonia, enterocolitis, peritonitis, and endometritis secondary to placental retention [19]. Endotoxemia was long assumed to be the common denominator and laminitis trigger, but experimental administration of endotoxin to healthy horses does not consistently cause laminitis [4]. We now know that the common thread with all of these conditions is the systemic inflammatory response [22], a state of systemic inflammation accompanied in severe cases by hemodynamic instability or collapse. Laminitis, then, is the unfortunate consequence of prioritized destruction of the invading pathogen or of circulating endotoxin in these equine cases of SIRS.

Exposure to black walnut heartwood rapidly induces a vigorous systemic inflammatory response, presumably to destroy or inactivate the toxic principle(s). Laminitis quickly ensues, complete

with unregulated MMP activation and basement membrane destruction [18]. Looking at it from the opposite direction, however, could it be that the toxic principle(s) in black walnut heartwood is the walnut tree's defense against parasitic insects, and the mechanism it uses is uncontrolled inflammation? The walnut tree would not distinguish between a boring insect and a horse bedded on its shavings; the defensive/destructive result would be the same. Once again, laminitis is the unfortunate consequence of a systemic inflammatory response.

These musings aside, anti-inflammatory therapy assumes far greater importance than just attenuating foot pain if inflammation is one of the earliest events and perhaps even the cascade trip-switch. Granted, pain management is a worthy goal on its own, particularly in patients with moderate to severe laminitis. However, if the collateral damage caused by an aggressive local or systemic inflammatory response is to be minimized, anti-inflammatory therapy must be instituted as early as possible in the disease process, and even before clinical signs of laminitis appear when laminitis can be anticipated (e.g. grain overload, sepsis).

## ADVANCES IN THE TREATMENT OF LAMINITIS

Perhaps the most important recent advance in the treatment of laminitis is our adoption of the concept of *multimodal* therapy. The more we have learned about the various biochemical and vascular events which occur in most cases of laminitis, the more it has become clear that one drug and one approach simply isn't enough.

### Multimodal anti-inflammatory therapy

As mentioned, anti-inflammatory therapy is an essential component of treatment. While phenylbutazone may be sufficient for patients with mild laminitis, the more severe cases generally require more in the way of anti-inflammatory and analgesic therapy. Not only should anti-inflammatory therapy be instituted immediately and continued for as long as necessary in these cases, it should be multimodal and tailored for the individual patient.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are still the mainstay of anti-inflammatory therapy in horses with laminitis, but drugs that are selective COX-2 inhibitors in horses, such as firocoxib (Equioxx®) [25] and meloxicam (Metacam®) [26], may be more appropriate than nonspecific NSAIDs such as phenylbutazone and flunixin meglumine. Provided that they offer comparable pain relief, the selective COX-2 inhibitors may have the advantage of sparing the gut barrier from possibly further damage [26].

Heparin has long been used by some for the treatment of laminitis, mostly for its anticoagulant properties. However, recent research has shown heparin to also be an effective anti-inflammatory agent by virtue of its ability to inhibit neutrophil degranulation and thus MPO release. Myeloperoxidase is involved in the production of reactive oxygen species, which are potent oxidizing agents, by activated neutrophils. In an *in vitro* study, both unfractionated heparin and fractionated low molecular weight heparin inhibited MPO activation and its uptake by the endothelial cells of equine digital arteries and veins [27]. In fact, both heparins proved more effective in protecting the digital veins than the digital arteries, which may be particularly relevant in light of the relatively greater responsiveness of equine digital veins to

vasoconstrictors. The value of heparin as an antioxidant, and thus an anti-inflammatory, agent has yet to be validated in *in vivo* models of laminitis, but its long history of clinical use in horses shows it to be safe at dosages in the order of 70 units/kg, IV, q12 h [27].

Nutraceuticals may also prove to have a place in multimodal anti-inflammatory therapy. Curcuminoids (active principles in turmeric), for example, have recently been shown to inhibit MPO release and activity *in vitro* [28]. Various other plant-derived antioxidants may be worthy of study for this purpose, too [29].

The TIMPs are an active area of pharmaceutical research, and soon we may have access to medications which upregulate or mimic these natural MMP inhibitors. In the meantime, some practitioners are using doxycycline in laminitic horses and ponies, primarily for its nonspecific MMP inhibiting effect. However, no objective studies have yet been published on the value of doxycycline in the treatment of laminitis in horses. Furthermore, caution has been advised with this approach. The MMPs play a crucial role in remodeling of the extracellular matrix and thus in tissue repair and regeneration, plus their coordinated actions serve an important regulatory function, so excessive inhibition through any means may be counterproductive [6].

**Multimodal pain management**

In patients with severe laminitis, NSAIDs generally are inadequate for pain management. These patients need a multimodal analgesic approach which may variously include NSAIDs, opiates such as transdermal fentanyl, epidural analgesics (most appropriate for hindlimb pain), physical therapy tools such as transcutaneous electrical nerve stimulation, relief of weight bearing such as slinging for a period of time, diligent nursing care, deep digital flexor tenotomy, and of course whatever trimming and shoeing strategies are appropriate for the case.

The neuropathic element of chronic pain in horses with laminitis has recently been investigated. Changes in the morphology of the palmar nerves indicative of injury to these sensory nerves, and the presence of markers of neuronal injury in the cell bodies of the neurons that innervate the affected limbs were found in naturally occurring cases of refractory laminitis [30]. These changes are similar to those seen in human patients experiencing neuropathic pain, and they explain why NSAIDs usually aren't enough to manage the pain in horses with severe laminitis. Although, anti-inflammatory medications may be important in preventing these neuronal changes, which are believed to be caused by local inflammation. While nonspecific opiates in horses carry certain risks, most relevant here being compulsive walking and gastrointestinal stasis, centrally acting pain-modifying therapy is an area of clinical research on which we should continue to focus.

In addition to providing immediate and often substantial pain relief, deep digital flexor tenotomy can be a course-changing and even life-saving intervention *if* it is performed *before* damage to the lamellar bond and digital vasculature are extreme. Criteria for case selection and timing still are not well established, but in our clinical experience the sooner the tenotomy is performed, the better the outcome. Seldom have we regretted performing a tenotomy; rather, we have too often regretted not doing it sooner. Venography of the digital vasculature can be a useful guide in making the decision whether and when to perform a tenotomy.

**New directions**

In addition to advances in hoof care, particularly as it pertains to restoring normal biomechanics to the foundered foot, and advances in biochemical interventions, we anticipate that the next 7 years of laminitis research will increase our understanding of the gut barrier. The microflora of the hindgut have received much attention, particularly in connection with the carbohydrate-overload model of laminitis [8,31], but the concomitant and necessary increase in mucosal permeability has been less well studied. A defective gut barrier not only is important in the pathogenesis of laminitis caused by carbohydrate overload [32,33] but also with laminitis precipitated by severe intestinal disorders such as strangulating obstructions and enterocolitis [26]. The preservation or prompt restoration of a healthy gut barrier will likely prove a significant advance in our ability to prevent and treat laminitis from these causes.

## ADVANCES IN THE PREVENTION OF LAMINITIS

This section is necessarily short, as we are not much further ahead in our ability to prevent laminitis. It fundamentally still comes down to risk management: knowing the risk factors applicable to an individual horse and adjusting the horse's management accordingly. Unfortunately, the veterinarian's and the farrier's power here is limited to what the owner or trainer is willing or able to implement.

One positive step in the past 7 years has been that horse owners are now more aware than ever of the importance of weight management and carbohydrate intake in overweight horses and ponies. For better or for worse, terms such as insulin resistance and equine metabolic syndrome have caught on with horse owners. Unfortunately, the simple, inexpensive, and effective remedy of daily aerobic exercise has not been embraced with the same vigor. Despite studies documenting a significant and rapid improvement in insulin sensitivity just with dietary modifications and daily exercise [34-36], the emphasis remains on pharmaceutical interventions such as L-thyroxine supplementation [37] and more recently metformin [37,38].

There has also been an upswing in the early recognition and management of pituitary pars intermedia dysfunction (PPID), also called equine Cushing's disease. It is now common practice to test any suspect horse for PPID or simply to start the horse on pergolide. Although pergolide probably is being overprescribed and used in horses that do not have PPID, its overuse is likely a lesser sin than its underuse when it comes to the prevention and effective treatment of laminitis in horses that do have PPID.

Distal limb cryotherapy has been established as a practical and effective means of preventing laminitis, provided that it is applied before clinical signs of laminitis appear [12]. The target temperature of around 5$^{\circ}$C within the foot is easily attained with ice baths or boots, however it must be instituted and maintained during the developmental phase of the disease. With the carbohydrate-overload model, destruction of the lamellar bond is underway within the first 24 hrs after dosing with oligofructose [39], and with the black-walnut model within the first 4 hrs after oral dosing [18]. Identifying the at-risk patient and instituting cryotherapy early is therefore imperative for successful prevention of laminitis.

In summary, the past several years of laminitis research have significantly advanced our understanding of the underlying mechanisms of laminitis in horses. In the next few years we will likely see major strides in our quest to unravel the pathogenesis of this complex disease, thanks in large part to advances in molecular biological techniques that are already being used in the study of laminitis [18,23]. Translating these new findings from the bench to the stall will enhance our ability to prevent and more effectively treat this disease.

Author's note: This article was written by me (Christine M. King) on commission in 2008 and published under the names of three other people. This article is some of my best work to date, yet it is credited to others—an act of intellectual dishonesty, the ramifications of which I did not appreciate at the time. This article is entirely my own original work, exactly as I submitted it. I retain the copyright.

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**Figure 1. Basic components of an open system.** (Adapted from Anon [5].)

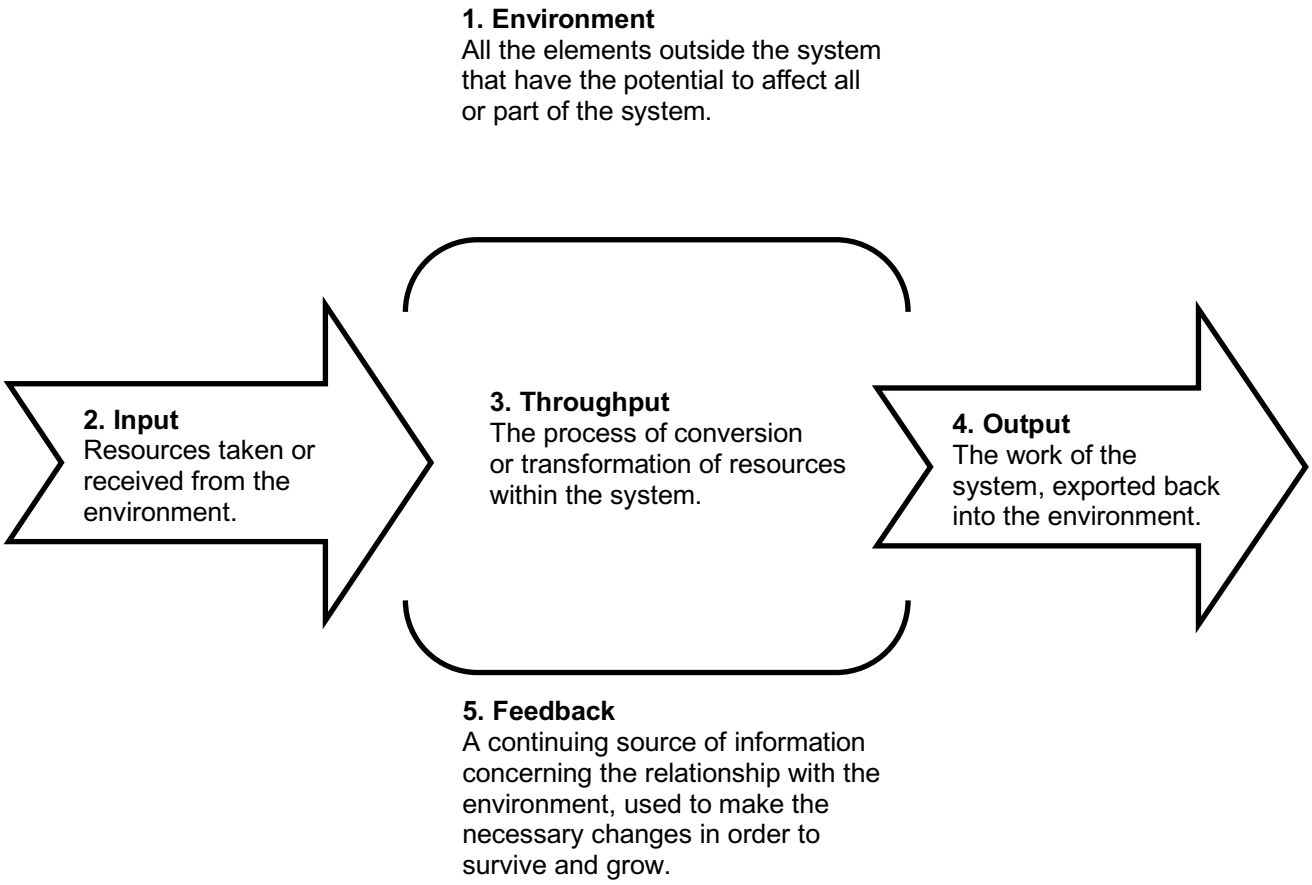
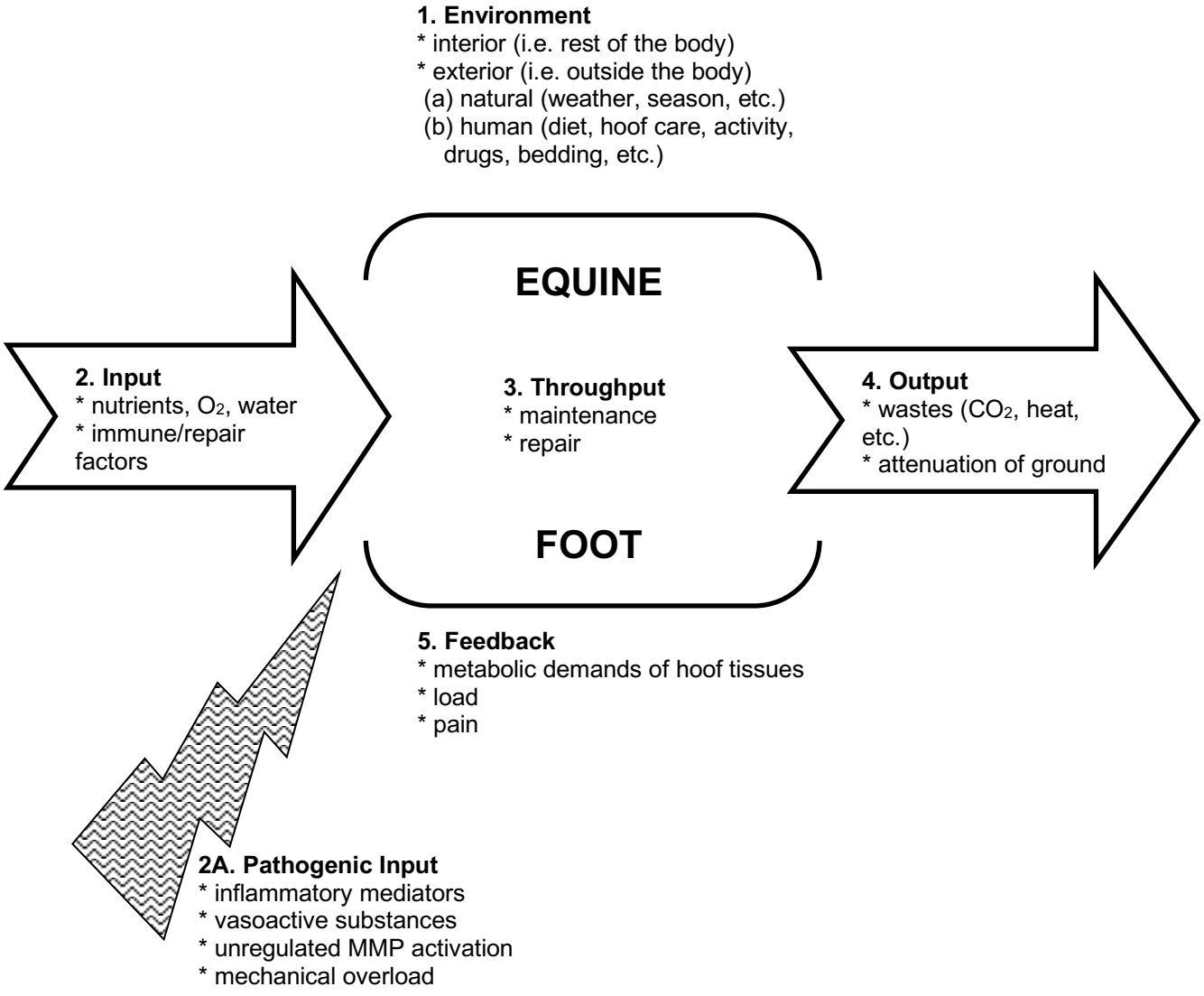


**Figure 2. The equine foot as an open system.** Its openness renders it vulnerable to various potentially harmful influences.




MMP: matrix metalloproteinase (see text for details)

**Table 1. Mechanisms by which laminitis may occur under specific clinical conditions.**

| Clinical condition | Ischemia/reperfusion injury | Unregulated MMP activation | Inflammation | Mechanical overload |
|---|---|---|---|---|
| Carbohydrate overload (e.g. grain, high NSC grasses) | ✓ via gut-derived vasoactive amines [17], platelet aggregation [40], and with chronic intake insulin resistance [41] | ✓ via gut-derived bacterial exotoxins [31] and possibly also preformed MMP-2 [6] | ✓ trigger(s) unknown but probably hindgut bacterial elements [16,31] | |
| Black walnut heartwood | ✓ toxic principle(s) unknown, may simply be inflammatory cytokines [18] | ✓ MMP-9 upregulated [18] | ✓ inflammatory mediators triggered by toxic principle(s) [18] | |
| Supporting limb laminitis | ✓ constant tension in DDFT reduces BF in lamellar dermis [11] | ? probable, secondary to ischemia | ? probable, secondary to ischemia and perhaps also to systemic factors associated with injury | ✓ static overload [11] |
| Concussion ("road founder") | ? proposed but probably secondary to tissue damage from overload | ? probable, secondary to inflammation | ? probable, owing to mechanical overload | ✓ assumed; dynamic overload of weak hooves |
| SIRS | ? via endotoxin and/or vasoconstrictive elements of inflammatory cascade, + activated platelets [21], insulin resistance [42] | ✓ circulating MMP-2 documented in some of these conditions [6] | ✓ potent systemic inflammatory response2 [2] | |
| PPID | ✓ via hypercortisolemia +/- insulin resistance [43] | ? probable, secondary to hypoperfusion | ? probable, secondary to hypoperfusion | |
| Obesity/metabolic syndrome | ✓ via insulin toxicity, which can cause hypoperfusion [13] and systemic hypertension [41] | ? probable, secondary to hypoperfusion [6,13] | ✓ considered a systemic inflammatory state [20] | ? possible in very overweight patients with very small feet |
| Glucocorticoid administration | ✓ via insulin resistance [37,41,43-45]; also cortisol theorized to sensitize digital vessels to vasoconstrictors [43] | ? probable, secondary to hypoperfusion | ? probable, secondary to hypoperfusion | |

MMP = matrix metalloproteinase
NSC = nonstructural carbohydrates (includes starches, simple sugars, fructans)
DDFT = deep digital flexor tendon
BF = blood flow
SIRS = systemic inflammatory response syndrome; occurs with sepsis (pleuropneumonia, peritonitis, endometritis secondary to retained placenta, enterocolitis, strangulating bowel obstructions, septic thrombophlebitis, etc.)
PPID = pituitary pars intermedia dysfunction (also called equine Cushing's disease)