A Hard Look at Laminitis

BY DR. CHRISTY CORP-MINAMIJI

The causes and mechanics of laminitis still stump many researchers, but progress is being made to understand and, thus, treat this destructive disease better

As prey animals, horses evolved with superior sight and hearing and an ability to fight off ailments such as infections. But what about laminitis?

"During evolution, horses that were septic (had infection in the blood) enough to founder succumbed to the disease process or became a carnivore's dinner," said Dr. James Belknap, associate professor of equine surgery at The Ohio State University's College of Veterinary Medicine. "The laminar tissues of the equine foot evolved as a complex structure in which the innermost cells of the epidermal laminae must maintain a threshold number of attachments to the underlying connective tissue attached to the coffin bone to essentially suspend the coffin bone; constantly allow a percentage of the structure to become 'unattached' to allow the hoof wall to grow toward the ground; and be elastic enough to stretch (and not tear) as the horse moves."

Today this high-performance structure can rapidly undergo catastrophic failure as a complication of many diseases horses get, making laminitis a major cause of equine morbidity and mortality (illness and death). So, what is laminitis, and how has our understanding of this destructive condition shifted over the years?

Defining the Disease

Breaking down the term laminitis, we can define it as an inflammation (-itis) of the laminae (also called lamellae), the soft tissue structures suspending the distal phalanx (coffin bone) within the hoof capsule. However, breaking down is exactly what happens to the structure of the laminae during laminitis. According to Adams and Stashak's *Lameness in Horses*, "Laminitis is not a primary disease but usually occurs as a sequelae to four different clinical entities:"

1. Diseases associated with sepsis/endotoxemia;
2. Excessive weight placed on a limb due to injury to the opposite limb;
3. Equine Cushing's disease in the older horse; or
4. Equine metabolic syndrome (EMS), including pasture-associated laminitis.

Many horse owners are familiar with the various clinical signs of a laminitic horse: lameness, heat in the foot or coronary band, and deformity of the hoof wall. The degrees of lameness are described in the Obel grading system:

Grade 1: At rest, the horse alternately and incessantly lifts his feet, often at intervals of a few seconds. Lameness is not evident at the walk, but a short, stilted gait is noted at the trot.

Grade 2: The horse moves willingly at a walk, but with a stilted gait. A foot can be lifted off the ground without difficulty.

Grade 3: The horse moves very reluctantly and vigorously resists attempts to have a foot lifted off the ground.

Grade 4: The horse refuses to move and will not do so unless forced.

Laminitis progresses through three general stages: developmental, acute, and chronic. The developmental stage is the period during which the horse is at risk of laminitis but clinical signs have not developed (e.g., following a severe colic or grain overload). Treatments such as cold therapy have proved effective in interrupting the laminitis process during this stage. In the acute phase the horse shows clinical signs but does not have radiographic (X-ray) evidence of coffin bone rotation or sinking. The chronic stage occurs following coffin bone rotation and/or displacement.

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In some chronic laminitis cases the coffin bone rotates and is displaced within the hoof capsule

Hoof Anatomy and Biomechanics Basics

To understand the most recent laminitis research breakthroughs, let's first take a look at the structures comprising the equine foot and what they do.

The structures and tissues from the coronary band down to the ground by definition make up the equine foot. The foot's rigid external structures (the hoof wall and sole) are collectively referred to as the hoof capsule. The primary bone located entirely within the foot is the distal phalanx, which

is connected to the hoof capsule and suspended by the laminae around the outside (lateral), front (dorsal), and margins (medial, or inner), and by the deep digital flexor tendon (DDFT) at the back and bottom (palmar and plantar).

To understand the biomechanical changes taking place within the foot during a laminitic insult, Dr. Andrew Parks, professor of Large Animal Medicine at the University of Georgia's College of Veterinary Medicine, suggested asking the question: "What is the relationship between the distal phalanx and the hoof capsule?" He explained that while we know the weight of the horse travels down the bony column and is distributed across the ground, this weight distribution varies, depending on the ground surface hardness. In a shod horse or one standing on a hard surface, the weight is distributed around the foot's perimeter. However, in a barefoot horse standing on a soft surface, the weight is more evenly distributed across the sole.

The anatomical/biomechanical question, said Parks, is how is that weight transferred from the bony column to the sole and hoof wall? He pointed out that much of our understanding of internal hoof structure biomechanics during a disease process is speculative because we are currently limited in our ability to measure the forces upon structures such as the laminae. However, he offered two clinical observations on the laminae's role in weight transfer. First, when the laminae fail, the coffin bone drops within the hoof capsule, as seen in laminitis. Second, horses that have had significant amounts of sole resected (removed) for various conditions can often walk relatively comfortably with their weight distributed along the hoof wall. "These two observations, when taken together, suggest that the weight is largely going through the lamellae," said Parks.

What Are the Laminae?

For anyone familiar only with the outside of a horse's hoof, the laminae will be difficult to picture and understand. The word "lamina" is also defined as a thin plate or scale, or the expanded part of a foliage leaf. Scientists typically describe anatomy as gross (the big picture) or histologic (the structures at the cellular level). Grossly, the laminae look a bit like the pages of a book that have been fanned slightly apart. The epidermal laminae cover the inside of the hoof wall, projecting inward to interlock with the dermal laminae, which cover the sides and front of the coffin bone (picture opening two phone books and sticking them together so their pages alternate).

Looking more closely, we find that each lamina is covered with small secondary laminae. Imagine the pages of

the books are covered with Velcro; these secondary laminae enhance the strength of the laminar interdigitation.

At the histologic level the laminae comprise laminar basal epithelial cells that adhere to each other and to an underlying extracellular matrix called the basement membrane. According to Belknap, the laminar basal epithelial cell appears to be the critical point in laminitis development. "The laminar basal epithelial cell is a cell that has to have its act together," he said. Belknap noted that while the various laminitis triggers might operate via different pathways within the equine body, "most likely where the causes converge is at the adhesion of the laminar basal epithelial cells to each other and to the underlying matrix." When this happens, the laminar structure begins to fail.

Research Advancements

While the causes of laminitis have been recognized for decades, researchers' understanding of the pathogenesis of this disease, or what happens within the tissues after the inciting cause, has proved elusive until recently. Previously, said Belknap, clinicians and laminitis researchers "tried to lump all types of laminitis into a common pathway." More recent research indicates this might not be the case.

The common target is most likely any process that disturbs the laminar epithelial cells' orchestrated "dance," said Belknap. This could range from inflammation in the septic horse to abnormal insulin signaling associated with metabolic syndrome—all potentially disturbing these cells that need to function at an optimal level and resulting in a coffin bone that is no longer suspended. Because researchers investigate laminitis pathways at the cellular level, it's critical they precisely identify the regulation of specific proteins.

The sequencing of the equine genome in 2007 was a breakthrough that rapidly accelerated current laminitis research, according to Belknap, allowing us to take advantage of many molecular biology tools developed in human medical research. Now, he said, researchers can use cutting-edge molecular biology techniques to answer in several months questions that remained unanswered for decades regarding different laminitis causes and treatment efficacy.

Laminitis has been a difficult disease to treat "because we didn't understand it," said Belknap. For the past 30 years researchers have focused on the vascular (circulatory) system, which was thought to be the common pathway for all laminitic mechanisms. But their understanding of the disease is no longer so simplified. Researchers are gaining an understanding of some of the paradoxes of laminitis, such as why a horse with metabolic laminitis has a much better chance of returning to athletics than a septic horse with the same clinical signs. Belknap said the answer might lie in the fact that the laminar basal epithelial cells undergo a more gradual dysplasia (detrimental change) in horses with EMS than in sepsis cases.

With the ability to view components at the molecular level, researchers can better determine the mediators involved in the various models and stages of laminitis. For instance, said Belknap, though two years ago, "everyone was saying 'inflammation' (was the laminitic pathway for all models), over the next year or so we may show that it is not—or that it isn't everything." Take, for example, the inflammatory mediators researchers have identified in the hoof during developmental and acute stages. In the septic horse, said Belknap, those mediator levels are a thousandfold the levels found in a healthy horse. However, in a horse developing pasture-associated laminitis linked to EMS, those levels are negligible.

According to Dr. Chris Pollitt of the Australian Equine Laminits Research Unit at

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the University of Queensland, in a horse with EMS, high blood insulin levels most likely act through insulinlike growth factor receptors on the lamellae to trigger "inappropriate lamellar proliferation, lamellar weakening, and, thus, laminitis." In the Cushingoid horse Belknap believes the excess corticosteroid levels circulating in the horse's blood will prove to be the determining factor in laminitis development. And in a supporting limb laminitis case the most likely pathogenesis "involves inadequate perfusion of the lamellar tissue due to reduced digital blood flow in the supporting limb associated with excessive and continuous compensatory weight-bearing loads."

However, the primary factor limiting our understanding of—and ability to treat or prevent—laminitis is neither complicated nor advanced. "It comes down to funding," said Belknap. "That's the biggest drawback to everyone right now. There are approximately 10-15 labs in the world working on laminitis. One productive laboratory that provided critical laminitis data for over three decades recently quit performing laminitis research. We can't afford to lose anybody."

Take-Home Message

Laminitis is a devastating disease that causes permanent hoof structural damage. Until recently, laminitis treatments have been aimed at addressing the signs and effects of laminitis rather than interrupting the disease itself. Recent advances in molecular biotechnology enable researchers to pinpoint various pathways by which laminitis occurs. Identifying these pathways and the chemicals produced within the hoof might lead to methods of preventing and treating the actual disease process. BH

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