Chapter 4

Laminitis in Perspective

The laminitis literature

Much has been written on the subject of laminitis. There are records dating back to ancient times and the disease is probably as old as mankind's dual historical association with horses and grain over the last 2000-3000 years. There is no human medical equivalent to laminitis and veterinary science has been left on its own to elucidate the mechanism of this disease. The closest disease parallel is perhaps the obscure human disease *epidermolysis bullosa* where autoantibodies interfere with basement membrane attachment proteins and cause sheets of skin to separate along the dermo-epidermal junction. As humans walk on padded hock joints and don't rely on hooves, in principle still skin-like structures, we can be forgiven for missing the pathological link (if there is one). Laminitis does not appear to fit into any familiar, disease-causing pattern, despite, as you will read below, years of trying to fit this very square peg into several round holes. It is easy to describe the signs of laminitis and diagnose it once it has occurred. This is not the problem. What is required is an understanding of the disease process so that preventive, even curative, strategies can be developed. This is the only hope for horses and laminitis.

Once the lamellar foundations have been significantly damaged, the continuous physiological strain on the hoof dermo-epidermal junction makes repair virtually impossible. Laminitis appears to be less of a disease, but more of a natural process gone wrong. Rather like the workings of the worst malignant cancer; a process that still defeats the best medical minds of human medicine.

The laminitis research conducted during the last decade at the AELRU of School of Veterinary Science at The University of Queensland, with the help of RIRDC funding, was undertaken in the context of scientific dogma, much of it published in textbooks and journals and accepted as fact. This chapter reviews some key points of laminitis knowledge to put the current work of the Australian Equine Laminitis Research Unit in an historical perspective.

The developmental phase

A 30-40 hour developmental phase, during which lamellar separation is triggered, precedes the appearance of the foot pain of laminitis. During the developmental phase, and prior to the clinical appearance of foot pain, the horse or pony usually experiences a problem with one or more of the following organ systems: gastrointestinal, respiratory, reproductive, renal, endocrine, musculoskeletal, integumentary and immune. Multi-systemic aberrations in organs anatomically remote from the foot result in the lamellar tissues of the feet being exposed to factors that lead to separation and disorganisation of lamellar anatomy. The exact nature of the laminitis trigger factors, apparently reaching the lamellar tissues via the circulation, has yet to be fully elucidated.

Sometimes no developmental phase is recognised; the horse or pony is discovered in the acute phase with no apparent ill health or inciting problem occurring beforehand. The intramuscular injection of potent, long-acting, corticosteroid preparations for the treatment of skin disease, may precipitate iatrogenic (man-made) acute laminitis.

The acute phase

The developmental phase merges into the acute phase of laminitis when the first signs of foot pain appear **(Figure 4.1)**. The acute phase lasts from the onset of clinical foot pain and lameness at the walk and trot, to the time when there is clinical evidence of displacement of the distal phalanx within the hoof capsule. Some fortunate horses experience the foot pain of acute laminitis, but do not develop distal phalanx displacement and appear to make a complete recovery.

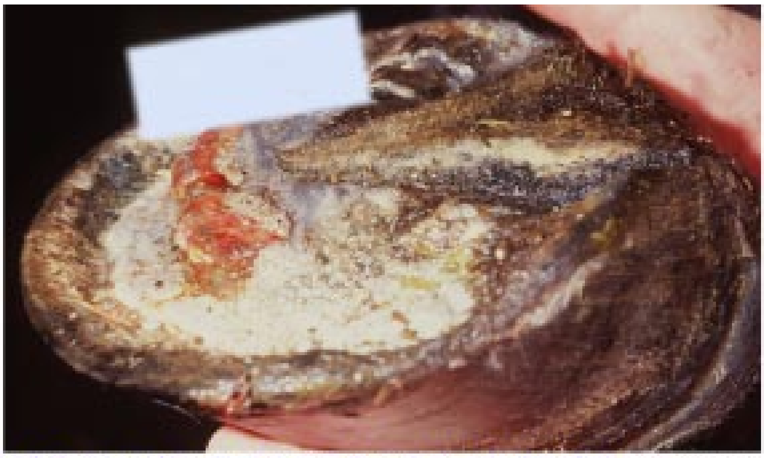
The chronic phase

After the acute phase, if the horse does not die from the disease process inciting the development of laminitis, it will develop some degree of downward displacement of the distal phalanx within the hoof capsule, the hallmark of chronic laminitis. Early displacement of the distal phalanx within the hoof capsule can be detected with good quality radiographs. The chronic phase can last indefinitely with clinical signs ranging from persistent, mild lameness, continued severe foot pain, further degeneration of lamellar attachments, to penetration of the sole of the hoof by the distal phalanx **(Figure 4.2)**, recumbency, hoof wall

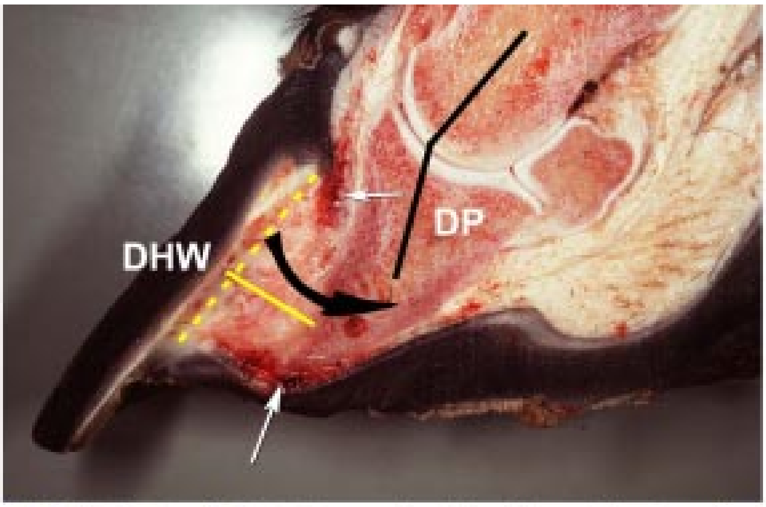
◄FIGURE 4.1 A horse with acute laminitis shifting weight from one foot to the other. Laminitis usually affects the forefeet more severely than the hind, presumably because the forequarters carry a greater proportion of the horse's weight (about 60%). Often the hind feet appear to be spared completely. In the chronic laminitis case pictured, the mare is shifting weight from one fore foot to the other (the right foot is flexed and off the ground). The shifting weight behaviour of horses with laminitis is undoubtedly performed to relieve pain. The common explanation is that when the pain in one foot becomes unbearable the foot is lifted off the ground. Pain then mounts in the weight bearing foot until the horse feels compelled to relieve it by shifting weight to the other foot. Horses with chronic laminitis shift weight like this for months, sometimes years.

deformation and even sloughing of the hooves. With increasing chronicity, the hoof wall and the distal phalanx lose their normal parallel arrangement and become increasingly separated by a wedge of keratinised material called the lamellar wedge. The distal phalanx rotates and is no longer in line with the proximal and middle phalanges (the long and short pastern bones) **(Figure 4.3)**.

It is important to realise that the process initiating the destruction of the lamellar attachment apparatus begins to operate during the developmental phase, before foot pain, the first clinical sign of laminitis, appears. During the developmental phase, the specific problems of the horse often have to be attended to urgently (e.g. colitis, retained placenta, pleuropneumonia and rhabdomyolysis) and unfortunately the feet may not enter into the therapeutic equation until the signs of foot pain appear. By the time foot pain is apparent, lamellar pathology is underway. In other words, foot pain is the clinical sign that lamellar disintegration is occurring. To wait and see if foot pain is the sequel to a metabolic crisis is to miss the opportunity to prevent or at least ameliorate lamellar pathology.



▲FIGURE 4.2 Prolapse of the distal phalanx through the sole of the foot. After giving birth to her foal this 17 hand Warmblood mare failed to pass the foetal membranes (the afterbirth) and developed acute severe metritis (infection of the uterus). Two days of septicaemia and fever followed and then the mare began to show the clinical signs of laminitis. Within a few days the tip of the distal phalanx was protruding through the sole of the foot.



▲FIGURE 4.3 Sagittal section of a foot with severe chronic laminitis and a large lamellar wedge. A feeding mistake caused this 2-year old Thoroughbred racehorse to founder. The attachment between the distal phalanx (DP) and the dorsal hoof wall (DHW) has failed and hoof and bone are now widely separated (compare with Fig 2.2). The dotted line shows the original position of the distal phalanx. The solid black line shows that the distal phalanx has rotated (in the direction of the curved black arrow) off the normally straight axis of the proximal and middle phalanges. The material now between the inner hoof wall and the bone is abnormal and consists of epidermal tissue proliferating to form a weak, disorganised mass called the lamellar wedge (yellow line). The descent of the unattached distal phalanx into the hoof capsule has distorted the growth of the proximal hoof wall tubules and has caused the sole to become convex instead of concave (dropped sole). Two dark haemorrhagic zones (white arrows) show the sites of greatest pressure and trauma.

The Obel grades of lameness

In 1948, the pioneering Swedish veterinarian Nils Obel graded the lameness associated with overt laminitis according to its clinical severity. Horses with Obel grade I laminitis shift weight from one foot to the other, but will move relatively freely. With Obel grade II laminitis, the lameness is more obvious, especially when turning, and the gait is stilted and shuffling. One foot can be lifted without causing extreme discomfort in the contralateral foot. In Obel grade III laminitis, the horse is reluctant to move and resists any attempt to lift a foot because of the pain this will induce in the contralateral foot. Obel grade IV laminitis is the most severe grade and the horse is immobile and often recumbent. There is a good correlation between Obel grade lameness and the severity of lamellar histopathology. The clinical significance of this will be discussed later.

Laminitis is a sequel to an event remote from the foot

Laminitis can result from a variety of seemingly unrelated pathological events occurring elsewhere in the body. However, most often, the pathology involves the gastrointestinal tract. Excess consumption of grain or lush pasture, duodenitis/proximal jejunitis, colitis, the acute abdomen of colic, and acute febrile diarrhoea can all precipitate laminitis. Non-gastrointestinal causes such as retained placenta, septic metritis, pneumonia/ pleuritis can also cause laminitis and have septicaemia and endotoxemia in common with gastroenterological causes of laminitis. Horses that severely "tie-up" (develop severe rhabdomyolysis) may also develop laminitis, for reasons that are currently unexplained. Alimentary carbohydrate overload laminitis, commonly called "grain founder," has become one of the better-understood mechanisms of laminitis. It can be induced experimentally and has become the laminitis model.

Grass founder

Ponies, and occasionally horses, will develop laminitis or "grass founder" while grazing on lush, rapidly growing pasture. Under certain conditions of climate, a soluble sugar called fructan may reach very high concentrations in the stem of grass (up to 50% dry matter). When consumed by horses, fructan (or oligofructose) is rapidly fermented by hindgut microorganisms, triggering a gastrointestinal disturbance that somehow leads to the foot disease laminitis. Mammals have no enzyme to digest fructan, so when consumed it passes undigested into the caecum where it undergoes rapid microbial fermentation causing a population explosion of hindgut streptococci. This hypothesis is supported from practical experience with a patented formulation of the antibiotic virginiamycin (Founderguard, Vetsearch International, Sydney). When fed to horses Founderguard specifically knocks out hindgut streptococci. Without these bacteria in the hindgut excess pasture fructan can be consumed safely without the risk of laminitis. When given to grass fed ponies (four days ahead of access to the risky pasture). Founderguard prevents laminitis in situations where the risk of laminitis is normally high.

Grain founder

In field cases, grain founder occurs following the consumption of excessive amounts of grain, either from accidental access by the horse or by a misguided, intentional, dietary increase by its keeper. Although the amount of grain required to induce laminitis varies between individuals, the consumption of 5-8 kg of wheat grain by the average 400-450kg horse causes faecal acidity (pH 4-5 instead of the normal 6.8-7.5), lactic acidemia, profuse watery diarrhoea and fever, all of which are associated with laminitis.

The likelihood of laminitis following grain consumption correlates directly with the starch content of the grain, the amount which passes undigested to the hindgut and the rate at which the undigested carbohydrate is fermented. The type of grain and the manner in which it is processed in the stomach and small intestine are also important in determining the amount of starch that passes undigested to the hindgut. Grains such as wheat, sorghum, corn and barley are considered to be most dangerous with respect to the risk of laminitis. The feeding of oats is relatively safe. Gorging on bread can result in significant amounts of readily fermentable carbohydrate passing to the hindgut and is also a recorded cause of laminitis.

Alimentary carbohydrate overload model

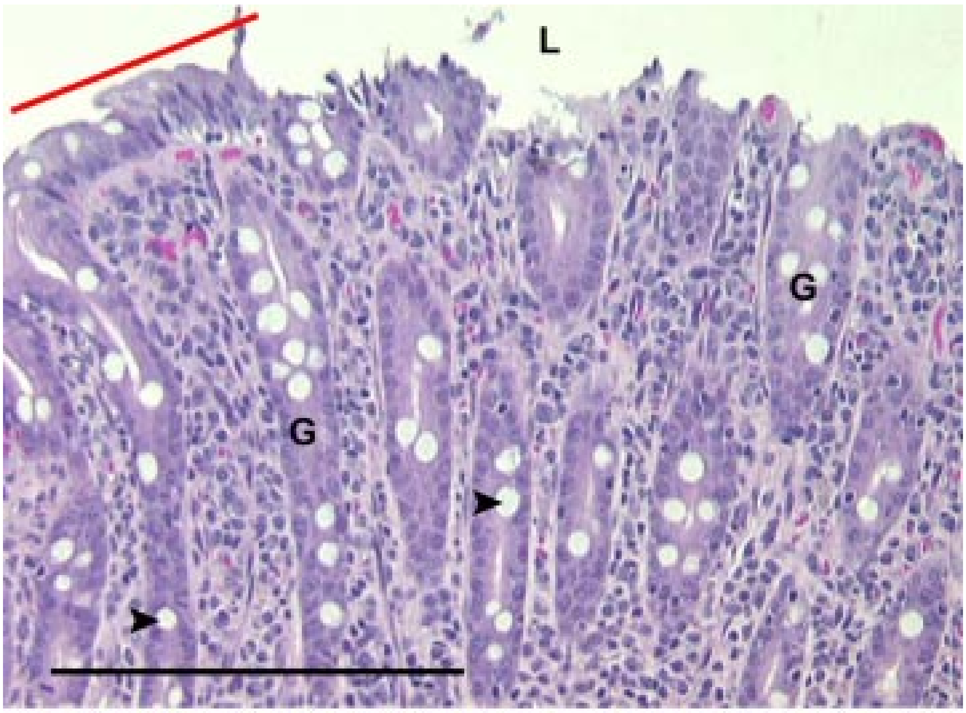
Much of what we know about laminitis and the metabolic events surrounding it has been derived from studies on horses that have been experimentally dosed with excess soluble carbohydrate (the alimentary carbohydrate overload model). The diet of horses in their natural state is grass based and consists mainly of complex, structural carbohydrate in the form of cellulose, hemicellulose and lignin. These are indigestible to mammals without the aid of active microbial hindgut fermentation and a large portion of the equine abdomen is occupied by the caecum and colon where complex carbohydrates are fermented to absorbable end products.

Domestic horses and ponies sometimes encounter large quantities of starch and fructan in their diet when they consume cereal grain or the lush sward of cultivated, fertilised pastures. Pony breeds, having evolved metabolic adaptations for survival in harsh, low nutrient environments, are particularly prone to laminitis, if given unrestricted access to lush pasture. Most of the consequences of carbohydrate overload occur after the arrival of the carbohydrate in the hindgut and relate to the rapid proliferation of hindgut bacteria accelerated by the presence of excess substrate.

Upon mixing with the normally neutral caecal contents, excess starch or fructan undergoes rapid fermentation to lactic acid. With the arrival of more and more substrate, fermentation continues and the unnaturally acidic conditions favor the rapid proliferation of the bacteria (*Streptococcus bovis, Streptococcus equinus* and *Lactobacillus spp*.). This results in very acidic conditions in the hindgut with pH as low as 4. Two isomers of lactic acid, D-and L-lactate, are produced in almost equal proportions by bacterial fermentation in the equine hindgut. However, only L-lactate is produced by the metabolic activities of mammals, so the concentration of D-lactate in venous blood can be used as an accurate indicator of bacterial lactic fermentation in the hindgut.

Low pH in the large intestine initiates a series of secondary events that often, but not always, culminate in laminitis. One of the most important consequences is the death and lysis of large numbers of Gram-negative bacteria of the family Enterobacteriaceae and the release of the lipopolysaccharide components of their cell walls (endotoxins). Endotoxin is absorbed from the gut into the bloodstream during developmental laminitis and endotoxaemia following alimentary carbohydrate overload creates a very severe illness for the horse. However, experimental administration of endotoxin itself has never been able to cause laminitis. In addition, endotoxaemia can be effectively controlled by a range of drugs (e.g. polymyxin B, flunixin meglumine [Finadyne]) and laminitis develops regardless of their use.

As early as 24 hours after carbohydrate overload, the epithelial cells lining the caecum undergo degenerative changes and the bowel becomes leaky. By 48-72 hours there is widespread desquamation and sloughing of caecal epithelial cells sufficient to allow passage of lactic acid, endotoxin and laminitis trigger factors into the circulation **(Figure 4.4)**. The consequences can be catastrophic. About 10-15% of horses die from cardiovascular shock after the accidental consumption of excess grain. High heart rates, rapid breathing, fever,



▲FIGURE 4.4 Micrograph of the leaking large bowel (caecum) of a horse developing carbohydrate overload laminitis. The large bowel wall normally has an intact layer (the mucosal barrier) of tightly joined epithelial cells covering its surface. This prevents harmful bacteria and their toxins from being absorbed into the circulation. The large bowel wall is glandular and the cells of the mucosal barrier line both the glands (G) and the lumen (L) of the bowel. The mucosal lining also contains numerous mucous secreting cells called goblet cells (arrowheads). The mucosal barrier cells under the red line are still joined together and have a normal appearance. However the remainder of the mucosal barrier has been destroyed providing a pathway for laminitis trigger factors to enter the circulation and eventually cause laminitis when they reach the feet. H&E stain. Bar = 100µm.

sweating, colic, diarrhoea and depression are the signs of horses battling grain overload. Just when the horse turns the corner and responds to treatment and the severity of the clinical signs decreases, the signs of foot pain appear; laminitis has arrived on the scene.

Use of virginiamycin to prevent laminitis

The bacteria responsible for lactic acid production, as a result of carbohydrate overload, (*Streptococcus bovis, Streptococcus equinus* and *Lactobacillus spp*.) are sensitive to a range of antibiotics. The laminitis inducing effect, following carbohydrate overload, does not occur if the activities of the bacteria are controlled. Virginiamycin, in the patented formulation Founderguard (Vetsearch International, Sydney), administered at 5g/kg body weight, 4 days before carbohydrate overload, prevented laminitis and D-lactic acid production in all cases. The correct formulation of virginiamycin is important for the active ingredient to enter and mix properly with the caecal and colonic digesta. Unfortunately, virginiamycin has to be present in the caecum before the arrival of carbohydrate for laminitis prevention to occur. When virginiamycin was administered 6-8h after dosing with carbohydrate, laminitis did occur. For this reason Founderguard is considered a useful laminitis prophylactic for horses and ponies with a high carbohydrate intake, but has little value therapeutically.

Lamellar blood flow etiology

Despite decades of research, the exact cause of the failure of the lamellar suspensory mechanism is still being debated by veterinary scientists. A common explanation is that lamellar blood flow is somehow compromised during the developmental phase of laminitis and this causes ischaemic (blood supply failure) necrosis of lamellar tissues. Without oxygen and the supply of the energy required to maintain adhesion between lamellar epidermal cells and their basement membrane the structure fails. Plausible as this idea seems, the laminitis literature is quite divided on the subject of sublamellar perfusion. Is laminitis caused by dilation or constriction of lamellar blood vessels? Are the lamellae perfused or not prior to the appearance of lamellar pathology?

Vasoconstriction theories

Studies of horses with acute laminitis, made using X-rays and radiopaque dyes (similar to the technique used to determine the amount of tissue muscle damage after heart attacks and strokes) showed that the blood supply to the lamellar region was indeed compromised. However, the decreased lamellar perfusion observed was based on blood vessel studies made when clinical laminitis was already underway. The vessel constriction and reduced digital blood flow demonstrated was likely the result of lamellar injury rather than the cause of it.

Other studies used small radioactive particles that lodged in the lamellar capillaries of normal horses causing the feet to become strongly radioactive. The radioactivity was detected using a gamma camera by the technique known as scintigraphy. When horses have laminitis, the capillary sized particles no longer lodge in the foot and bypass the lamellar circulation. Vascular shunts between arteries and veins are present in the lamellar circulation and it was because these structures were open that the particles bypassed the capillary circulation. The technique showed that a decrease in lamellar capillary perfusion was present in horses with acute laminitis. The question that was not answered was “did the vascular shunting cause the laminitis?” Many have been satisfied that this was the case, but the evidence needs closer scrutiny. The experiments were performed after lamellar pathology had occurred and therefore cannot be used to imply pathogenesis. During the experiments, foot blood flow actually increased during the developmental phase, until just prior to the onset of clinical laminitis.

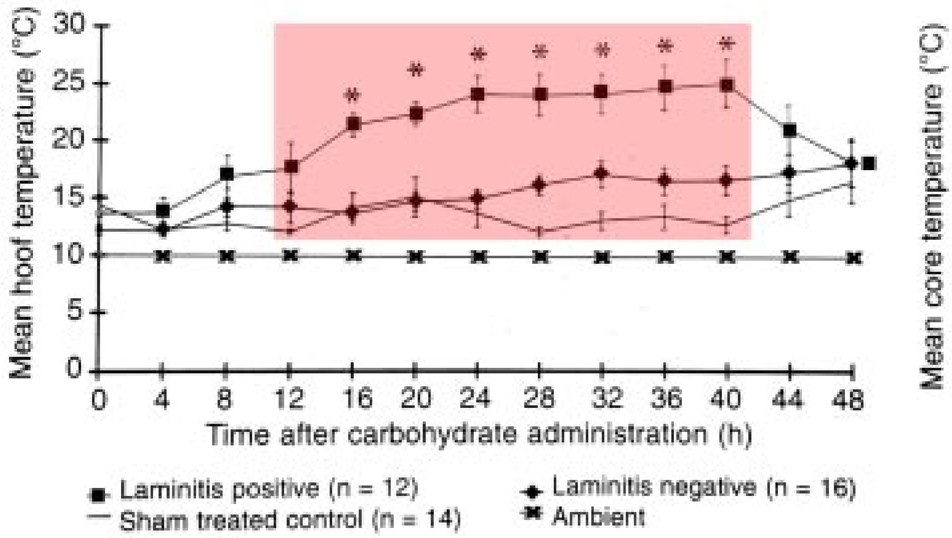
The horse tranquilizer acepromazine also dilates blood vessels and appears to prevent laminitis in some circumstances. This has been attributed to the drug being a vasodilator (inhibiting vasoconstriction in the hoof) and thus preventing lamellar ischaemia. However, the drug has other metabolic effects. In particular it increases insulin secretion and the production of glucose by the liver. This could result in increased utilisation of glucose by hoof tissues and protect them from the effects of glucose starvation. A unifying theory of laminitis aetiology based on lamellar hoof glucose metabolism has in fact been proposed.

Vasodilation theories

In contrast to the popular vasoconstriction/ischaemia theories, experiments that measured digital blood flow directly during developmental and acute laminitis showed that blood flow actually increased (vasodilation) prior to the development of laminitis foot pain. Many researchers do not support lamellar ischaemia as a primary cause of laminitis. Non-invasive, scintigraphic studies of the digital circulation show a statistically significant elevation of sublamellar blood flow prior to lameness.

Vasodilation is associated with laminitis

To determine if it was lamellar vasoconstriction or vasodilation which preceded laminitis, lamellar hoof temperature was measured continuously in horses at risk of developing laminitis in a variety of clinical situations. Variations in hoof temperature were assumed to signify fluctuations in lamellar blood flow. The unambiguous presence or absence of laminitis was based on histopathological grading of lamellar tissues of horses that were euthanased for humane reasons. Analysis of mean hoof temperature graphs showed that the 6 horses judged laminitis positive had experienced a period of prolonged digital vasodilation during the developmental phase. The 8 laminitis negative horses experienced no such period of vasodilation and had hoof temperatures never significantly above that of normal horses.



▲FIGURE 4.5 Mean temperatures (+/- standard error) of hooves from laminitis positive, laminitis negative and untreated control horses. All horses that passed through the laminitis developmental stage (pink box) with hot feet developed laminitis. Horses that were able to maintain cool feet did not have laminitis at the end of the developmental period. A group of normal horses had foot temperatures similar to the laminitis negative horses. All the horses were housed in climate controlled laboratory with an ambient temperature set at 10 °C. This result suggested that a period of sublamellar vasodilation was required before laminitis could occur.

Despite the horses appearing equally ill with similar clinical signs of fever, gut stasis (paralytic ileus), diarrhoea, elevated heart rate and low faecal pH, the only parameter which significantly differentiated the laminitis positive from laminitis negative horses, during the developmental phase was foot temperature. Thus for laminitis to occur, a period of sublamellar vasodilation during the developmental phase must occur **(Figure 4.5)**. If the digital circulation attains vasoconstriction during this period then laminitis does not occur.

It was assumed that the period of increased digital perfusion in laminitis positive horses, concomitant with the severe metabolic crisis brought on by alimentary carbohydrate overload, metritis/retained placenta or pleuropneumonia exposed lamellar tissues to a concentration of blood borne factors sufficient to trigger lamellar separation.

A hypothesis that lamellar separation could occur if uncontrolled MMP activation damaged the lamellar basement membrane was developed. Evidence that metalloproteinase production increased and metalloproteinase activation occurred was required for this theory to be validated.

Key Points

- A problem with one or more of the major organ systems produces trigger factors that cause lamellar separation during the developmental phase of laminitis. The appearance of clinical foot pain and lameness marks the start of the acute phase of laminitis.

- Acute laminitis usually progresses to chronic laminitis with downward displacement of the distal phalanx within the hoof capsule causing varying degrees of lameness (Obel grading) depending on the extent of the lamellar pathology.

- Disturbances of the gastrointestinal tract are commonly involved in the pathology of laminitis. These problems are often caused by the consumption of excess starch or fructan when animals consume large amounts of grain or have unlimited access to lush pasture, respectively.

- In the caecum, the presence of excess starch or fructan produces an environment that favours the rapid proliferation of Gram-positive bacteria that produce lactic acid and causes the release of endotoxin from Gram-negative bacteria.

- Control of lactic acid-producing bacteria by Virginiamycin, administered prior to carbohydrate overload, prevents laminitis and D-lactic acid production by bacteria.

- A period of sublamellar vasodilation occurs during the developmental phase in horses that become laminitic, raising the possibility of blood borne laminitis trigger factors.