Equine Laminitis
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Contributors

**Dominique Alfandari**
University of Massachusetts
Department of Veterinary and Animal Sciences
Amherst
MA 01003
USA

**Simon R. Bailey**
Associate Professor and Reader
Faculty of Veterinary and Agricultural Sciences
University of Melbourne
Victoria
Australia

**Gary M. Baxter**
Associate Dean for Clinical Services, Director
Veterinary Teaching Hospital
University of Georgia
Athens
GA
USA

**James K. Belknap**
Professor of Equine Surgery
Department of Veterinary Clinical Sciences
College of Veterinary Medicine
The Ohio State University
Columbus
OH
USA

**Samuel J. Black**
University of Massachusetts
Department of Veterinary and Animal Sciences
Amherst
MA 01003
USA

**Raul J. Bras**
Rood and Riddle Equine Hospital
Podiatry Department
Lexington
KY
USA

**Teresa A. Burns**
Clinical Assistant Professor
Equine Internal Medicine
Department of Veterinary Clinical Sciences
College of Veterinary Medicine
The Ohio State University
Columbus
OH
USA

**Hans Castelijns**
Equine Podiatry Consultant
Cortona
Tuscany
Italy

**Helen Davies**
Associate Professor in Veterinary Anatomy
Faculty of Veterinary and Agricultural Sciences
The University of Melbourne
Victoria
Australia

**Thomas J. Divers**
Cornell University
College of Veterinary Medicine
Ithaca
NY
USA

**Bernd Driessen**
Professor of Anesthesiology
Section of Anesthesia
Department of Clinical Studies-New Bolton Center
School of Veterinary Medicine
University of Pennsylvania
Kennett Square, Pennsylvania
USA

**Andy E. Durham**
The Liphook Equine Hospital
Forest Mere
Liphook
Hampshire
UK

**Susan C. Eades**
Department of Veterinary Clinical Sciences
School of Veterinary Medicine
Louisiana State University
Baton Rouge
LA
USA

**Randy B. Eggleston**
Clinical Professor of Large Animal Surgery
Department of Large Animal Medicine
College of Veterinary Medicine University of Georgia
Athens
GA
USA
Erica Pawlak  
University of Massachusetts  
Department of Veterinary and Animal Sciences  
Amherst  
MA 01003  
USA

John F. Peroni  
Associate Professor Large Animal Surgery  
Department of Large Animal Medicine  
College of Veterinary Medicine  
University of Georgia  
Athens  
GA  
USA

Christopher C. Pollitt  
Emeritus Professor of Equine Medicine  
Australian Equine Laminitis Research Unit  
School of Veterinary Science  
The University of Queensland  
Gatton Campus  
Queensland 4343  
Australia

Jeff Ridley  
Farrier, AFA, CJE, TE  
Leighton  
IA  
USA

Amy Rucker  
Midwest Equine  
Columbia  
MO  
USA

Harold C. Schott, II  
Professor  
Department of Large Animal Clinical Sciences  
College of Veterinary Medicine  
Michigan State University  
East Lansing  
MI  
USA

Debra Taylor  
Associate Professor  
Department of Clinical Sciences  
College of Veterinary Medicine  
Auburn University  
AL  
USA

Ramiro E. Toribio  
Professor of Equine Medicine  
Department of Veterinary Clinical Sciences  
College of Veterinary Medicine  
The Ohio State University  
Columbus  
OH  
USA

Andrew van Eps  
Associate Professor of Equine Medicine  
Australian Equine Laminitis Research Unit  
School of Veterinary Science  
The University of Queensland  
Gatton Campus  
Queensland 4343 Australia

Richard Wayne Waguespack  
Southeastern Veterinary Surgery Center  
Columbus  
GA  
USA

Donald M. Walsh  
Founder, Animal Health Foundation  
Director of Clinical Research, Homestead Veterinary Hospital  
Villa Ridge  
MO  
USA

Le Wang  
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)  
National Institutes of Health (NIH)  
Bethesda  
MD 20892  
USA

Laura Zarucco  
Dipartimento di Scienze Veterinarie  
Scuola di Agraria e Medicina Veterinaria  
Università degli Studi di Torino  
Grugliasco  
Italy

Fengqiu Zhang  
University of Massachusetts  
Department of Veterinary and Animal Sciences  
Amherst  
MA 01003  
USA
I was once asked to introduce Professor James Belknap and present to him an award at a prestigious International Equine Conference on Laminitis. The award was for scientific excellence in the field of laminitis research, and the venue was a noisy gala dinner in West Palm Beach, USA. I thought it best not to elaborate too grandly about his already numerous and excellent contributions to the science of laminitis, so without much preamble I happily presented the award with acclamation from the audience. That was over 10 years ago and could have been the culmination of his career if he had slipped into university administrative roles as so many top academics do. However, fortunately for us, his hunger to decipher laminitis prevailed and his scientific production continued setting him apart from his peers and placing him at the forefront of the laminitis scientific community. He is the pre-eminent thinker and instigator of cutting-edge laminitis research, so it is entirely appropriate that he contributes to and edits this important first in the laminitis literature. Jim has the historical background and vision to choose the appropriate authors and rigorously oversee their contributions to deliver an historic, first of its kind publication; a multiauthor text with the scope to deliver new information on nearly every aspect of Equine Laminitis. This ranges from the latest molecular perturbations at the cellular level, state-of-the-art radiography, to the effectiveness of various clinical shoeing techniques applied to horse’s feet. 

I try to keep abreast of the laminitis literature and didn’t expect to learn much by reading the chapters of this book, but I was agreeably shocked to discover how little I knew and much that was new and interesting. It was like meeting old friends and colleagues and talking ‘laminitis.’ In a book of this sort, the rigours of peer review are relaxed a little and the authors are able to not only present the expert details of their specialization, but to speculate and ‘think outside the box.’ Thus, we learn of visions for future research, why certain procedures failed or succeeded, and exciting – yet to be published – data.

Reading this book will bring you up to date with the latest information on the horse’s foot and its major affliction, laminitis. It will help you better understand the disease and thus formulate effective preventive and treatment strategies. It will even help you deliver improved lecture and workshop material. I was recently lecturing internationally and, stuck with the habit of updating my lecture material at the last minute and with early access to the chapters of the book, I was able to quickly add new, pertinent material (referenced of course) to my PowerPoints. Thus, the text is a timely and essential ‘must-have’ addition to the bookshelf or computer/tablet of all who work with and are fascinated by the horse’s foot.

Although long overdue, a book such as this, written after we have struggled with laminitis into the modern era of molecular biology and veterinary diagnostics, can at last capture important progress that has arisen from peer-reviewed, validated basic and clinical research (all of which is presented by the chief investigators and their teams in the chapters that follow). An example is the recognition that three different categories of laminitis exist: sepsis-related; endocrinopathic; and supporting limb laminitis. Knowing that treatment should be anti-inflammatory, insulin-reducing or circulation-promoting, respectively, has translated into more effective clinical management. Another realization is that, regardless of the laminitis category, the essential clinical problem is displacement of the distal phalanx and its wide-ranging anatomical consequences. Chapters devoted to digital radiographic imaging that can be enhanced with contrast media show how to assess the new laminitis case, monitor the effects of therapeutic farriery on the position of the distal phalanx, and follow the progression of laminitis into its chronic phase. It was refreshing to read that nonsteroidal anti-inflammatory drugs (NSAIDs), while having many useful properties for laminitis therapy, likely have little or no efficacy in directly preventing the condition (Dr J Divers, Medical treatment of the laminitic patient – anti-inflammatory therapy; see Chapter 31). Dr Divers’ personal insight that prognosis after sepsis-related laminitis can be correlated to the positive or negative analgesic response to initial phenylbutazone dosing is noteworthy, therapeutic prognostication.

Many teachers of laminitis and certain textbooks still hold with some form of blood supply problem being central to the pathophysiology of all types of laminitis. This long-held tenet has endured long after publication of evidence to the contrary, and I anticipate this textbook will accelerate revision towards more evidence-based pathogenesis. Indeed, Professor Belknap in his introduction to this book states “Lamellar ischemia, originally thought to be the driving force behind all types of laminitis, only appears to play a primary role in supporting limb laminitis.” Perhaps the documented presence of vasoconstrictive agents that has been the focus of extensive laminitis research plays only a contributing, synergistic role, in combination with the overwhelming inflammatory mechanisms as suggested by Dr Simon Bailey in his chapter, ‘Vasoactive drug therapies for
laminitis – pharmacological and clinical aspects.’ Recent research indicates that drugs used to promote digital vasodilation for decades, including acepromazine (likely the second most commonly used drug in laminitis therapy after phenylbutazone) are ineffective, and that lamellar blood flow is probably more responsive to dynamic loading/unloading of the foot than to any pharmacological intervention.

A novel focus of the book are chapters devoted to a single cell; the lamellar basal epithelial cell (LBEC), the building block of hoof lamellae. Ultimately, layers of LBECs are responsible for the suspension of the distal phalanx by the hoof wall, and these chapters suggest that dysregulation of the LBEC and its intimate attachments to its neighbors and to the lamellar dermis via its basement membrane is at the heart of the laminitis lesion. It is now clear that the LBEC is not just a casualty of the events occurring within the lamellae, but is likely to be an active participant in the events leading to its structural failure (Dr Leise’s chapter ‘Inflammation’). In other words, any current hierarchical description of laminitis should start with the LBEC and progress to failure of the suspensory apparatus of the distal phalanx. This concept makes the term laminitis redundant, since the only category of laminitis with a proven inflammatory basis is the sepsis-related form. For clarity, laminitis descriptors should be enrolled to ensure meaning (e.g., clinical laminitis, hyperinsulinemic laminitis, histopathologic laminitis, etc.).

Balance is essential in a book such as this, and it is important that readers should be presented with views counter to those generally accepted. This applies particularly to the question of raising the heels of horses with chronic laminitis. This common practice, deemed beneficial to reduce the pull of the deep flexor tendon, is challenged in the chapter ‘Digital Biomechanics Relevant to Laminitis’ by Professors Merritt and Davies. By increasing the angle of the hoof, more shear loading may be applied to the lamellar junction and despite the force of the deep digital flexor tendon being reduced, this may be more likely to cause tearing of the lamellar junction and promote its failure. Thus, the mechanical benefits of raising or lowering the heels are currently in dispute, and the reader will benefit from reading the complete chapter and that of Dr A. Parks ‘Anatomy and Function.’ Likewise, deep flexor tenotomy surgical technique is put into perspective as a salvage procedure, rather than a treatment, and an option only likely to increase the comfort of the animal for a variable amount of time, and rarely to allow the animal to return to a low level of athletic activity (Dr W. Waguespack, ‘Deep Digital Flexor Tenotomy’). On the other hand, other well-respected authors in this text promote both heel elevation and deep flexor tenotomy, giving the reader the opportunity to question these techniques and formulate therapeutic options for their own laminitis patients based on reasonable hypotheses.

Finally, as the editor points out in his introduction, a thorough understanding of the different parameters of the diseases leading to lamellar injury and the biomechanics of the foot are required to successfully treat the wide variety of clinical scenarios grouped under laminitis. This text will serve Dr Belknap’s vision and amply promote an understanding of laminitis and enable clinicians (veterinarians, farriers, and trimmers) to work together with new information at their disposal to approach each individual laminitis case.

At the American Association of Equine Practitioners Annual Convention (New Orleans) in 2003, I concluded my ‘Laminitis – In-Depth’ presentation by stating: “The biological basis of laminitis has become molecular and the discipline of molecular biology has laminitis in its cross-hairs. These are exciting times to be involved in equine research – we now have tools our forefathers would not have thought possible. A coherent body of knowledge will soon emerge that will demystify laminitis.” Professor Belknap has taken up the molecular biology toolset, and a true understanding of laminitis is indeed emerging from the mist. To achieve this, he created multicenter, international research teams (including Australia), and the outcomes of his work – and that of his collaborators – are presented within the pages of this book.

Ten years ago at the International Equine Conference on Laminitis, at West Palm Beach, I awarded Professor Belknap the award for scientific excellence in the field of laminitis research. I’m certainly glad I did because, as this text proves, there is no doubt that James Belknap has gone on to become the preeminent laminitis researcher of our time. We are fortunate indeed that he has dedicated time and effort away from his research to put together an encyclopedia of laminitis information to benefit us all in our efforts to comfort horses and ponies with the bane of laminitis.

Christopher C. Pollitt
Brisbane, Australia
Author of The Illustrated Horse’s Foot – a Comprehensive Guide, 2016, Elsevier, MO.
Abbreviations

\(\alpha\)-MSH \hspace{1cm} \text{alpha-melanocyte-stimulating hormone}\ 
\(\beta\)-MSH \hspace{1cm} \text{\(\beta\)-melanocyte-stimulating hormone}\ 
\(\beta\)-END \hspace{1cm} \text{\(\beta\)-endorphin}\ 
\(\gamma\)-MSH \hspace{1cm} \text{\(\gamma\)-melanocyte-stimulating hormone}\ 
11\(\beta\)-HSD \hspace{1cm} \text{11\(\beta\)-hydroxysteroid dehydrogenase}\ 
2-ITT \hspace{1cm} \text{two-step insulin tolerance test}\ 
5-HT \hspace{1cm} \text{5-hydroxytryptamine}\ 
AA \hspace{1cm} \text{arachidonic acid}\ 
ACTH \hspace{1cm} \text{adrenocorticotropic hormone}\ 
ADAMTS4 \hspace{1cm} \text{a disintegrin and metalloprotease with thrombospondin motifs 4}\ 
ADP \hspace{1cm} \text{adenosine 5'-diphosphate}\ 
AGE \hspace{1cm} \text{advanced glycation end-product}\ 
AIRg \hspace{1cm} \text{acute insulin response to glucose}\ 
AJ \hspace{1cm} \text{adherens junction}\ 
AMP \hspace{1cm} \text{adenosine monophosphate}\ 
AMPK \hspace{1cm} \text{adenosine monophosphate-activated protein kinase}\ 
APC \hspace{1cm} \text{adenomatous polyposis coli}\ 
APTT \hspace{1cm} \text{activated partial thromboplastin time}\ 
ATF3 \hspace{1cm} \text{activating transcription factor-3}\ 
ATP \hspace{1cm} \text{adenosine 5'-triphosphate}\ 
AUC \hspace{1cm} \text{area under the curve}\ 
AVA \hspace{1cm} \text{arteriovenous anastomosis}\ 
BCS \hspace{1cm} \text{body condition score}\ 
BM \hspace{1cm} \text{basement membrane}\ 
BMZ \hspace{1cm} \text{basement membrane zone}\ 
BWHE \hspace{1cm} \text{black walnut heartwood extract}\ 
cAMP \hspace{1cm} \text{cyclic adenosine monophosphate}\ 
CD \hspace{1cm} \text{cluster differentiation}\ 
CGITT \hspace{1cm} \text{combined glucose-insulin tolerance test}\ 
cGMP \hspace{1cm} \text{cyclic guanosine monophosphate}\ 
CGRP \hspace{1cm} \text{calcitonin gene-related peptide}\ 
CHO \hspace{1cm} \text{carbohydrate overload}\ 
CIVD \hspace{1cm} \text{cold-induced vasodilation}\ 
CK1\(\alpha\) \hspace{1cm} \text{casein kinase 1\(\alpha\)}\ 
CLIP \hspace{1cm} \text{corticotropin-like intermediate lobe peptide}\ 
CLP \hspace{1cm} \text{cecal ligation and puncture}\ 
CNS \hspace{1cm} \text{central nervous system}\ 
CNS \hspace{1cm} \text{crest-neck score chapter 23}\ 
COP \hspace{1cm} \text{center of pressure}\ 
COPr \hspace{1cm} \text{colloid osmotic pressure}\ 
COR \hspace{1cm} \text{center of rotation}\ 
COX-2 \hspace{1cm} \text{cyclooxygenase-2}\ 
CP \hspace{1cm} \text{calprotectin}\ 
CPNB \hspace{1cm} \text{coronary plexus}\ 
CRI \hspace{1cm} \text{continuous peripheral nerve blockade}\ 
CV \hspace{1cm} \text{circumflex vessel}\ 
DAMP \hspace{1cm} \text{damage-associated molecular pattern}\ 
DDF \hspace{1cm} \text{deep digital flexor}\ 
DDFT \hspace{1cm} \text{deep digital flexor tendon}\ 
DGGE \hspace{1cm} \text{denaturing gradient gel electrophoresis}\ 
DI \hspace{1cm} \text{disposition index}\ 
DIC \hspace{1cm} \text{disseminated intravascular coagulation}\ 
DIF \hspace{1cm} \text{distal interphalangeal}\ 
DIP \hspace{1cm} \text{distal interphalangeal joint}\ 
DDT \hspace{1cm} \text{Dickkopf}\ 
DM \hspace{1cm} \text{diabetes mellitus}\ 
DMP \hspace{1cm} \text{dry matter}\ 
DMSO \hspace{1cm} \text{dimethyl sulfoxide}\ 
DoP \hspace{1cm} \text{degree of polymerization}\ 
DP \hspace{1cm} \text{distal phalanx}\ 
DRG \hspace{1cm} \text{dorsal root ganglia}\ 
DST \hspace{1cm} \text{dexamethasone suppression test}\ 
DTO \hspace{1cm} \text{di-tri-octahedral}\ 
DDFT \hspace{1cm} \text{developmental time point}\ 
ECF \hspace{1cm} \text{extracellular fluid}\ 
ECGF \hspace{1cm} \text{endothelial cell growth factor}\ 
ECM \hspace{1cm} \text{extracellular matrix}\ 
EGF \hspace{1cm} \text{epidermal growth factor}\ 
ECM \hspace{1cm} \text{euglycemic–hyperinsulinemic clamp}\ 
EHSC \hspace{1cm} \text{equine hindgut streptococcal species}\ 
EMS \hspace{1cm} \text{equine metabolic syndrome}\ 
EMSAL \hspace{1cm} \text{equine metabolic syndrome-associated laminitis}\ 
EMT \hspace{1cm} \text{epithelial to mesenchymal transition}\ 
eNOS \hspace{1cm} \text{endothelial nitric oxide synthase}\ 
ESC \hspace{1cm} \text{ethanol-soluble carbohydrate}\ 
EVA \hspace{1cm} \text{endothelin-1}\ 
EVA \hspace{1cm} \text{ethyl vinyl acetate}\ 
FEA \hspace{1cm} \text{finite element analysis}
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<td>FFA</td>
<td>free fatty acid</td>
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<tr>
<td>FISH</td>
<td>fluorescence <em>in-situ</em> hybridization</td>
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<td>FSIGTT</td>
<td>frequently-sampled intravenous glucose tolerance test</td>
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<td>GABA</td>
<td>γ-aminobutyric acid</td>
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<td>GH</td>
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<td>glucose-dependent insulinotropic polypeptide</td>
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<td>IGF-1 receptor</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemistry</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
<tr>
<td>iNOS</td>
<td>inducible nitric oxide synthase</td>
</tr>
<tr>
<td>IRc</td>
<td>insulin receptor</td>
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<tr>
<td>IR</td>
<td>insulin resistance</td>
</tr>
<tr>
<td>IRS</td>
<td>insulin receptor substrate</td>
</tr>
<tr>
<td>IRT</td>
<td>insulin response test</td>
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<tr>
<td>ITT</td>
<td>insulin tolerance test</td>
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<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>IVGTT</td>
<td>intravenous glucose tolerance test</td>
</tr>
<tr>
<td>KA</td>
<td>keratinized axis</td>
</tr>
<tr>
<td>LBEC</td>
<td>lamellar basal epithelial cell</td>
</tr>
<tr>
<td>LCJ</td>
<td>lamellar–circumflex junction</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>LM</td>
<td>light microscopy</td>
</tr>
<tr>
<td>LMW</td>
<td>low-molecular-weight</td>
</tr>
<tr>
<td>LMWH</td>
<td>low-molecular-weight heparin</td>
</tr>
<tr>
<td>Ln 332</td>
<td>laminin-332</td>
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<tr>
<td>LPS</td>
<td>lipopolysaccharide</td>
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<tr>
<td>LRP</td>
<td>lipoprotein receptor-related protein</td>
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<tr>
<td>LTF</td>
<td>laminitis trigger factor</td>
</tr>
<tr>
<td>MAA</td>
<td>macroaggregated albumin</td>
</tr>
<tr>
<td>MAPK</td>
<td>mitogen-activated protein kinase</td>
</tr>
<tr>
<td>MCM</td>
<td>membrane-coating material</td>
</tr>
<tr>
<td>MCP-1</td>
<td>monocyte chemotactant protein 1</td>
</tr>
<tr>
<td>MDA</td>
<td>malondialdehyde</td>
</tr>
<tr>
<td>MIRG</td>
<td>modified insulin-to-glucose ratio</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinase</td>
</tr>
<tr>
<td>MODS</td>
<td>multiple organ dysfunction syndrome</td>
</tr>
<tr>
<td>MPO</td>
<td>myeloperoxidase</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MT</td>
<td>membrane-type</td>
</tr>
<tr>
<td>NADH</td>
<td>reduced nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NF-κB</td>
<td>nuclear factor kappa-B</td>
</tr>
<tr>
<td>NIR</td>
<td>near-infrared</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>NOS</td>
<td>nitric oxide synthase</td>
</tr>
<tr>
<td>NPY</td>
<td>neuropeptide Y</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>NSC</td>
<td>nonstructural carbohydrate (WSC + starch)</td>
</tr>
<tr>
<td>OCT</td>
<td>optimal cutting temperature</td>
</tr>
<tr>
<td>OF</td>
<td>oligofructose</td>
</tr>
<tr>
<td>OGTT</td>
<td>oral glucose tolerance test</td>
</tr>
<tr>
<td>OIH</td>
<td>opioid-induced hyperalgesia</td>
</tr>
<tr>
<td>OST</td>
<td>oral sugar test</td>
</tr>
<tr>
<td>PAA</td>
<td>penta-acetic acid</td>
</tr>
<tr>
<td>PAI</td>
<td>plasminogen activator inhibitor</td>
</tr>
<tr>
<td>PAL</td>
<td>pasture-associated laminitis</td>
</tr>
<tr>
<td>PAMP</td>
<td>pathogen-associated molecular pattern</td>
</tr>
<tr>
<td>PAR</td>
<td>protease-activated receptor</td>
</tr>
<tr>
<td>PAS</td>
<td>periodic acid–Schiff</td>
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<tr>
<td>PBC</td>
<td>parabasal epithelial cell</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PCV</td>
<td>packed cell volume</td>
</tr>
<tr>
<td>PDGF</td>
<td>platelet-derived growth factor</td>
</tr>
<tr>
<td>PDK1</td>
<td>phosphoinositide-dependent kinase-1</td>
</tr>
<tr>
<td>PEL</td>
<td>primary epidermal lamella/lamellae</td>
</tr>
<tr>
<td>PGK1</td>
<td>phosphoglycerate kinase 1</td>
</tr>
<tr>
<td>PHF</td>
<td>Potomac Horse Fever</td>
</tr>
<tr>
<td>PI</td>
<td>pars intermedia</td>
</tr>
<tr>
<td>PI3K</td>
<td>phosphatidylinositol 3-kinase</td>
</tr>
<tr>
<td>PIP</td>
<td>proximal interphalangeal</td>
</tr>
<tr>
<td>PIP2</td>
<td>phosphatidylinositol 4,5-bisphosphate</td>
</tr>
<tr>
<td>PMAT</td>
<td>plasma membrane monoamine transporter</td>
</tr>
<tr>
<td>PMB</td>
<td>polymixin B</td>
</tr>
<tr>
<td>PMN</td>
<td>polymorphonucleocyte</td>
</tr>
<tr>
<td>PO</td>
<td>per os (oral)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>POA</td>
<td>post oligofructose administration</td>
</tr>
<tr>
<td>POMC</td>
<td>proopiomelanocortin</td>
</tr>
<tr>
<td>PPI</td>
<td>protein phosphatase 1</td>
</tr>
<tr>
<td>PPAR-α</td>
<td>peroxisome proliferator-activated receptor-α</td>
</tr>
<tr>
<td>PPID</td>
<td>pituitary pars intermedia dysfunction</td>
</tr>
<tr>
<td>PRR</td>
<td>pattern recognition receptor</td>
</tr>
<tr>
<td>PSH</td>
<td>plasma thiol</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>PU:PD</td>
<td>polyuria/polydipsia</td>
</tr>
<tr>
<td>PV</td>
<td>pars ventralis</td>
</tr>
<tr>
<td>QUICKI</td>
<td>quantitative insulin sensitivity check index</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell</td>
</tr>
<tr>
<td>RISQI</td>
<td>reciprocal of the square root of insulin</td>
</tr>
<tr>
<td>RNS</td>
<td>reactive nitrogen species</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>RPS6</td>
<td>ribosomal protein S6</td>
</tr>
<tr>
<td>RT-qPCR or qRT-PCR</td>
<td>real-time quantitative PCR</td>
</tr>
<tr>
<td>RTX</td>
<td>resiniferatoxin</td>
</tr>
<tr>
<td>SAA</td>
<td>serum amyloid A</td>
</tr>
<tr>
<td>SADP</td>
<td>suspensory apparatus of the distal phalanx</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SDFT</td>
<td>superficial digital flexor tendon</td>
</tr>
<tr>
<td>SDL</td>
<td>secondary dermal lamella/lamellae</td>
</tr>
<tr>
<td>SDS–PAGE</td>
<td>sodium dodecyl sulfate–polyacrylamide gel electrophoresis</td>
</tr>
<tr>
<td>SEL</td>
<td>secondary epidermal lamella/lamellae</td>
</tr>
<tr>
<td>Sg</td>
<td>glucose effectiveness</td>
</tr>
<tr>
<td>SGLT-1</td>
<td>sodium glucose transporter-1</td>
</tr>
<tr>
<td>SI</td>
<td>insulin sensitivity index</td>
</tr>
<tr>
<td>siRNA</td>
<td>small interfering RNA</td>
</tr>
<tr>
<td>SIRS</td>
<td>systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SIS</td>
<td>skin immune system</td>
</tr>
<tr>
<td>SLL</td>
<td>supporting limb laminitis</td>
</tr>
<tr>
<td>SLRP</td>
<td>small leucine-rich proteoglycan</td>
</tr>
<tr>
<td>SLVB</td>
<td>sublamellar vascular bed</td>
</tr>
<tr>
<td>SOD</td>
<td>superoxide dismutase</td>
</tr>
<tr>
<td>SP</td>
<td>Substance P</td>
</tr>
<tr>
<td>SRL</td>
<td>sepsis-related laminitis</td>
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<tr>
<td>STAT</td>
<td>signal transducing activators of transcription factors</td>
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<tr>
<td>TA</td>
<td>thyroxine</td>
</tr>
<tr>
<td>TAT</td>
<td>terminal arch</td>
</tr>
<tr>
<td>TB</td>
<td>thrombin–antithrombin</td>
</tr>
<tr>
<td>TCF</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TEM</td>
<td>T-cell factor</td>
</tr>
<tr>
<td>TGFβ</td>
<td>transforming growth factor-β</td>
</tr>
<tr>
<td>TIMP</td>
<td>tissue inhibitor of metalloproteinases</td>
</tr>
<tr>
<td>TLR</td>
<td>toll-like receptor</td>
</tr>
<tr>
<td>TNFα</td>
<td>tumor necrosis factor alpha</td>
</tr>
<tr>
<td>TP</td>
<td>total protein</td>
</tr>
<tr>
<td>t-PA</td>
<td>tissue-type plasminogen activator</td>
</tr>
<tr>
<td>TRH</td>
<td>thyrotropin-releasing hormone</td>
</tr>
<tr>
<td>TRPV-1</td>
<td>transient receptor potential cation channel, subfamily V, member 1</td>
</tr>
<tr>
<td>TUNEL</td>
<td>terminal deoxynucleotidyl transferase</td>
</tr>
<tr>
<td>TxA₂</td>
<td>dUTP nick end labeling</td>
</tr>
<tr>
<td>TZD</td>
<td>thromboxane A₂</td>
</tr>
<tr>
<td>THF</td>
<td>Thiazolidinedione</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractionated heparin</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>VLDL</td>
<td>very low-density lipoprotein</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>WSC</td>
<td>water-soluble carbohydrate</td>
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</table>
CHAPTER 1

Historical Perspective on Equine Laminitis

Donald M. Walsh and Teresa A. Burns

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 at once sent for me. I discovered her to be suffering from laminitis, and saw her again in the evening, when she was much worse. The attack proved to be a most severe one. The owner informed me that she had not been allowed any corn for two months, and that she had no distance to travel on the road from the common. Though on such a poor pasture, the mare was very fat she had never been unwell before this attack. This is the first case I have seen of laminitis occurring when the animal was on grass.”

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.
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]. Saltpeter 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 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 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 laminitic (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 lamini-
tis ‘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 experi-
mental horses [40], and the original grain starch and oligofruct-
ose 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 admin-
istered via a nasogastric tube to the horse. This model is con-
sidered 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 admin-
istered, horses typically recover fully without sustaining sig-
nificant 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 rea-
son. However, this model has contributed greatly to the current
understanding of the early pathophysiological 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 collec-
tively been referred to as endocrinopathic laminitis in horses
and ponies. This category of laminitis, which is the most com-
mon form afflicting equids currently, has been long assumed
to share pathophysiological 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 experimen-
tal model of equine metabolic syndrome–associated laminitis
(EMSAL) [25, 49, 50]; however, consistent models of laminitis
associated with PPID or exogenous corticosteroid administra-
tion remain to be described (attempts to experimentally induce
laminitis in normal horses with exogenous steroid administra-
tion have been unsuccessful). Knowledge of whether these forms
of endocrinopathic laminitis are pathophysiologically similar
will depend on the development of consistent, repeatable mod-
els 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 publi-
cations that exist in the scientific literature regarding support-
ing 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 consis-
tent 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 dis-
ease, 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 hypothet-
ical 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 con-
dition 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 diced 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 laminitic 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 NANRIC 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 laminitic 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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CHAPTER 2

Laminitis: An Overview

James K. Belknap

Few diseases bring more of an emotional response from owners, trainers, veterinarians, and farriers than Equine Laminitis due to the devastating nature of the disease, exemplified by the excruciating pain suffered by many of the afflicted animals. In spite of intensive therapy, the loss of an athletic career or the life of the animal occurs all too-frequently. In the professional world of veterinary medicine and farriery, few topics can stir up a more boisterous argument than the discussion of which treatments are the most effective for laminitis. As in most diseases fraught with controversy in either equine or human medicine (e.g., human sepsis, cancer), the conflict is often a result of the grave nature of the disease combined with the frustration of health professionals confronted with inadequate knowledge regarding the pathogenesis – and therefore the effective treatment – of the disease. Similar to human medicine, veterinary research workers have been able to take advantage of the many rapid advancements in biomedical research during the past two decades to greatly broaden the current understanding of the pathophysiologic mechanisms in laminitis that take place systemically and locally in the lamellar tissue. This progress has not only allowed us to delineate the disease into three general categories – endocrinopathic, sepsis-related, and supporting limb laminitis – but has also begun to greatly change the available treatments of the different types of the disease. When looking back at the literature over the past two decades, many of the earlier advances in scientific investigation moved the field forward by refuting the efficacy of the medical therapies regarded as standards of treatment for the disease. More recently, however, it has become possible to apply new knowledge of pathophysiologic mechanisms and advanced research tools to establish new therapeutic targets and to rapidly assess novel therapies. Although the present understanding of Equine Laminitis is still evolving, the reader will be able to employ the information in this book to develop a current evidence-based knowledge of the disease and therapies.

Advances in imaging technology have greatly enhanced both the clinical and investigative side of laminitis. The ease of use and high resolution of digital radiography markedly enhances our ability to initially assess the laminitis case, to immediately assess the effects of therapeutic farriery on distal phalanx positioning, and to follow the progression of disease in laminitis cases. As discussed in the following text, the results of recent studies using the high-resolution images of digital radiography now allow us to use objective measurements to diagnose and closely monitor the laminitis case. Whilst magnetic resonance imaging (MRI) has been of more value for research than for clinical management at this point in time, it is becoming a valuable tool for clinical management in complex laminitis cases. In addition to advances in imaging, advances in biochemistry have translated into a more effective clinical management of the systemic components of laminitis cases, especially in endocrinopathic laminitis where rapidly improved testing and more accurate interpretation of the test results are available for the management of insulin dysregulation and pituitary dysfunction. This has been a major asset to the clinical management of these types of patients.

The biomechanical component of the disease remains a challenge, however, and has not benefitted as much from recent technological advances. The lamellae, as part of the hoof capsule, are truly a specialized integumentary structure with many similarities on a cellular level to the skin. The hoof evolved as a vital structural component of the musculoskeletal system, with the lamellar attachments suspending the distal phalanx (and therefore supporting the weight of the horse) within the hoof capsule. The end result is that the biomechanics of the foot is as important a factor in the pathogenesis and treatment of laminitis as is the establishment of pharmaceutical targets (discussed above). The structural integrity of the digital lamellae appears to depend on both the maintenance of the cell shape of all lamellar epithelial cells and the maintenance of adhesion of the innermost layer of epithelial cells, the lamellar basal epithelial cell (LBEC) layer, to the underlying dermis. Although the forces sustained by the lamellar epithelium are phenomenally greater than those sustained by any other epithelial cell in the body (including the skin), the lamellar epithelium appears to have only similar mechanisms to the skin epithelium (a similar cytoskeleton and the same protein adhesion complexes to adhere the basal layer to the underlying dermis) to counteract these forces. As described in the following chapters, lamellar failure appears to be a mixture
of stretching of the lamellar epithelium which is likely due to the dysregulation of epithelial cytoskeletal dynamics, and dysadhesion from the underlying dermis, which likely occurs through the dysregulation of cell adhesion complexes. Once lamellar failure occurs, these same distractive forces will result in the displacement of the distal phalanx. The unique and critical role of the lamellar epithelium in providing structural stability to an anatomical structure exposed to immense physical forces is most likely the reason that multiple systemic diseases which may have mild to no signs in other organs of the body result in structural breakdown of lamellar integrity and thus are lumped under the term laminitis. In order to successfully treat the disorders that cause lamellar failure, we therefore not only need to define and treat the systemic and cellular events leading to dysregulation of the lamellar cells, but also – and just as importantly – we need to mitigate the distractive forces leading to lamellar stretching and separation. To further our ability to successfully treat this disease, we are reliant on ongoing studies in physiology and cellular biology, as well as in equine digital biomechanics and the ability of therapeutic shoeing to address biomechanical concerns. Due to the complex nature of the structure of the equine foot, we still have limited scientific data to accurately define the biomechanical forces at play in both the normal and laminitic equine digit. Without scientific methodology to define these forces, we are also still unable to precisely establish the efficacy of different farriery and shoeing techniques to support and address the biomechanical aspect of the disease. Thus, we still rely on anecdotal reports and the combined veterinary and farrier clinical experience in the management of laminitic feet. Advances have been made primarily due to the ingenuity of farriers; however, due to an inability to objectively test different types of shoeing, a great deal of controversy persists in the care of the foot as part of management of the laminitis case. In this book, we present the current understanding of biomechanical principles taking place in the equine digit, and have attempted to provide a general overview of the current options for foot management for the different types of displacement. In the management of laminitis cases, vigilance is required not only in attempting to avoid complications, but also being able to rapidly diagnose and treat complications when they occur. Therefore, we have dedicated chapters to patient and environmental management for the avoidance of complications, and diagnostic and therapeutic techniques for the management of complications when they occur.

Finally, we need to acknowledge the pioneering efforts of many individuals, and the support of many institutions that have allowed advances in our understanding and treatment of the disease. Although the chapters related to the pathophysiology are written primarily by research workers who have conducted much of the cutting edge research over the past decade to expand our knowledge of the disease, we need to recognize many of the investigators of the past 30–50 years, many of whom had an impact on training current research teams in the field; these experts include Harold Garner (University of Missouri), Jim Moore (University of Georgia), and Chris Pollitt (University of Queensland). We must also give credit to the funding agencies around the world who have provided millions of dollars for laminitis research during the past few decades; these include (but are certainly not limited to) the Grayson Jockey Club Research Foundation, Animal Health Trust, Morris Animal Foundation, U.S. Department of Agriculture, and the Rural Industries Research and Development Corporation (Australia) and Mars Equine (UK/Australia). The Dorothy Havemeyer Research Foundation and American Association of Equine Practitioners must also be mentioned for funding international workshops on laminitis research, bringing together investigators from around the world to not only share data but also to chart the course of future research. On the hoof care side, credit must also be given to individuals such as Robert Eustace, Ric Redden, Burney Chapman, Gene Ovnicek, and Mike Steward, all of whom have played important roles in promoting innovative changes to our treatment of this devastating disease.
CHAPTER 3
Anatomy and Function of the Equine Digit

A.H. Parks

Introduction

The object of therapeutic hoof care for horses with laminitis is to stabilize as best as possible the distal phalanx (DP) within the hoof capsule by minimizing the forces that place excessive tension on the lamellae. To best understand the distribution of forces within the foot, and how they change with movement, it is important to understand the anatomic relationship between the structures of the foot, kinetic events that occur between the ground and the hoof, and the moments that occur about the distal interphalangeal joint. The distal limb contains all the main elements of the musculoskeletal system except muscles, and is covered by highly specialized integument. As such, it is a mechanical system for conveying forces to support weight and provide locomotion. At the core of this system are the bones, joints, and ligaments of the foot.

Anatomy

For this discussion, we are going to use terminology relating to the front feet (i.e., palmar). The foot contains a portion of the middle phalanx, the DP, and the navicular bone. The DP has three surfaces – the articular surface, solear surface, and parietal surface (Fig. 3.1). The junction of the parietal and solear surfaces forms the solear margin; the junction of the articular and parietal surface at the dorsal aspect of the foot forms the proximal or coronary border, part of which forms the extensor process, and the third border is formed on the palmar aspect of the bone by the junction of the solear and articular surfaces. The three surfaces converge at their medial and lateral palmar extremities to form the palmar processes of the distal phalanx. The parietal surface has a roughened texture with multiple perforations; the roughened surface is adapted for soft tissue attachments (primarily the sublamellar dermis) and the perforations permit passage of blood vessels into the adjacent soft tissues (sublamellar and lamellar dermis) of the hoof wall. The solear surface can be divided into two functional surfaces: (i) the larger planum cutaneum, which corresponds to the solear surface of the hoof (this surface does not have perforations and is smooth except where it forms the palmar processes); and (ii) the flexor surface (facies flexoria) (Fig. 3.1), which is a smaller area adjacent to the articular surface on which the deep digital flexor tendon and the distal sesamoidean ligament insert. The articular surface is divided into two functional areas also for the respective articulations – a large one (facies articularis) that articulates with the middle phalanx, and a much smaller one (facies articularis sesamoidea) located in the palmar central aspect that articulates with the navicular bone. The larger facies articularis is divided into two shallow cavities, divided by a low ridge, that articulate with the condyles of the distal middle phalanx.

Attached to the dorsal border of the palmar processes of the distal phalanx are the paired, approximately rhomboid-shaped ungual cartilages (commonly termed ‘collateral cartilages’; Fig. 3.2). Approximately 50% of each cartilage extends palmar to the DP. Additionally, approximately 30–50% of the cartilages extend proximal to the coronary band. Each cartilage is thicker distally than proximally, and the medial surface incorporates numerous channels through which veins of a vascular plexus run [1]. The thicker distal portion of the cartilages projects axially so that it is positioned immediately proximal to the bars of the solear surface of the hoof capsule in healthy horses. Additionally, fibrocartilage from the distal axial border of the cartilage blends with the digital cushion. The exact function of these cartilages is unknown, but they are believed to be important in both the normal expansion of the foot that occurs with ambulation and the related function of providing a mechanism for the distal limb to absorb the shock of impact (functioning in conjunction with the venous plexus within the ungual cartilages).

The navicular bone is spindle-shaped, with two surfaces and two borders. The dorsally located articular surface, covered with hyaline cartilage, is further divided into a main surface that articulates with the palmar aspect of the distal articular surface of the middle phalanx and a much smaller articular surface that articulates with a corresponding surface on the DP. The flexor surface on the palmar aspect of the bone, covered with fibrocartilage, facilitates passage of the deep digital flexor tendon. The proximal border is rough and approximately straight. The distal border is also roughened and perforated by several synovial invaginations.
The distal interphalangeal joint is formed by three separate articulations: one between the middle phalanx and the DP; another between the middle phalanx and the navicular bone; and the third between the DP and the navicular bone. Functionally, the DP and the navicular bone move in tandem so that together they function as a singular articular surface that rotates about the distal articular surface of the middle phalanx. The structure of the articular surfaces are such that the joint is a ginglymus joint (i.e., the primary direction of movement permitted is flexion and extension). However, the sagittal ridge on the articular surface of the DP is low and broad, as is the opposing intercondylar groove of the distal middle phalanx, so that the joint permits a modest amount of rotation and a lesser amount of movement in the frontal plane (mostly lateral to medial movement with a minor component of rotation) termed collateral motion (Fig. 3.3).

The ligaments of the distal limb maintain the position of the bones and ungual cartilage in the appropriate relationship to each other, and restrict the range of motion of the bones in relation to each other. The two most important groups of ligaments in the distal limb are the collateral ligaments of the distal interphalangeal joint (Fig. 3.4), which hold the middle and distal phalanx in opposition to each other) and the suspensory ligaments of the navicular bone which, in conjunction with the distal sesamoidean impar ligament, maintain the position of the navicular bone adjacent to the palmar aspect of the middle and distal phalanges). In addition to the ligaments supporting the distal interphalangeal joints, there are a series of ligaments that attach the ungual cartilages to the adjacent structures, including the adjacent bones.

Flexion and extension of the distal interphalangeal joint occurs both actively and passively. Active flexion follows contraction of the deep digital flexor muscle, which increases the tension in the deep digital flexor tendon (Fig. 3.5). The digital portion of the deep digital flexor tendon passes down the palmar aspect of the pastern around the flexor surface of the navicular bone to insert on the flexor surface of the distal phalanx. Active extension/dorsiflexion of the distal interphalangeal joint follows contraction of the common digital extensor muscles mediated via the common digital extensor tendon (Fig. 3.5) through its insertion on the extensor process of the distal phalanx (Fig. 3.1). Passive flexion of the distal interphalangeal joint and dorsiflexion of the metacarpophalangeal joint occur in the course of load-bearing at rest and during the first half of the stride.