



## Glucocorticoids and Laminitis in Horses\*

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### ABSTRACT:

Clinical situations associated with high glucocorticoid levels in horses sometimes involve the development of laminitis. Laminitis is a clinical component of equine Cushing's syndrome associated with pituitary pars intermedia dysfunction. Laminitis reportedly develops when dexamethasone or triamcinolone is used to treat inflammation in horses. Substantial new data point to a role for inflammation in the development of laminitis, suggesting that glucocorticoids should inhibit its development. That glucocorticoids might cause laminitis is paradoxical and lacks a satisfactory explanation. Possible and plausible pathophysiologic explanations for the risk of laminitis that accompanies high glucocorticoid levels in horses have been proposed and are reviewed in this article.

**T**here is a strong association between laminitis and increased glucocorticoid action in horses. Laminitis is a common clinical sign in equine Cushing's disease, a condition in which increased secretion of pituitary pars intermedia-derived pro-opiomelanocortin (POMC) peptides leads to perpetually enhanced adrenal secretion of cortisol, the physiologic glucocorticoid in the equine species.<sup>1</sup> Synthetic glucocorticoids with potent antiinflammatory actions have been routinely used to manage many diverse conditions and diseases, including heaves, dermatitis, purpura hemorrhagica, central nervous system inflammation, hepatitis, immune-mediated diseases, cancer, shock, and inflammatory eye diseases. However, using glucocorticoids to manage inflammation in horses

must be weighed against the well-recognized risk of developing laminitis associated with these antiinflammatory agents. Highly potent synthetic glucocorticoids such as dexamethasone and triamcinolone appear to confer an increased risk of laminitis compared with less potent compounds such as prednisolone.

There has not been a satisfactory explanation for the pathogenesis of laminitis resulting from increased glucocorticoid action. Indeed, reports in the literature dealing with this problem are scant. Eyre and coworkers<sup>2</sup> reported that the vasoconstrictive responses of equine digital arteries to catecholamines could be potentiated by betamethasone and hydrocortisone.<sup>2</sup> There is no shortage of published data to support the hypothesis that reduced blood flow in a hoof is likely an important aspect of laminitis.<sup>3-5</sup> How-

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ever, most publications in this area are based on experimental models that entail administering either starch or aqueous black walnut extract into the gastrointestinal (GI) tract to produce alimentary-type laminitis. Substantial evidence shows that laminitis resulting from treatment using either starch or aqueous black walnut extract has been associated with increased proinflammatory mediators together with lamellar infiltration by inflammatory cells.<sup>6-9</sup> Specific published examples of inflamma-

sol-mediated stress response is to ensure that adequate nutrients are being supplied to the brain and other areas of the body that might be compromised by a stressful event or injury. Cortisol induces hyperglycemia and leads to fat mobilization and protein catabolism (amino acid mobilization) to support higher energy requirements and an elevated demand for protein biosynthesis at compromised locations.<sup>16</sup> Proteins with relatively fewer critical functions are degraded into amino acids for mobilization

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## ***Using some glucocorticoids to treat equine medical conditions involves a risk of laminitis.***

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tory changes associated with alimentary-type laminitis include increased expression of interleukin (IL)-1 $\beta$  in the hoof-lamellar interface and at other locations in the body<sup>6</sup>; movement of lipopolysaccharide (bacterial endotoxin), a proinflammatory agent, into the circulation<sup>10</sup>; increased expression of cyclooxygenase-2 mRNA by vascular smooth muscle cells obtained from digital vessels<sup>11</sup>; platelet activation, platelet aggregation, and formation of platelet-neutrophil complexes<sup>12</sup>; increased expression of endothelin-1 in hoof lamellar tissues<sup>7</sup>; increased activity of collagen-degrading matrix metalloproteinases in hoof lamellar tissues<sup>8</sup>; and recruitment of polymorphonuclear granulocytes in affected lamellae.<sup>9,13</sup>

Because multiple diverse inflammatory changes accompany the development of alimentary-type laminitis, it could be concluded that glucocorticoids should protect against and not increase the risk of developing this condition. A number of researchers, citing failed attempts to experimentally induce laminitis with high-level glucocorticoid administration, have challenged the concept that glucocorticoids actually cause equine laminitis.

### **ROLE OF GLUCOCORTICOIDS IN HEALTH**

The physiologic glucocorticoid in horses is cortisol, a steroid hormone produced and secreted by the adrenal cortices, the vital functions of which include regulation of blood glucose and maintenance of normal blood pressure.<sup>14</sup> Almost all cells of the body contain glucocorticoid receptors. Cortisol production increases in response to stress (e.g., trauma, infection, intense heat or cold, surgery, restraint, debilitating disease) and is a physiologic adaptation that promotes survival.<sup>15</sup> One beneficial corti-

into the circulation sooner than proteins with essential functions, such as brain neurotransmitters and muscle contractile proteins. Another effect of cortisol is reversal and down-regulation of inflammatory responses resulting from a stressful event.<sup>17</sup>

It has been suggested that stress might predispose some horses to laminitis or even cause it; however, whether this is due to increased endogenous cortisol secretion has not been determined. Pain caused by laminitis represents severe stress for horses, irrespective of the underlying cause. Therefore, protracted laminitis results in elevated endogenous cortisol secretion, which could contribute to the disease's persistence and refractoriness.

### **SYNDROMES OF GLUCOCORTICOID EXCESS**

In 1932, Dr. Harvey W. Cushing described the human syndrome resulting from long-term glucocorticoid exposure.<sup>18</sup> In horses, the most common cause of Cushing's syndrome is believed to be pituitary pars intermedia dysfunction, in which excessive quantities of POMC peptides, including adrenocorticotrophic hormone (ACTH), corticotropin-like intermediary peptide,  $\beta$ -endorphin, and  $\alpha$ -melanocyte-stimulating hormone, are released from the pituitary in an unregulated manner.<sup>1</sup> Persistent POMC peptide-stimulated elevation of cortisol secretion by the adrenal cortices represents an important and central component of the pathophysiology of pituitary pars intermedia dysfunction in horses.

Cushing's syndrome also arises when synthetic glucocorticoids are exogenously administered to horses. There have been rare reports of equine Cushing's syndrome resulting from primary adrenal neoplasia.<sup>19</sup> In "peripheral"

Cushing's syndrome, certain tissues become exposed to elevated cortisol levels because of glucocorticoid regeneration from abundant supplies of cortisone, the circulating inactive metabolite of cortisol.<sup>20</sup> Conversion of cortisone to cortisol occurs locally via 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) enzyme activity.<sup>21</sup> Mechanisms controlling 11 $\beta$ -HSD1 activity are not well understood, although there is compelling evidence that certain fat depots in obese humans and horses generate cortisol at the tissue or cellular level.<sup>22</sup> We have shown that 11 $\beta$ -HSD1 activity is increased in both skin and hoof lamellar tissues obtained from laminitic horses, suggesting that locally increased glucocorticoid action might contribute to the morbidity rate of laminitis through autocrine and paracrine mechanisms.<sup>23</sup>

### CONSEQUENCES OF GLUCOCORTICOID EXCESS

In most instances, the pathologic consequences of excess glucocorticoids represent a simple extension of the physiologic effects of cortisol in the body.<sup>1,18</sup> Glucocorticoid excess leads to widespread protein catabolism in skin, connective tissues, bone, and skeletal muscle. These effects lead to skin atrophy, poor wound healing,<sup>24</sup> muscle wasting and weakness,<sup>25</sup> and, ultimately, bone resorption (i.e., osteoporosis).<sup>26</sup> The antiinflammatory and immunosuppressive effects of excess glucocorticoids contribute to a relatively immunocompromised state resulting from inhibition of many inflammatory mechanisms.

A well-recognized feature of Cushing's disease in

several hormones and metabolically active signals such as tumor necrosis factor- $\alpha$ , IL-6, leptin, adiponectin, mineralocorticoid-releasing factor, resistin, and cortisol (due to 11 $\beta$ -HSD1 activity).<sup>27</sup> Therefore, patients with Cushing's syndrome are affected by elevated, adrenally derived glucocorticoids, together with clinically significant increased levels of adipose-derived hormones.<sup>28</sup>

Glucocorticoids inhibit the action of insulin<sup>29,30</sup> and stimulate hepatic gluconeogenesis, dual functions that promote glucose availability to cells in the central nervous system and other cells that do not depend on insulin for glucose uptake. Proposed mechanisms of glucocorticoid-induced insulin resistance include reduced numbers of insulin receptors, reduced receptor affinity for insulin, defective intracellular signaling, or a combination of these. In addition, the adipose-derived hormone resistin inhibits the action of insulin in humans.<sup>31</sup> It has not been determined whether adipose-derived hormones contribute to insulin resistance in equine Cushing's syndrome.

### RISK OF LAMINITIS WHILE TREATING HORSES WITH GLUCOCORTICOIDS

Veterinary practitioners must consider the potentially harmful effects of treating horses with synthetic glucocorticoids, which vary greatly in potency. The likelihood of laminitis appears to be greater with more potent agents, such as triamcinolone and dexamethasone, and reduced with less potent ones, such as prednisone and prednisolone. The reduced risk of laminitis may be related to the

***Although the risk of laminitis is greater when using dexamethasone or triamcinolone rather than prednisolone, the risk is always unpredictable.***

humans is accumulation of body fat distributed in an unusual but characteristic manner. Intraabdominal (omental) adiposity typically increases; the extremities become thin because of muscle wasting; and fat accumulates in the abdominal wall, face, and upper back.<sup>27</sup> The pathologic consequences of excessive intraabdominal adiposity have received extensive attention in the past few years. Although adipose tissue has traditionally been regarded as a simple fat repository, it has been shown that omental adipocytes, such as those arising from the action of glucocorticoid excess, are unique. They produce

possibly very low bioavailability of prednisone in horses following oral administration.<sup>32</sup> Based on what is known regarding the pathogenesis of alimentary-type laminitis, glucocorticoids should theoretically not cause laminitis and might even be useful in treating and preventing this condition. Possible explanations for the pathogenesis of glucocorticoid-associated laminitis follow.

There have been little published data on the association between glucocorticoids and laminitis because of the unpredictability of the relationship. The probability of healthy horses developing laminitis during short-

term treatment with dexamethasone or triamcinolone appears to be very small.<sup>33</sup> Glucocorticoids appear to have caused laminitis in some horses in which preexisting but subclinical laminitis had already developed and had been unrecognized. We propose that excessive glucocorticoids cause structural changes that weaken the hoof-lamellar attachment over many months, thus predisposing horses to laminitis for other traditional reasons.<sup>34</sup> In horses that have already sustained lamellar weakening, treatment using glucocorticoids may precipitate laminitis in a short time, suggesting that laminitis resulted from the treatment. Glucocorticoids exert numerous effects, including those on blood vessels, the skin, the intestines, the action of insulin, and body-fat composition, that could contribute to the pathophysiology of laminitis.

## GLUCOCORTICOID EFFECTS ON BLOOD VESSELS

Poor blood flow is a well-documented pathologic aspect of laminitis.<sup>2</sup> Both betamethasone and hydrocortisone have been shown to potentiate the vasoconstrictive actions of the catecholamines epinephrine, norepinephrine, and serotonin on large digital vessels; however, whether potentiation of catecholamine-induced vasoconstriction is sufficient to explain the development of laminitis per se has not been determined.<sup>2</sup> Ex vitro studies on the contractile and relaxing functions of blood vessels pertaining to equine laminitis should ideally be conducted on arterioles and venules obtained from the hoof-lamellar interface rather than the large digital vessels. Acquiring suitable vessels from this intracapsular location is problematic, and their relatively small size also presents practical difficulties.

Blood flow through critical tissues is primarily governed by contractility of vascular smooth muscle in strategically located, small-diameter arterioles. We recently showed that dexamethasone and triamcinolone tend to increase contractility of vascular smooth muscle cells, resulting in reduced blood flow.<sup>35</sup> Vascular tone is regulated by complex interplay between blood pressure, circulating hormones, neurotransmitters, and endothelium-derived factors integrated with vascular smooth muscle cells that change the luminal diameter and hydraulic resistance of blood flow.<sup>36</sup> Contraction of vascular smooth muscle is modulated by intracellular cytosolic calcium ion concentration, which is increased by mobilization of intracellular calcium stores and influx of calcium ions through designated voltage-gated cal-

cium channels in the plasma membrane.<sup>36</sup> Calcium influx into cells, ionic calcium release in cytosol, and calcium sensitivity of the contractile machinery of vascular smooth muscle cells are all regulated and modulated by plasma membrane potential, which is determined by potassium, chloride, and calcium channels.

According to results of preliminary studies from our laboratory, treating horses with triamcinolone or dexamethasone depressed potassium currents in vascular smooth muscle cells obtained from the digital artery.<sup>35</sup> These findings could help explain the potentiating effect of glucocorticoids on the vasoconstrictive actions of catecholamines reported previously. Further studies involving small resistance vessels obtained from the hoof-lamellar interface are clearly needed.

Endothelially derived nitric oxide (NO) and endothelin-1, potent vasorelaxing and vasoconstricting substances, respectively, strongly influence vascular smooth muscle tone. Glucocorticoids act indirectly (via insulin resistance) to cause endothelial cells to produce a preponderance of constricting factors and to reduce NO production.<sup>37,38</sup> Chronic insulin resistance is thus accompanied by proconstrictive events in blood vessels.

## GLUCOCORTICOID EFFECTS ON THE INTEGUMENT

The hoof-lamellar interface is a highly specialized part of the integument. It is conceivable that initiating events of laminitis, characterized by separation of the epidermis from the underlying dermis, result from glucocorticoid-induced lamellar weakening due to increased protein catabolism. The hoof-lamellar attachment is a highly dynamic interface that is perpetually remodeled to meet the needs of tissue "wear and tear." This attachment normally serves to offset tensile forces derived from the deep digital flexor tendon and considerable forces applied by the weight of the horse, rider, and saddle as well as exercise. Normal physiologic repair mechanisms, including fibroblast growth and biosynthesis of collagen, are inhibited by glucocorticoids, possibly predisposing horses to laminitis (i.e., mechanical failure at the attachment interface).<sup>25,39-41</sup> We contend that actual structural changes in the hoof-lamellar interface characterized by broad growth lines (i.e., "lamellar rings"; Figure 1) and a dropped sole result from chronic glucocorticoid action.<sup>34</sup> These changes appear similar to those commonly associated with painful laminitis. Although not necessarily painful, glucocorticoid changes in the attachment interface may predispose horses to laminitis.

A critical step in the pathogenesis of acute laminitis appears to be failure of basal keratinocytes to attach to underlying lamellar basement membrane (LBM).<sup>9</sup> Factors that might weaken the strength of this dermoepidermal attachment interface can cause laminitis. Keratinocyte-attachment failure is accompanied by matrix metalloproteinase-induced degradation of LBM during alimentary-type laminitis. Keratinocytes are richly endowed with glucocorticoid receptors, and dexamethasone has been shown to decrease anchoring proteins that connect basal keratinocytes to LBM.<sup>39</sup> Furthermore, cortisol has been shown to actually inhibit keratinization of bovine hooves.<sup>41</sup>

Basal keratinocytes obtained from equine hooves have an exceptionally high glucose requirement.<sup>42</sup> It has not been determined whether glucocorticoid-associated insulin resistance could compromise the health of keratinocytes and weaken their attachment to the underlying LBM.

### GLUCOCORTICOID EFFECTS ON THE GASTROINTESTINAL TRACT

Increased permeability of the mucosal lining of the entire GI tract of laboratory animals has been attributed to exogenous dexamethasone and increased release of endogenous glucocorticoids during stress.<sup>43-45</sup> Increased permeability was sufficient to allow luminal constituents access to the mucosal immune system, and dysfunction of the intestinal barrier results in enhanced uptake of potentially noxious material (e.g., antigens, toxins, other proinflammatory molecules) from the gut lumen. Stress-associated increases in the permeability of the mucosal lining of the alimentary tract in humans represent an important cause of morbidity.

Laminitis often arises during the course of intestinal disease in horses, suggesting that toxic factors of intestinal origin play an important role in its pathogenesis.<sup>46,47</sup> The starch overload method for experimentally inducing laminitis leads to both increased intestinal permeability and intestinal floral changes.<sup>48</sup> Excess glucocorticoids might also contribute to the risk of laminitis developing in horses through increased intestinal permeability and absorption of toxic factors from the intestinal lumen.

### GLUCOCORTICIDS AND THE ACTION OF INSULIN

High levels of glucocorticoids interfere with the action of insulin, leading to insulin resistance, a condition commonly seen in horses affected by glucocorticoid excess. Insulin resistance is characterized by hyperinsulinemia, hyperglycemia, and hypertriglyceridemia and eventually results in subjection of endothelial cells to inappropriately elevated glucose concentrations. Excessive glucose exposure leads to increased endothelin-1 production and reduced release of NO by endothelial cells.<sup>49</sup> A preponderance of constricting factors on underlying vascular smooth muscle is another potential causative or predisposing factor for laminitis because insulin resistance has been associated with poor blood flow. Insulin resistance occurs in mature, obese horses that are prone to laminitis<sup>20</sup> as well as in certain pony breeds.<sup>50</sup>

### GLUCOCORTICIDS AND OBESITY

Sustained high levels of glucocorticoids promote accretion of omental obesity, a feature of Cushing's syndrome.<sup>22</sup> Adipocytes that are "recruited" by glu-



cocorticoids not only serve as repositories of fat (i.e., an energy reserve) but also produce hormones such as resistin and leptin that cause insulin resistance.<sup>28</sup> Thus glucocorticoids act both directly and indirectly, through accretion of omental adipocytes, to cause insulin resistance.

## REGULATION OF CORTISOL IN PERIPHERAL TISSUES

Circulating cortisol, synthesized by and released from the adrenal cortices, is bound to corticosteroid-binding globulin, which provides a reservoir to lessen rapid fluctuations that would arise because of episodic ACTH secretion. In the healthy state, cortisol is inactivated, primarily in the proximal convoluted tubule and pars recta of the kidneys, to its 11-keto-derivative cortisone.<sup>21</sup> Under certain circumstances, 11 $\beta$ -HSD1, which is widely expressed throughout the body, converts inactive cortisone to cortisol.<sup>51</sup> We previously demonstrated that 11 $\beta$ -HSD1 activity in both skin and hoof lamellar tissue may be increased in horses with laminitis, although the extent to which this elevation in enzyme activity is important in the pathogenesis or clinical progression of laminitis is unknown.<sup>23</sup> The role of glucocorticoid in human omental obesity has recently been described as “tissue-specific Cushing’s syndrome.”<sup>30,52</sup> Assuming that glucocorticoids cause laminitis or predispose horses to it, this predisposition may be amplified by the presence of 11 $\beta$ -HSD1. As new drugs are developed to specifically inhibit 11 $\beta$ -HSD1, newer treatment options for glucocorticoid-associated laminitis in horses may become available.

## GLUCOCORTICOID-INDUCED REMODELING VERSUS LAMINITIS

We believe that conditions associated with glucocorticoid excess (exogenous or endogenous) lead to structural changes in the connective tissues of the hoof-lamellar junctional zone that might be viewed simplistically as a “weakening” effect on the attachment interface. Over time, these changes result in lengthening and attenuation of the primary and secondary dermal lamellae that are not necessarily associated with pain, inflammation, or lameness (Figure 2). An important result of these lamellar changes is gradual and progressive “pulling apart” of the underlying dermis (and os pedis) from the lamellar interface. During inspection, characteristic features of glucocorticoid-affected hooves include progressive widening and palmar divergence of growth lines (i.e., “laminar” or “stress” lines; Figure 1) as well as widening of the white line zone. Radiographic examination of an affected hoof reveals changes similar to



**Figure 1. Abnormal hoof growth.** Note the poor quality of the hoof wall and prominent growth rings (“lamellar lines”). Divergence of the prominent rings (arrow) is evident at the palmar aspect of the hoof, suggesting that the growth rate of the hoof has been inhibited at the dorsal, but not palmar, aspect. Although the appearance of this hoof could be attributed to laminitis, it could also be attributed to the long-term effects of glucocorticoid excess in the absence of signs of lameness or pain.

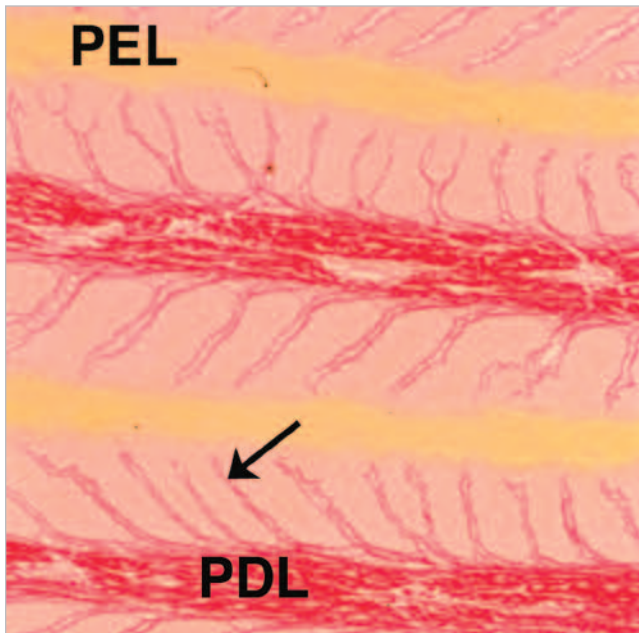
those seen in horses with classic laminitis, including pedal bone rotation and pedal osteitis. Osteopenia and remodeling of the os pedis (i.e., atrophied appearance with a distal “ski tip”) arise from the combined effects of glucocorticoid-induced osteoporosis, the pull of the deep digital flexor tendon, and “weakening” of the lamellar connective tissue matrix between the os pedis and lamellar interface.

## CONCLUSION

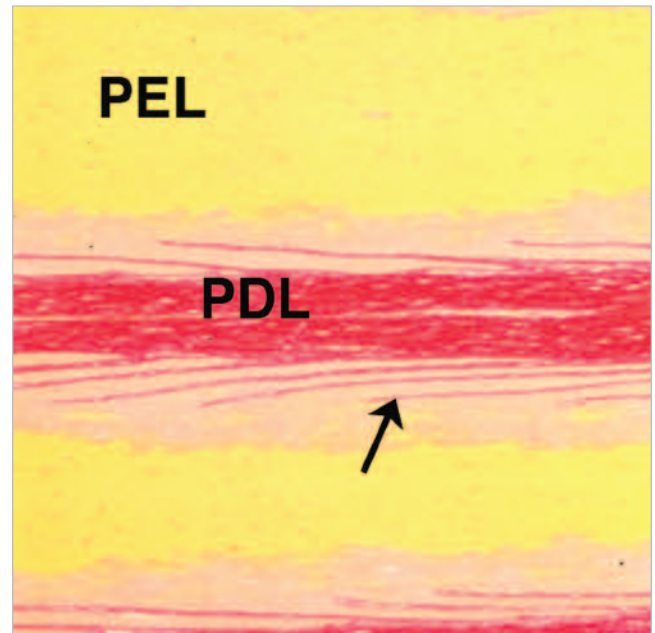
Conditions and circumstances associated with glucocorticoid excess are accompanied by increased risk of laminitis developing in adult horses. However, there is substantial controversy as to whether glucocorticoids can cause laminitis de novo. If they can, the pathogenesis of laminitis arising from the effects of glucocorticoid is probably different from that associated with diseases of the GI tract and endotoxemia. Numerous possible and plausible theoretical mechanisms have been hypothesized.

Veterinarians must exert caution with respect to using glucocorticoids in adult horses. Extreme caution should be exercised in administering systemic glucocorticoids to horses that have been affected by laminitis, and these horses must be carefully monitored for development of laminitic pain. The risk of laminitis appears to be greater when using dexamethasone or triamcinolone

**Figure 2.** Low-powered photomicrographs showing the relationship between epidermal and dermal lamellae. Primary epidermal (PEL) and primary dermal (PDL) lamellae as well as secondary epidermal and dermal (arrows) lamellae are evident. (Picrosirius red stain; red = fibrillar collagen; yellow = keratin)



**Normal hoof.** Note the normal relationship between the primary and secondary lamellar components.



**Abnormal hoof.** Note that the secondary dermal lamellae are elongated and attenuated, which is consistent with weakening of the hoof-lamellar interface. This tissue section was obtained from a pony with pituitary pars intermedia dysfunction (equine Cushing's disease) and prominent growth rings. The owner indicated that the pony had never exhibited signs of lameness or laminitic pain. Whether this degree of a hoof-lamellar histopathologic abnormality could be attributed simply to the effect of excessive glucocorticoids in the absence of bona fide laminitis is deserving of further investigation.

compared with using prednisone or prednisolone. When possible, glucocorticoids should be administered locally, such as by inhalation in horses affected by recurrent airway obstruction.

We also hypothesize that structural changes in equine hooves that resemble laminitis may arise because of the actions of excessive glucocorticoids. Although these changes are not painful per se or associated with inflammation, they could predispose affected horses to developing genuine laminitis for other reasons. Further investigation into the effect of glucocorticoids at the hoof-lamellar interface is clearly needed.

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## ARTICLE #4 CE TEST



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### 1. Which hormone is not derived from POMC in the pars intermedia?

- a. thyroid-stimulating hormone
- b. ACTH
- c.  $\beta$ -endorphin
- d.  $\alpha$ -melanocyte-stimulating hormone
- e. corticotropin-like intermediary peptide

### 2. Peripheral Cushing's syndrome has been attributed to increased \_\_\_\_\_ activity in local tissue.

- a. 3 $\beta$ -hydroxysteroid dehydrogenase
- b. 11 $\beta$ -HSD I
- c. 11 $\beta$ -hydroxysteroid dehydrogenase type 2
- d.  $\beta$ -hydroxylase
- e. corticosteroid-binding globulin

### 3. \_\_\_\_\_ is not a hormonally active protein produced by adipocytes.

- a. Leptin
- b. Resistin
- c. IL-6
- d. Procoagulant factor
- e. Tumor necrosis factor- $\alpha$

### 4. Hyperadrenocorticism in horses can almost always be attributed to

- a. adrenal neoplasia.
- b. pars intermedia dysfunction.
- c. pars ventralis adenoma.
- d. ACTH-secreting carcinoma.
- e. pars distalis adenocarcinoma.

**5. Glucocorticoids are not recommended in treating**

- a. encephalomyelitis.
- b. dermatitis.
- c. laminitis.
- d. bronchiolitis.
- e. heaves.

**6. Which explanation for the development of laminitis during increased glucocorticoid action is not plausible?**

- a. the proconstrictive effect in vascular smooth muscle cells
- b. reduced NO release from endothelial cells
- c. insulin resistance
- d. the antithrombotic effect on endothelial cells
- e. ionic flux changes in vascular smooth muscle cells

**7. Which statement regarding the relationship between drugs and laminitis is correct?**

- a. Triamcinolone causes laminitis on a predictable basis.
- b. Dexamethasone commonly causes laminitis when used for more than 5 days.
- c. Prednisolone is a common cause of laminitis.
- d. The development of laminitis resulting from glucocorticoids is unpredictable.
- e. Laminitis is an unpredictable consequence of using antibiotics.

**8. Which abnormality does not result from insulin resistance?**

- a. hyperinsulinemia
- b. hyperglycemia
- c. hypertriglyceridemia
- d. reduced endothelial NO production
- e. reduced endothelial endothelin-1 production

**9. Increased  $11\beta$ -HSD1 activity in the hoof-lamellar interface results in \_\_\_\_\_ activity.**

- a. increased local aldosterone
- b. increased systemic cortisol
- c. decreased local cortisol
- d. increased local cortisol
- e. increased local epinephrine

**10. Which observation is evidence that laminitis caused by black walnut toxicosis is an inflammatory process?**

- a. increased expression of cyclooxygenase-2 mRNA in digital vessels
- b. increased IL-1 levels in affected hooves
- c. increased levels of matrix metalloproteinases in affected hooves
- d. neutrophil recruitment
- e. all of the above