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METABOLIC CHARACTERISTICS AND SUSCEPTIBILITY TO LAMINITIS IN MORGAN AND THOROUGHBRED HORSES

COLETTE HELENE JANSON

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METABOLIC CHARACTERISTICS AND SUSCEPTIBILITY TO LAMINITIS IN MORGAN AND THOROUGHBRED HORSES

Abstract
Laminitis, an inflammation of the lamina in the equine foot, is one of the least understood of the common equine diseases and is considered to be one of the greatest problems facing the horse owner and veterinarian today. The incidence of, and breed susceptibility to, this disease has never been formally assessed. Many practitioners feel that susceptibility may be related to metabolic imbalances. The purpose of this study was to tabulate current clinical information from a nationwide survey, to examine two breeds of horses, one of which has a greater incidence of laminitis, and to investigate metabolic parameters which may relate to increased susceptibility.

The incidence, etiology, and breed susceptibility to laminitis, as well as therapies and rates of success in treating the condition, were assessed through a nationwide poll of 235 equine practitioners. Laminitis was shown to occur in 0.92% of the horse population with the Quarter Horse being the most susceptible breed. The principal causative agents reported were overeating and obesity. In practices limited to either Quarter Horses or Thoroughbreds (the two most common breeds in the United States), the Quarter Horse was found to have an incidence of laminitis eight times greater than the Thoroughbred, and the recovery rate of the Quarter Horse is 1.3 times higher. Thoroughbreds, however, showed a fivefold higher death rate primarily due to complications of the disease. Most practitioners expressed frustration with the current treatments available, and although certain therapies such as antibiotics and forced exercise appear to be used almost exclusively by practitioners having higher recovery rates, therapeutic measures among most practitioners are haphazard and often without any scientific rationale.

It is proposed that perhaps different forms of the disease exist and are caused by different factors which may be breed specific. Therefore, treatment of laminitis may have to be tailored to the specific type of this disease exhibited by an animal.

Concentrations of serum phospholipids, triglycerides, total cholesterol, non-esterified fatty acids, and glucose were determined for 9 months (September 1972 to May 1973) in 15 fasting horses (8 Morgans and 7 Thoroughbreds).

Morgan horses had higher concentrations of total lipid than did Thoroughbreds, although the relative proportions of each type of lipid were similar in the two breeds. In both breeds of horses, concentrations of serum triglycerides in the cold months (December to March) were lower than those in the warm months. The significance of these findings is discussed.

Glucose, epinephrine and insulin tolerance tests, as well as glucagon and propionate responses, bromsulfphthalein clearance, and thyroid function tests, were utilized to measure differences between Morgan and Thoroughbred horses in metabolic patterns associated with susceptibility to laminitis and fatty liver.

The Morgan horse showed lesser ability to clear and metabolize glucose in response to glucose, insulin and epinephrine administration. The amount of insulin secreted by the Morgan was also less than in the Thoroughbred, and the Thoroughbred horse was shown to be more prone to hypoglycemic shock. Increased mobilization and clearance of non-esterified fatty acids during epinephrine administration and insulin tolerance tests were seen in the Morgan but not in the Thoroughbred, possibly indicating a difference in the primary energy source between the two breeds. Volatile fatty acids do not appear to contribute significantly to

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hepatic impairment. The Morgan horse appears metabolically predisposed to, and therefore more susceptible
to, laminitis and the associated fatty liver than the Thoroughbred.

**Keywords**
Biology, Zoology
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METABOLIC CHARACTERISTICS AND SUSCEPTIBILITY TO LAMINITIS IN MORGAN AND THOROUGHBRED HORSES

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METABOLIC CHARACTERISTICS AND SUSCEPTIBILITY TO LAMINITIS
IN MORGAN AND THOROUGHBRED HORSES

by

COLETTE HELENE JANSON
B.A., BRIDGEWATER STATE COLLEGE, 1967
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A DISSERTATION

Submitted to the University of New Hampshire
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Graduate School
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May, 1980
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TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>x</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>PART I LAMINITIS IN THE USA: ITS ETIOLOGY, PREVALENCE &amp; TREATMENT</td>
<td>8</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>9</td>
</tr>
<tr>
<td>I. INTRODUCTION</td>
<td>10</td>
</tr>
<tr>
<td>II. PURPOSE</td>
<td>10</td>
</tr>
<tr>
<td>III. SURVEY METHOD</td>
<td>11</td>
</tr>
<tr>
<td>IV. RESPONSE TO QUESTIONNAIRES</td>
<td>12</td>
</tr>
<tr>
<td>V. DISCUSSION</td>
<td>16</td>
</tr>
<tr>
<td>VI. REFERENCES</td>
<td>24</td>
</tr>
<tr>
<td>VII. APPENDIX: LAMINITIS SURVEY QUESTIONNAIRE</td>
<td>48</td>
</tr>
<tr>
<td>PART II SERUM LIPIDS AND GLUCOSE IN MORGAN AND THOROUGHBRED</td>
<td>50</td>
</tr>
<tr>
<td>HORGES</td>
<td>51</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>52</td>
</tr>
<tr>
<td>I. INTRODUCTION</td>
<td>52</td>
</tr>
<tr>
<td>II. MATERIALS AND METHODS</td>
<td>52</td>
</tr>
<tr>
<td>III. RESULTS</td>
<td>55</td>
</tr>
<tr>
<td>IV. DISCUSSION</td>
<td>56</td>
</tr>
<tr>
<td>V. REFERENCES</td>
<td>58</td>
</tr>
</tbody>
</table>
LIST OF TABLES

PART I

1. BREED DISTRIBUTION ACCORDING TO GEOGRAPHIC REGION ....... 28
2. BREED SUSCEPTIBILITY TO LAMINITIS ACCORDING TO REGION .. 29
3. ETIOLOGICAL FACTORS IN LAMINITIS ACCORDING TO REGION ... 30
4. COMPARISONS RELATIVE TO LAMINITIS BETWEEN PRACTICES LIMITED TO THOROUGHBREDS VS. PRACTICES LIMITED TO QUARTER HORSES ........................................ 31
5. TREATMENTS AND RATIONALES FOR THEIR USE .................. 32
6. COMPARISON OF BREED DISTRIBUTION BETWEEN VETERINARIANS HAVING > 89% AND THOSE WITH < 26% RECOVERY RATES ........ 33

PART II

1. LIPID AND GLUCOSE LEVELS IN SERA OF TWO EQUINE BREEDS .. 61
2. SEASONAL MEANS FOR SERUM LEVELS OF TRIGLYCERIDES AND NEFA .......................................................... 62

PART III

1. RATE OF DISAPPEARANCE OF GLUCOSE FROM THE CIRCULATION FOLLOWING AN INTRAVENOUS INFUSION IN MORGAN AND THOROUGHBRED HORSES ........................................ 102
2. SERUM THYROID HORMONE LEVELS ................................. 103
3. SUMMARY OF RESULTS FROM GLUCOSE TOLERANCE TEST ........ 104
4. SUMMARY OF RESULTS FROM EPINEPHRINE TOLERANCE TEST ..... 105
5. SUMMARY OF RESULTS FROM INSULIN TOLERANCE TEST .......... 106
6. SUMMARY OF RESULTS FROM GLUCAGON TOLERANCE TEST ....... 107
LIST OF FIGURES

PART I

1. INCIDENCE OF LAMINITIS IN CONTINENTAL UNITED STATES .... 34
2. COMPARISON OF BREED DISTRIBUTION VS. BREED SUSCEPTIBILITY TO LAMINITIS IN CONTINENTAL UNITED STATES ........ 36
3. THERAPIES UTILIZED IN THE TREATMENT OF LAMINITIS ........ 38
4. CATEGORIES OF DRUG THERAPY USED IN TREATING LAMINITIS .. 40
5. CATEGORIES OF FOOT CARE IN TREATING LAMINITIS .......... 42
6. CATEGORIES OF DIET ALTERATION IN THE TREATMENT OF LAMINITIS ............................................. 44
7. COMPARISON OF TREATMENTS FOR LAMINITIS AMONG EQUINE PRACTITIONERS HAVING GREATER THAN 89% RECOVERY RATES AND THOSE HAVING LESS THAN 26% RECOVERY RATES ............. 46

PART III

1. ABSOLUTE SERUM GLUCOSE CONCENTRATION AFTER INTRAVENOUS GLUCOSE INFUSION IN MORGAN AND THOROUGHBRED HORSES ...... 108
2. SERUM IMMUNOREACTIVE INSULIN AFTER INTRAVENOUS GLUCOSE INFUSION IN MORGAN AND THOROUGHBRED HORSES ............. 110
3. SERUM NON-ESTERIFIED FATTY ACIDS (NEFA), CHOLESTEROL, AND TRIGLYCERIDES FOLLOWING INTRAVENOUS GLUCOSE INFUSION IN MORGAN AND THOROUGHBRED HORSES ..................... 112
4. BROMSULFOPHTHALEIN CLEARANCE (BSP) IN MORGAN AND THOROUGHBRED HORSES ............................................. 114
5. SERUM GLUCOSE IN MORGAN AND THOROUGHBRED HORSES IN RESPONSE TO EPINEPHRINE ADMINISTRATION .......... 116
6. SERUM TRIGLYCERIDES, CHOLESTEROL, AND NON-ESTERIFIED FATTY ACIDS (NEFA) OF MORGAN AND THOROUGHBRED HORSES IN RESPONSE TO EPINEPHRINE ADMINISTRATION ................. 118
7. SERUM GLUTAMIC-OXALACETIC TRANSAMINASE (SGOT) IN MORGAN AND THOROUGHBRED HORSES IN RESPONSE TO EPINEPHRINE ADMINISTRATION ......................................... 120
8. SERUM IMMUNOREACTIVE INSULIN AND GLUCOSE OF MORGAN AND THOROUGHBRED HORSES IN RESPONSE TO INSULIN ADMINISTRATION ..................................................... 122
9. SERUM CHOLESTEROL, NON-ESTERIFIED FATTY ACIDS (NEFA), AND TRIGLYCERIDES IN MORGAN AND THOROUGHBRED HORSES IN RESPONSE TO INSULIN ADMINISTRATION .................. 124
10. IMMUNOREACTIVE INSULIN AND GLUCOSE IN MORGAN AND THOROUGHBRED HORSES IN RESPONSE TO INTRAVENOUSLY ADMINISTERED GLUCAGON .................................................. 126
11. SERUM NON-ESTERIFIED FATTY ACIDS (NEFA), TRIGLYCERIDES, AND CHOLESTEROL IN MORGAN AND THOROUGHBRED HORSES IN RESPONSE TO INTRAVENOUSLY ADMINISTERED GLUCAGON .......... 128
12. SERUM GLUCOSE AND IMMUNOREACTIVE INSULIN IN MORGAN AND THOROUGHBRED HORSES IN RESPONSE TO AN INTRAVENOUS INFUSION OF SODIUM PROPIONATE .......................... 130
ABSTRACT

METABOLIC CHARACTERISTICS AND SUSCEPTIBILITY

TO LAMINITIS IN MORGAN AND THOROUGHBRED HORSES

by

COLETTE HELENE JANSON

University of New Hampshire, May 1980

Laminitis, an inflammation of the lamina in the equine foot, is one of the least understood of the common equine diseases and is considered to be one of the greatest problems facing the horse owner and veterinarian today. The incidence of, and breed susceptibility to, this disease has never been formally assessed. Many practitioners feel that susceptibility may be related to metabolic imbalances. The purpose of this study was to tabulate current clinical information from a nationwide survey, to examine two breeds of horses, one of which has a greater incidence of laminitis, and to investigate metabolic parameters which may relate to increased susceptibility.

The incidence, etiology, and breed susceptibility to laminitis, as well as therapies and rates of success in treating the condition, were assessed through a nationwide poll of 235 equine practitioners. Laminitis was shown to occur in 0.92% of the horse population with the Quarter Horse being the most susceptible breed. The principal causative agents reported were overeating and obesity. In practices limited to either Quarter Horses or Thoroughbreds (the two most
common breeds in the United States), the Quarter Horse was found to have an incidence of laminitis eight times greater than the Thoroughbred, and the recovery rate of the Quarter Horse is 1.3 times higher. Thoroughbreds, however, showed a fivefold higher death rate primarily due to complications of the disease. Most practitioners expressed frustration with the current treatments available, and although certain therapies such as antibiotics and forced exercise appear to be used almost exclusively by practitioners having higher recovery rates, therapeutic measures among most practitioners are haphazard and often without any scientific rationale.

It is proposed that perhaps different forms of the disease exist and are caused by different factors which may be breed specific. Therefore, treatment of laminitis may have to be tailored to the specific type of this disease exhibited by an animal.

Concentrations of serum phospholipids, triglycerides, total cholesterol, non-esterified fatty acids, and glucose were determined for 9 months (September 1972 to May 1973) in 15 fasting horses (8 Morgans and 7 Thoroughbreds).

Morgan horses had higher concentrations of total lipid than did Thoroughbreds, although the relative proportions of each type of lipid were similar in the two breeds. In both breeds of horses, concentrations of serum triglycerides in the cold months (December to March) were lower than those in the warm months. The significance of these findings is discussed.

Glucose, epinephrine and insulin tolerance tests, as well as glucagon and propionate responses, bromsulfphthalein clearance, and thyroid function tests, were utilized to measure differences between
Morgan and Thoroughbred horses in metabolic patterns associated with susceptibility to laminitis and fatty liver.

The Morgan horse showed lesser ability to clear and metabolize glucose in response to glucose, insulin and epinephrine administration. The amount of insulin secreted by the Morgan was also less than in the Thoroughbred, and the Thoroughbred horse was shown to be more prone to hypoglycemic shock. Increased mobilization and clearance of non-esterified fatty acids during epinephrine administration and insulin tolerance tests were seen in the Morgan but not in the Thoroughbred, possibly indicating a difference in the primary energy source between the two breeds. Volatile fatty acids do not appear to contribute significantly to the overall energy metabolism of the short-term fasted equine. Thyroid tests showed the Morgan to tend toward hypothyroidism, and bromsulfphthalein clearance after a glucose load indicated some degree of hepatic impairment. The Morgan horse appears metabolically predisposed to, and therefore more susceptible to, laminitis and the associated fatty liver than the Thoroughbred.
INTRODUCTION

Laminitis (or Founder) is an inflammation of the lamina in the equine foot resulting from congestion with blood. Most of the available information describing laminitis is empirical and derived from clinical observations with only a few reports being based on controlled studies. The occurrence of laminitis has been associated with both infectious agents and non-infectious, environmental factors;\(^1\) however, the etiology is not well understood. Practicing veterinarians often characterize the disease by various types depending on the probable, immediate inciting event: either systemic (e.g. post-parturient laminitis or alimentary laminitis, the most common forms of which include grain founder and grass founder); or, as a result of external injury (e.g. percussion laminitis). Any of these forms may be acute or chronic depending on the duration of the illness. The pathogenesis of laminitis is similar for all types and includes metabolic, as well as cardiovascular, features.\(^4,9\)

A variety of physiological characteristics that alter carbohydrate and lipid metabolism, namely obesity,\(^6\) hypothyroidism,\(^11\) insulin deficiency or insulin insensitivity,\(^12\) and the administration of certain medications\(^18\) (e.g. corticosteroids and ACTH) are all risk factors for laminitis. Also, during the course of a laminitic episode glucose, serum glutamic-oxalacetic transaminase (SGOT) and serum cholesterol concentrations are elevated.\(^4\) From these observations, it can be hypothesized that increased susceptibility of certain horses to this disease may be evident in specific metabolic patterns in these
horses.

Most literature describing metabolism in the horse is recent but limited in scope. The equine has been shown to be intermediate between ruminants and non-ruminants in the utilization of glucose. The horse preferentially utilizes circulating glucose for energy but is able to utilize volatile fatty acids (VFA) and non-esterified fatty acids (NEFA) when blood glucose levels are low. The pony, unlike the horse, can metabolize large amounts of NEFA during starvation and is prone to hyperlipemia and hyperlipoproteinemia. The pony also utilizes VFA more efficiently than the horse. Studies to determine whether horse breeds differ in energy metabolism are not apparent in the literature; however, some reports have shown that glucose and lipid levels in all equines fluctuate with the season, changes in temperature, and amount of exercise, and that hormones, such as thyroid hormone, insulin, catecholamines, and the adrenocortical hormones play an important part in the maintenance of homeostasis during these changes.

Imbalances of insulin, adrenocortical hormones and thyroid hormones are known to increase susceptibility to laminitis. However, studies of metabolic alterations as a result of these hormone imbalances in the equine are few, and correlations of the findings with the laminitic syndrome are not reported. In other species, insulin facilitates glucose entry into the cell and stimulates fat synthesis, as well as glycogen deposition. Glucagon, the antagonist of insulin, promotes glycogen breakdown and lipolysis. Glucose tolerance and insulin tolerance tests are of great value in detecting insulin-resistant individuals and also in evaluating thyroid and adrenocortical hormone imbalances. Insulin action is mediated by the catecholamines
and glucocorticoids, as well as by glucagon.\textsuperscript{15}

It is during stress, however, that the essential role of these hormones in maintaining homeostasis becomes particularly apparent. Stress can be defined as any physical, chemical or emotional factor which alters the organism's metabolic equilibrium. Stress can alter carbohydrate metabolism causing an abrupt rise in blood glucose, followed by increased oxidation of glucose and depletion of glycogen stores.\textsuperscript{15} Lipid catabolism, characterized by NEFA mobilization and increased oxidation of lipid for energy is also a common feature of the stress reaction.\textsuperscript{15}

Some of the biochemical changes associated with the stress reaction, namely fatty infiltration of the liver, and increased total serum cholesterol, are commonly observed in chronic laminitis.\textsuperscript{5} Although stress reactions can be induced in a variety of ways, carbohydrate loading in some animals such as sheep and cows can initiate the typical alterations in glucose and lipid metabolism.\textsuperscript{7,19} Carbohydrate overload has also been used to induce laminitis in the equine.\textsuperscript{8} Furthermore, there is a consensus among equine practitioners that laminitis often occurs following a combination of stresses,\textsuperscript{12} and the rationale for treating laminitis rests on this hypothesis. Therefore, it appears that laminitis may be a stress-related disease, and comparisons of biochemical parameters between laminitis-susceptible horses and those which are less susceptible might suggest predisposing features. Furthermore, hormonal changes which occur during stress can be simulated by the administration of specific dosages of these hormones, and differences in the biochemical responses between horses with varying susceptibilities to laminitis can be measured.
This thesis has been written in the form of three separate manuscripts. Part one presents the results from a nation-wide survey of equine practitioners regarding incidence and treatment of laminitis. The second part which focuses on differences in serum glucose and lipid classes between Morgan and Thoroughbred horses (two breeds of horses with widely different susceptibility to laminitis) has been published in the American Journal of Veterinary Research. The third part, which will also be submitted to the American Journal of Veterinary Research, describes differences in glucose and lipid metabolism between Morgan and Thoroughbred horses as measured by glucose, insulin, and epinephrine tolerance tests. Thyroid and liver functions following some of these tests, as well as the responses of serum glucose and lipids to glucagon injection and propionate infusion, are also described.
REFERENCES


PART I

LAMINITIS IN THE USA:

ITS ETIOLOGY, PREVALENCE AND TREATMENT
SUMMARY

The incidence, etiology, and breed susceptibility to laminitis, as well as therapies and rates of success in treating the condition, were assessed through a nationwide poll of 235 equine practitioners. Laminitis was shown to occur in 0.92% of the horse population with the Quarter Horse being the most susceptible breed. The principal causative agents reported were overeating and obesity. In practices limited to either Quarter Horses or Thoroughbreds (the two most common breeds in the United States), the Quarter Horse was found to have an incidence of laminitis eight times greater than the Thoroughbred, and the recovery rate of the Quarter Horse was 1.3 times better. The Thoroughbreds, however, show a fivefold higher death rate primarily due to complications of the disease. Most practitioners expressed frustration with the current treatments available, and, although certain therapies, such as antibiotics and forced exercise, appear to be used almost exclusively by practitioners showing higher recovery rates, therapeutic measures among most practitioners are haphazard and often without any scientific rationale.

It is proposed that perhaps different forms of the disease exist and are caused by different factors which may be breed specific. Therefore, treatment of laminitis may have to be specifically tailored to the specific type of this disease exhibited by a given animal.
INTRODUCTION

Laminitis, an inflammation of the lamina of the foot, is one of the least understood of the common equine diseases and is considered to be one of the greatest problems facing the horse owner and veterinarian today.\(^1\) Although usually associated with the equine, the disease also occurs in cows,\(^22,26\) sheep,\(^20\) and pigs\(^23,27\) with the symptoms being similar in all species. The incidence of, and possible breed susceptibility to, this disease has never been assessed, and most information has been derived from heresay or a small number of studies on very limited experimental populations.\(^14,15,28\) At the turn of the century, a number of articles appeared in veterinary manuals and journals that described the symptoms of the disease and offered some method of treatment.\(^8,13,24,25\) Since then little progress has been made in understanding exactly what causes this complex disease, but most equine practitioners do agree that it is metabolic in nature.\(^21,31\) Specifically, it occurs with greater frequency among obese, crest-necked horses\(^14\) and those with certain hormonal imbalances.\(^14,19\) The treatment of laminitis is also an extremely controversial issue. When equine practitioners were surveyed to discover their preferred methods of treatment, responses were varied and in many instances contradictory. Furthermore, a number of practitioners expressed frustration at the lack of information regarding this disorder.

PURPOSE

The purpose of the survey was to compile data concerning:
(1) geographical incidence of equine laminitis; (2) breed susceptibility; (3) factors which precipitate the laminitic episode;
(4) treatments and the rationales behind them; and (5) the rate of therapeutic success in order to gain a better perspective on this little understood disease.

SURVEY METHOD

In the Fall of 1972, questionnaires (c.f. sample, p. 48) were mailed to the 1252 Equine Practitioners listed in the 1972 Directory of the American Association of Equine Practitioners. These veterinarians were asked to estimate the number of horses seen in their practice, breed distribution of the horses treated, and the number of cases of laminitis treated during the past twelve months. They were also instructed to enumerate the complete recoveries, the horses suffering permanent damage and those which either died or had to be destroyed as a result of the disease. Breed susceptibility was determined by asking the practitioners to rate in rank order, from a list of breeds, the three breeds which they found to be most susceptible to the disease. A similar rank ordering was used to determine the chief causative factors. The third section of the questionnaire requested the practitioners to describe the mode of therapy used and the rationale associated with it. A space was also allotted for any additional descriptive information which they felt relevant. In order to correct for biased sampling, veterinarians were also asked to note whether their practice was limited to a particular breed and, if so, which one.

Fourteen months were allotted for return of the questionnaires. Tabulations were made by States, and the data was further grouped to represent nine geographical regions: (Pacific Region, Mountain Region, Northwest Central Region, Southwest Central Region, Northeast Central Region, Southeast Central Region, South Atlantic Region, Middle
Atlantic Region, and New England Region (c.f. map, p. 35)). Breed susceptibility and inciting-cause rankings were determined by assigning three points for first position, two points for second choice and one point for third in each questionnaire. Percentage figures were then derived from the total number of possible points. Statistical analyses consisting of correlation and regression analyses, were carried out on an IBM 360 computer.

RESPONSE TO QUESTIONNAIRES

Questionnaires were returned by 33% (418) of the equine practitioners and completed by 18% (235). The mean response by region for completed questionnaires ranged from 16% to 22%. Based on an unofficial 1972 USDA Equine Census,\(^\text{32}\) 18% of the equine population of continental United States was accounted for with a nearly equal percentage representation from each region. Therefore, although returns were fewer than anticipated, the overall uniformity of sampling appears to afford a basis for comparison.

Incidences of Laminitis - Laminitis was shown to occur in 0.92% of the horse population covered by the survey. The incidence of laminitis, recovery, permanent damage and death from complications associated with laminitis in each geographical region expressed as percentages of the horse population survey are shown in Figure 1. The highest incidence of the disease occurs in the Northwest and Southwest Central Regions and in the Mountain Region. Another point of interest is the high percentage of horses suffering permanent damage and those having to be sacrificed in both the New England and Middle Atlantic Regions.
Breed Distribution - Breed distribution for each geographical region and the overall national percentage are listed in Table 1. The predominant breed in six of the nine regions was the Thoroughbred which accounted for 44.3% of all horses reported. The Quarter Horse, the next most prevalent breed, made up only 21.9% of the population, followed by Mixed Breeds, 12.2%. All other breeds represented 10% or less of the population.

Breed Susceptibility - Table 2 lists breed susceptibility according to a geographical location, as well as overall breed susceptibility for the nation. These were determined from the percentages computed from the rating scale. This information is tabulated on a national basis along with the national breed distribution for comparative purposes (in Figure 2). In every region except the Northeast sector (Middle Atlantic and New England), Quarter Horses were cited most often as being susceptible and, thus, received the highest percentage rating. Furthermore, a significant correlation (p < 0.05) exists between the number of cases of laminitis and the number of Quarter Horses in a particular veterinary practice. Conversely, a significant correlation (p < 0.05) exists between a large Thoroughbred population and low incidence of laminitis.

Causative Factor - The tabulation of etiological factors according to region are reported in Table 3. These figures were obtained from percentages of the ratings based on a perfect score of 100%. Over-eating accounted for 30.7% of the total. Obesity (19.8%) and the consumption of lush grass (17.9%) were also highly rated. It is interesting to note that over-eating was the item mentioned most often in all the geographical regions.
Limited Practice - Fourteen percent of the practitioners reported practice limited largely to a single breed. Of these, 68% treated Thoroughbreds while 18% treated mostly Quarter Horses. The remaining 14% treated primarily Standardbreds (8%), Tennessee Walkers (4%), or other breeds (2%). Comparisons between Thoroughbred and Quarter Horse populations reported by these practitioners are shown in Table 4. It should be noted that the percent incidence of laminitis is eight times greater in Quarter Horses and their percent recovery rate is 1.3 times that of the Thoroughbred population. Thoroughbreds show a death rate due to complication 2.5 times that of Quarter Horses. Veterinarians with a Thoroughbred practice also reported miscellaneous causes in 76% of their cases, the major portion of which were previous severe illness from a variety of diseases or allergies. Those practitioners treating only Quarter Horses ranked over-eating as the most common causative agent (56%) and obesity second (21%).

Treatment - Figure 3 illustrates the percentage of veterinarians using various types of therapy in the treatment of laminitis. Nearly every equine practitioner listed steroids and anti-inflammatory drugs as part of their therapy. The preferred drugs indicated appear in Figure 4. Foot care of some sort was also recommended by 80% of the practitioners. Since this is a rather broad category, it has been subdivided into individual treatments and the percentages of each type can be seen in Figure 5. Of the other common methods used, laxatives and mineral oil were suggested by 68% of the practitioners, antihistamines by 58% and exercise by 46%. Alteration of the diet, a multi-faceted category, was recommended by 28% of the practitioners. The subdivisions of the dietary category appear in Figure 6.
Miscellaneous treatments (10%) encompass such remedies as tourniquets, anti-hypertensive drugs, sex and metabolic hormones, enzymes and blood letting. Although 97% of the responding practitioners stated methods of treatment, only 38% of these offered rationales for their therapy. A summary of these responses appears in Table 5.

*Recovery Rate vs. Breed Distribution and Treatment* - Equine practitioners reporting a 90% or better recovery rate and those with 25% or less were compared by breed distribution in their practice and the mode of treatment recommended. These groups represented 11.5% and 17.5% respectively of the responding veterinarians and 7.5% and 25% respectively of the equine population. Thoroughbreds were shown to make up 56% of the horse practice of veterinarians having poor (25% or less) recovery rates. These practitioners were found to also be treating 17% Standardbreds, 13% Quarter Horses, and 7% Mixed Breeds, with the rest of the breeds making up the remaining 7%. On the other hand, those reporting recovery rates of 90% or better, had practices consisting of 20% Thoroughbreds and 41% and 29% respectively Quarter Horses and Mixed Breeds. This data is presented in Table 6.

In comparing types of therapy, no statistically significant difference can be seen between high and low success groups in their utilization of steroids, anti-inflammatory agents and laxatives. However, those with high recovery rates were three times more apt to rely on antibiotics, forced exercise and nerve blocks than those with low recovery rates. It should also be noted that these three types of therapy were not shown to be the most common types of treatment when treatment was evaluated on the whole. It can also be noted that the low success group used antihistamines and ice or cold water soaks.
twice as often as the high success group, and almost exclusively they utilize diuretics and autohemotherapy. When considering diet alteration, 34.6% and 20.9% of the high and low success groups respectively suggested modifications in this area. Most important, however, is the type of modification suggested. The high recovery group listed food restriction as their principal alteration; whereas, the low recovery rate group listed dextrose and glucose infusions most often. The results of the overall comparisons between the two groups appear in Figure 7.

DISCUSSION

Incidence of Laminitis - This survey, although representing only 18% of the horse population and equine practitioners, does allow for generalizations since the returns are proportionally similar from each region, both in the number of practitioners responding and in the number of horses represented. Nearly eighty-five thousand horses covered by the survey suffered laminitis within a one-year period, an incidence of 0.92% of the population. If the 0.92% could be extrapolated to the total estimated equine population of the 1972 USDA Equine Census, approximately five hundred thousand horses may be affected by the disease yearly and, based on percentage recovery figures obtained from this survey, more than fifteen thousand horses suffer permanent damage while another two or three thousand die from complications of the disease or must be destroyed because of irreparable damage. Therefore, approximately twenty thousand horses are rendered useless in an economic sense.

Breed Susceptibility - This survey indicates several general trends with regard to breed susceptibility, etiology, type of treatment
and effectiveness of treatment. Almost all practitioners agree that susceptibility to laminitis increases in obese and crest-necked horses, but there have been no controlled studies to show this, and, unfortunately, there is no information from the literature to indicate that one breed is more susceptible than another. In studies at the University of Missouri Veterinary Hospital, \textsuperscript{15} Quarter Horses were thought to show greater susceptibility; however, later studies showed no significant difference between breeds. \textsuperscript{14} The present survey does point to the Quarter Horse as being most susceptible, and this was very evident when practices limited to Thoroughbreds were compared with those limited to Quarter Horses. The Quarter Horse was shown to have eight times the incidence of laminitis seen in the Thoroughbred. Also, in all geographical regions where the Quarter Horse and Mixed Breeds are predominant, the incidence of laminitis is high. In the New England area, practitioners also assign an increased susceptibility to the Morgan Horse. Both the Morgan and the Quarter Horse tend to be crest-necked and obese.

\textit{Causative Factors} - The three causative factors which received the most common responses are all somewhat related. These are overeating, obesity and ingestion of lush grass (especially in the Spring). Although none of these factors was qualified further, a majority of responses included the statement that the horses which exhibited laminitis as a result of these factors were also hypothyroid. It has been suggested in certain studies that hypothyroid horses and horses with various other hormonal imbalances may be more susceptible to laminitis, but no conclusions indicating a specific breed have been noted. \textsuperscript{11,19} Our survey was unable to show any correlation between a
particular breed and any of the etiological factors given. However, limited practices of either Quarter Horses or Thoroughbreds show that some factors may be breed specific. Obesity and over-eating were listed by 81% of the practitioners with Quarter Horse clientele but only by 16% of those treating only Thoroughbreds. Seventy-six percent of the latter attributed the onset of laminitis to previous serious illnesses, allergies and other miscellaneous causes. Over-eating was stated to result often in enterotoxemia. Recent studies inducing alimentary laminitis utilize carbohydrate loading, during which it has been shown that this overload may promote the uptake of certain toxins from the gut.\textsuperscript{4} This endotoxemia has been suggested by a number of investigators in both induced and naturally occurring cases.\textsuperscript{4,12,17,29} Over-eating could also alter intestinal microflora, resulting in lactate production and, consequently, lactic acidosis which ultimately leads to some of the cardiovascular symptoms of laminitis.\textsuperscript{18} Obesity, over-eating and ingestion of lush grass could also conceivably alter carbohydrate metabolism, and this could produce the high cholesterol levels and fatty liver seen in many cases of laminitis.\textsuperscript{6} Furthermore, many practitioners responding to this survey suggested that laminitis might be a stress-related disease manifesting itself after a combination of stresses. Obesity and over-eating were repeatedly referred to by these practitioners as possible stress factors.

\textit{Recovery Rate vs. Breed Distribution and Treatment} - The number of veterinarians reporting less than 26% success in treatment was surprising. The majority of these also expressed frustration with available treatments known today. Others noted that what is effective in one horse is not necessarily effective in another. Information
obtained from the practitioners with limited practices did show a correlation between effectiveness of treatment and the breed being treated. In practices limited to Quarter Horses the recovery rate is significantly higher than in Thoroughbred practices. Comparison of etiologic factors described previously showed certain diseases or allergies to be common predisposing factors in Thoroughbreds, but over-eating and obesity are predominant factors in Quarter Horses. It is possible that the purgative and diet alterations used by some may be more effective in treating alimentary laminitis rather than that caused by other agents. It is not unreasonable to suggest that perhaps several subtly different forms of laminitis might exist having different causes and metabolic features but presenting basically similar clinical manifestations. This statement is given further support by studies dealing with L-lactate production and the cardiovascular changes in laminitis. \(^8,16,18\) It was shown that forced exercise was useful in restoring the delivery of blood to, and removal of blood from, the digit since it reduces hypertension and edema which occur as a result of the congestion. \(^11\) Nerve blocks, which are often used in conjunction with exercise, help to decrease pain and permit the animal to be exercised. Perhaps this type of therapy may be most useful in treating non-alimentary laminitis. It is this type of therapy which is utilized most often by the high success group who treat primarily Thoroughbreds and who may be treating a non-alimentary type of laminitis. Therefore, evaluation of treatments used by the low success group may not necessarily mean that in every case the treatment itself is not useful, but that the failure may be attributed to the form of laminitis being treated.
Antihistamines were used twice as often by the low success group. Research studies have shown this type of treatment to be very disappointing. Histamines have been shown to be among the vasomotor substances present at the onset of laminitis. A possible explanation for the ineffectiveness of antihistamines has been shown in a study where antihistamines which usually mediate dilation of precapillary sphincters and capillary pooling, instead resulted in capillary congestion and edema because of the decreased venous return in laminitis.

Diuretics and autohemotherapy also constitute a fairly large percentage of the types of treatment used primarily by the low success group. The rationale offered is that diuretics lower the blood volume and reduce interstitial edema. However, studies have shown that they should perhaps not be used after the first day and not for any prolonged period of time since they may upset the mineralcorticoid balance and lead to complications. Autogenous blood therapy or autohemotherapy, a fairly old remedy, is used on the assumption that it has vasoconstrictor properties; however, it is generally considered to be of little value today.

Another treatment used almost exclusively by the low success group is ice or cold water foot baths. Although research is inconclusive, certain investigators suggest that the use of cold water be discouraged due to occlusion or constriction of the digital artery.

If one looks at treatments from the viewpoint of high success groups, one notices that exercise was recommended three times more often by this group. Evaluation of this topic has already been covered. This high success group also recommends antibiotic therapy.
five times more often than the low success group, although most practitioners had no rationale for its usage. It has been shown in a number of studies that secondary sepsis is often the factor responsible for permanent foot damage and death in laminitis.\(^9,10\) Antibiotics are suggested as preventative agents whenever the body temperature is elevated.\(^9\)

There were three forms of therapy that were found to occur with equal regularity in both the high and low success rate group. These were the use of steroids and anti-inflammatory drugs, the use of laxatives, and dietary modification (primarily supplementation of feed with certain amino acids). Nearly every practitioner utilized some type of steroid or anti-inflammatory agent, and sometimes both. Although these corticosteroids (and anti-inflammatory drugs) are given for the anti-inflammatory effect of increasing capillary integrity and decreasing blood pooling in dilated capillaries, practitioners today are criticized for their indiscriminant usage.\(^9\) Some suggest that often the enterotoxemia of laminitis is left untreated,\(^11\) yet others feel that even though venous damage is decreased by the corticosteroids, these same steroids tend to depreciate the integrity of the supportive structures by reducing the available substrate needed for protein synthesis and, therefore, lead to an impairment of local defenses and predispose the horse to secondary sepsis.\(^9\) Research has shown corticosteroids to be safe and useful in early laminitis, but they are contraindicated beyond the second day.\(^8\) Subsequently, agents which do not have such a depleting effect on protein synthesis in tissues deprived of adequate blood supply have been suggested.\(^7,8\) The drug of choice in this case is phenylbutazone.\(^8\) It provides
analgesic components not found in corticosteroids and does not exhibit a proteolytic effect even with prolonged use. The current survey does show a large percentage of practitioners who use this drug.

Laxatives and purgatives were formerly the mainstay of therapy before the advent of steroid therapy and are considered by the veterinarians in this survey to be essential in the treatment of alimentary laminitis. Mineral oil is preferred because of its ability to absorb toxins and evacuate the intestinal tract. Research does confirm the usefulness of this form of therapy in early laminitis for treating the inciting factors and removing toxins as soon as possible.

The final type of therapy utilized by both groups, although certainly not a widely used treatment, is feed supplementation during laminitis, primarily with the amino acid methionine. It has been shown in a number of studies that the biosynthesis of hoof keratin is dependent on methionine and cystine metabolism with cystine providing the disulfide bonds. Decreased incorporation of cystine into keratogenous cells may be responsible for the lack of mechanical integrity in the hoof which is thought to be responsible for morphologic changes in the lamina during laminitis. Increased methionine in the blood could provide three functions: increasing the rate of keratinization, detoxifying the phenol and indole present in abdominal disorders, and providing lipotropic factors to mobilize lipids.

CONCLUSION

This survey, although limited by the rather small percentage of returns and the rating methods used in certain areas of evaluation,
has, nevertheless, suggested the possibility of several forms of laminitis, each caused by different factors that may be somewhat breed specific. It has also shown that treatment of laminitis may have to be specific for the type exhibited by a given animal. Present treatment of this disease is rather haphazard, and the majority of practitioners are dissatisfied with the treatments suggested by most veterinary manuals. A need for further investigation in many areas of laminitis, especially those of etiology and treatment, has been demonstrated.
REFERENCES


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*Includes Tennessee Walkers, Palamino, Clydesdales, Appaloosa, etc.

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† All values expressed in percentages
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†All values expressed in percentages
### TABLE 4 - COMPARISONS RELATIVE TO LAMINITIS BETWEEN PRACTICES LIMITED TO THOROUGHBREDS VS. PRACTICES LIMITED TO QUARTER HORSES

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<td>Thoroughbred</td>
<td>.2</td>
<td>56.5</td>
<td>34.7</td>
<td>8.8</td>
</tr>
<tr>
<td>Quarter Horse</td>
<td>1.6</td>
<td>72.9</td>
<td>23.5</td>
<td>3.5</td>
</tr>
<tr>
<td>TREATMENT</td>
<td>RATIONALE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids and anti-inflammatory</td>
<td>Reduces inflammation and swelling; prevents mechanical breakdown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foot Care</td>
<td>Reduces swelling and congestion; either increases or decreases circulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>to the hoof; helps maintain integrity of the hoof</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laxatives</td>
<td>Clear out gastrointestinal tract; removes toxin and/or inciting cause;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>restores normal digestive processes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Reduces allergic reactions caused by histamines; prevents shock</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced exercise</td>
<td>Re-establishes circulation to hoof; prevents pooling of blood in the hoof</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet alteration</td>
<td>Control obesity; relieve toxemia; stimulate thyroid activity; increase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>energy intake; provides necessary substrates; deplete fat in the liver;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>stop L-lactate production</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve blocks and analgesics</td>
<td>Relieve pain; permit exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Reduce edema in hoof; reduce pressure and swelling in the digit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Minimize tissue damage; prevent secondary sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autohemotherapy</td>
<td>Stimulates the reticuloendothelial system; increases vasoconstriction</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**TABLE 6 - COMPARISON OF BREED DISTRIBUTION BETWEEN VETERINARIANS HAVING >89% AND THOSE WITH <26% RECOVERY RATES**

<table>
<thead>
<tr>
<th></th>
<th>High Success Group</th>
<th>Low Success Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responding Veterinarians Involved</td>
<td>11.5%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Horse Population of the Study Involved</td>
<td>7.5%</td>
<td>25.1%</td>
</tr>
<tr>
<td>Breed Distribution of the Horse Population Involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoroughbred</td>
<td>20%</td>
<td>56%</td>
</tr>
<tr>
<td>Quarter Horse</td>
<td>41%</td>
<td>13%</td>
</tr>
<tr>
<td>Standardbred</td>
<td>6%</td>
<td>17%</td>
</tr>
<tr>
<td>Mixed Breeds</td>
<td>29%</td>
<td>7%</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>4%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Figure 1. Incidence of laminitis in continental United States.

L = % equines afflicted with laminitis
C = % cases showing complete recovery
P = % cases suffering permanent damage
D = % cases dead or euthanized as a result of the disease
Figure 2. Comparison of breed distribution vs. breed susceptibility to laminitis in continental United States.
<table>
<thead>
<tr>
<th>National Breed Distribution (%)</th>
<th>Breeds</th>
<th>National Breed Susceptibility (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Morgan</td>
<td>0</td>
</tr>
<tr>
<td>45</td>
<td>Thoroughbred</td>
<td>5</td>
</tr>
<tr>
<td>40</td>
<td>American Saddlebred</td>
<td>10</td>
</tr>
<tr>
<td>35</td>
<td>Quarter Horse</td>
<td>15</td>
</tr>
<tr>
<td>30</td>
<td>Arabian</td>
<td>20</td>
</tr>
<tr>
<td>25</td>
<td>Belgian</td>
<td>25</td>
</tr>
<tr>
<td>20</td>
<td>Percheron</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>Standardbred</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>Mixed Breed</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Other</td>
<td>45</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>
Figure 3. Therapies utilized in the treatment of laminitis.
Steroids and Anti-inflammatory Drugs

Foot Care

Laxatives

Antihistamines

Forced Exercise

Diet Alteration

Nerve Blocks and Analgesics

Diuretics

Antibiotics

Autohemotherapy

Miscellaneous

% Practitioners Utilizing Treatment
Figure 4. Categories of drug therapy used in treating laminitis.
44.5%  
STEROIDS &  
CORTICOSTEROIDS

5%  
ACTH

3.5%  
UNSPECIFIED

47.0%  
PHENYL BUTAZONE
Figure 5. Categories of foot care in treating laminitis.
Ice and Cold
Water Soaks
and Packs

Hot Water
Soaks and
Packs

Sand or Mud

Alternate
Hot and Cold
Soaks

Shoe and
Pad Foot

Trim Foot

Remove
Shoes

Plantar
Boots or
Cast

% Practitioners Utilizing Treatment
Figure 6. Categories of diet alteration in the treatment of laminitis.
Decrease Amount of Feed
Supplement with Amino Acids
Glucose Infusions
Hold Feed
Vitamin Supplementation
Hay Only
Bran Only
Iodinated Casein or KI Salts
Miscellaneous

% Practitioners Utilizing Treatment
Figure 7. Comparison of treatments for laminitis among Equine Practitioners having greater than 89% recovery rates and those having less than 26% recovery rates. $> 89\%$ = $< 26\%$
Antihistamines
Antibiotics
Steroids
Anti-Inflammatory Drugs
Laxatives and Mineral Oil
Nerve Blocks
Forced Exercise
Ice and Cold Water Soaks
Hot Water Soaks
Misc. Foot Care
Diet Alteration
Autohemotherapy
Diuretics
Miscellaneous

% Practitioners Utilizing Treatment
LAMINITIS SURVEY QUESTIONNAIRE

Estimated number of horses in your practice _______________
Estimated number of cases of laminitis seen yearly _______________
From the estimate above, indicate:
  the number which recover completely _______________
  the number which suffer permanent damage _______________
  the number which die or must be euthanized as a result of
    the disease _______________
Is your practice limited to a particular breed? _______________
  If yes, which one? _______________
  If no, please indicate the percent of each of the breeds which
    make up your practice:
    A. Morgan _______________  F. Belgian _______________
    B. Thoroughbred _________  G. Percheron _____________
    C. American Saddle _____  H. Standardbred ___________
    D. Quarter Horse ________  I. Mixed Breed ___________
    E. Arabian _______________  J. Other _______________
    (Indicate Breed)
Which three of the following breeds do you feel are most susceptible
  to laminitis? (Assign a 1 for most susceptible, a 2 for next most
  susceptible, and a 3 for the next in line.)
    A. Morgan _______________  F. Belgian _______________
    B. Thoroughbred _________  G. Percheron _____________
    C. American Saddle _____  H. Standardbred ___________
    D. Quarter Horse ________  I. Mixed Breed ___________
    E. Arabian _______________  J. Other _______________
    (Indicate Breed)
Which three of the following etiological factors do you feel are most often responsible for the onset of laminitis? (Please rank order, 1 for most common, 2 for second most common, and 3 for the next.)

A. Lush Grass
B. Water When Overheated
C. Percussion
D. Obesity
E. Over-eating
F. Corticosteroid Injections
G. Lameness or Injury to Foot
H. Post Partum
I. Other (please state)

Please indicate the treatment which you have found to be most efficacious in the treatment of laminitis. (Please be as specific as possible.)

What is the rationale for the above treatment?

Please feel free to enter any additional comments which you feel would be of use to the survey.
PART II

SERUM LIPIDS AND GLUCOSE IN

MORGAN AND THOROUGHBRED HORSES
SUMMARY

Concentrations of serum phospholipids, triglycerides, total cholesterol, non-esterified fatty acids, and glucose were determined for nine months (September 1972 to May 1973) in 15 fasting horses (eight Morgans and seven Thoroughbreds).

Morgan horses had higher concentrations of total lipid than did Thoroughbreds, although the relative proportions of each type of lipid were similar in the two breeds. In both breeds of horses, concentrations of serum triglycerides in the cold months (December to March) were lower than those in the warm months. The significance of these findings is discussed.
INTRODUCTION

There is general agreement among horsemen that certain breeds of horses such as Morgans and Quarter Horses, can be maintained in good flesh or in a near-obese condition on minimal amounts of feed; whereas, other breeds such as Thoroughbreds, Standardbreds, and American Saddlebreds are considerably more difficult to maintain in this condition unless larger quantities per unit weight of horse are supplied. Furthermore, clinical studies on Morgans and Thoroughbreds with laminitis indicate that these breeds react differently to injections of a lipotropic drug. This observation may indicate that easy-to-maintain and hard-to-maintain breeds differ in lipid or energy metabolism or both.

The purpose of the present study was to examine differences in the concentrations of serum lipids and serum glucose between two types of fasting horses under similar conditions of management and diet. Morgans and Thoroughbreds were chosen as representatives of easy-to-maintain and hard-to-maintain breeds, respectively. Differences between the two breeds are discussed with respect to seasonal variations and ease of maintenance.

MATERIALS AND METHODS

Experimental Animals - Eight Morgan horses (3 geldings, 2 barren mares, 2 pregnant mares and 1 stallion) and 7 Thoroughbred horses

\footnote{O'Connor, J.T.: Unpublished Observations, 1972}

\footnote{Cho-Meth. Wolin, Farmingdale, New York 11725}
(3 geldings and 4 barren mares) were used in this study. All were clinically healthy and were maintained under the conditions listed below for at least 6 months prior to analysis of blood samples. Each equine's serum was analyzed intermittently over a nine month period (September through May) with some animals from each breed being analyzed each month.

**Housing** - The Morgans and Thoroughbreds were kept in individual, dirt floor, box stalls and were exercised approximately two hours a day, five days a week.

**Ration** - The ration provided was a commercially pelleted horse-feed\(^{c}\) consisting of 11.7% protein, 3.3% fat, 12.7% fiber, 55.2% nitrogen free extract, 10.3% moisture, and 6.9% ash. The amount of this ration given to each animal was determined on the basis of body weight (1.5 kg pellet/100 kg body wt.). The horses were fed half this amount twice daily at 7:00 A.M. and 3:00 P.M. At 12:00 noon they were given 0.9 kg alfalfa pellets,\(^{d}\) consisting of 16.4% protein, 3.0% fat, 26.2% fiber, 38.0% nitrogen free extract, 8.6% moisture, and 8.3% ash and approximately 1.0 kg hay.

**Blood Samples** - Feed was withheld from all animals for 16 to 18 hours prior to withdrawing blood, but free access to water was permitted. Samples were taken at 8:00 A.M. by jugular venipuncture and placed in capped tubes which were then left undisturbed at ambient room temperature for 3 to 5 hours to allow clotting. The serum was decanted, centrifuged at 200xg for 10 minutes to sediment any red

\(^{c}\)Choice 100 Pellets; Agway, Box 128, Buffalo, N.Y. 14240

\(^{d}\)17% Dehydrated Alfalfa; Ohio Blenders, Inc., Toledo, Ohio 43611
blood cells, placed in capped tubes and refrigerated at 4°C until analysis. All analyses were performed within 48 hours of serum collection.

**Serum Analyses** - All determinations were performed by colorimetric methods.

Phospholipid was determined by the method of Zilversmit and Davis using a phosphorus and phosphatide test kit.

Triglycerides were determined by a procedure based on the Hantzsch reaction using a triglycerides test kit. Non-esterified fatty acids (NEFA) were determined by the method of Duncombe using an NEFA test kit. The results, which were obtained as milliequivalents, were converted to mg oleic acid per 100 ml in order to provide comparisons with other lipid classes.

Total cholesterol was determined by the method of Watson using the cholesterol test kit. Preliminary tests in our laboratory with standards indicated that the values obtained with this kit for samples which contain both free and esterified cholesterol must be multiplied by 1.25 to obtain correct values for total cholesterol.

Glucose was determined by the glucose oxidase method using a glucostat test kit.

---

*e*Spectronic 20 Colorimeter, Bausch & Lomb, Inc., Rochester, N.Y. 14603
*f*Test kits from Boehringer Manneheim Corporation, New York, N.Y. 10017
*g*Oxford Tri-Chol Test Kit, Oxford Laboratories, Foster City, Ca. 94404
*h*Worthington Glucostat Test Kit, Worthington Biochemical Company, Freehold, N.J. 07728
Total lipid was calculated by addition of the least-squares means of the four lipid classes.

*Statistical Analysis* - All results obtained from chemical analyses were statistically analyzed by least-squares analysis of variance for differences among breeds, test days, and animals within breeds. The least-squares means for each breed were separated by using Duncan's Multiple Range Test.\(^5\)

Upon examination of variables where test days were significantly different, it appeared that the differences might be attributed to seasonal variations. An additional least-squares analysis of variance was computed which included breeds, animals within breeds, seasons (December to March vs. April to November), and the interaction between breeds and seasons. Wherever a significant interaction was found, a t-test was used to assess differences between seasonal breed means.

**RESULTS**

The mean serum lipid and glucose concentrations for each breed are presented in Table 1. Morgans had significantly higher concentrations of phospholipid and cholesterol than did Thoroughbreds; however, if each lipid class is expressed as a percentage of the total lipid, Morgans and Thoroughbreds differed very little in relative lipid composition.

Individual day to day variations may have accounted for the lack of significant differences in triglyceride and NEFA concentrations between the two breeds. No difference was found in serum glucose concentration.

Seasonal breed means for triglycerides and NEFA appear in Table 2.
Significantly lower serum triglyceride concentrations were seen in both horse breeds during the colder months (December-March).

DISCUSSION

Differences in the concentrations of blood lipids and blood glucose have been found between various breeds of dairy cows,\textsuperscript{15,16} beef cows,\textsuperscript{10,11} sheep,\textsuperscript{14} and mice.\textsuperscript{9} In beef, cows, sheep, and mice, higher concentrations of blood lipids, especially NEFA, are found in those breeds which gain weight more easily from a given ration.\textsuperscript{4,9,10,11,13} In the present study, the Morgans, which gain weight easily, tend to have higher concentrations of total lipid than do Thoroughbreds, which do not gain weight as easily. However, the relative percentages of each lipid class comprising the total lipid were very similar for both breeds, indicating that the difference seen in the total lipid concentrations was not due to a large difference in a given lipid class, but rather that the Morgans have more of all lipid classes.

The relationship between higher blood lipid concentrations and ease of maintenance is somewhat obscure. Since the concentration of lipids in the blood is the net result of absorption and mobilization processes as opposed by utilization and storage,\textsuperscript{1} it might be suggested that the higher blood lipids seen in the Morgans are the result of decreased basal metabolism, increased absorption of lipid by the intestine, more efficient conversion of carbohydrates to lipid, or less uptake of lipid by various tissues due to decreased insulin sensitivity. Much more work is necessary to determine the reason for the breed differences and to explain the correlation between ease of maintenance and higher blood lipids.
Both breeds of horses had a decrease in triglyceride concentrations in the winter months. When this seasonal variation was compared with seasonal variations in other species, some discrepancies were noticed. Triglyceride concentrations in cattle increase in the winter, whereas those in humans decrease, as they do in the horse. Explanations are not available for these trends or for differences between species. However, natural seasonal changes do occur throughout the year, and these should be kept in mind when interpreting results obtained at different times of the year.

The present study has demonstrated that ease of maintenance in the different breeds of horses is correlated with the concentrations of various blood lipids, and that the concentrations of various lipid classes in the blood may vary according to the time of year,
REFERENCES


TABLE 1 — Lipid and Glucose Levels in Sera of Two Equine Breeds

<table>
<thead>
<tr>
<th>Serum Constituent</th>
<th>Morgan (8)</th>
<th>Thoroughbred (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>187.8 ± 7.6*,**,</td>
<td>159.9 ± 7.7 **</td>
</tr>
<tr>
<td></td>
<td>42.7%</td>
<td>42.4%</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>93.8 ± 10.4</td>
<td>78.5 ± 8.2</td>
</tr>
<tr>
<td></td>
<td>21.1%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>139.0 ± 5.4 **</td>
<td>123.5 ± 4.5 **</td>
</tr>
<tr>
<td></td>
<td>31.4%</td>
<td>32.8%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>22.4 ± 3.7</td>
<td>15.2 ± 2.8</td>
</tr>
<tr>
<td>Non-Esterified Fatty Acid</td>
<td>5.0%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Total Lipid</td>
<td>443.0 ± 27.1 **</td>
<td>377.2 ± 23.2 **</td>
</tr>
<tr>
<td>Glucose</td>
<td>78.7 ± 7.1</td>
<td>79.8 ± 5.8</td>
</tr>
</tbody>
</table>

* Values are expressed as mg/100ml serum ± SEM and represent the least squares means of the nine monthly means (Sept. through May) for the number of animals shown in parentheses. Corresponding percentages shown in the next lower line in the case of lipid classes represent the fraction of the total lipid contributed by each class.

** Difference between breeds significant (P < 0.05).
### TABLE 2 --- Seasonal Means for Serum Levels of Triglycerides and NEFA

<table>
<thead>
<tr>
<th>Breed</th>
<th>Triglycerides (mg/100ml ± SEM)</th>
<th>NEFA (mg/100ml ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warm*</td>
<td>Cold*</td>
</tr>
<tr>
<td>Morgan</td>
<td>123.6 ± 7.4 **</td>
<td>49.0 ± 12.3 **</td>
</tr>
<tr>
<td>Thoroughbred</td>
<td>114.4 ± 9.9 **</td>
<td>39.9 ± 9.6 **</td>
</tr>
</tbody>
</table>

* Warm (Sept. - Nov. and April - May); Cold (Dec. - March)

** Seasonal breed means are significantly different (P < 0.01)
PART III

METABOLIC FEATURES ASSOCIATED WITH SUSCEPTIBILITY TO

CHRONIC LAMINITIS AND FATTY LIVER IN THE EQUINE
SUMMARY

Glucose, epinephrine and insulin tolerance tests, as well as glucagon and propionate responses, bromsulphthalein clearance (BSP) and thyroid function tests (T-4 levels and T-3 uptake), were utilized to measure differences between Morgan and Thoroughbred horses in metabolic patterns associated with susceptibility to laminitis and fatty liver. The Morgan horse showed lesser ability to clear and metabolize glucose in response to glucose, insulin and epinephrine administration. The amount of insulin secreted by the Morgan was also less than in the Thoroughbred, and the Thoroughbred horse was shown to be more prone to hypoglycemic shock. The Morgan horse is more capable of mobilizing non-esterified fatty acid (NEFA) that the Thoroughbred, and NEFA may be a primary energy source for the Morgan. A four-fold greater increase in serum NEFA level relative to the Thoroughbred was observed during epinephrine administration. Increased mobilization and clearance of NEFA was also seen in the Morgan, both in this test and in insulin tolerance tests. Volatile fatty acids do not appear to contribute significantly to the overall energy metabolism of the short-term fasted (18 hrs.) equine. Thyroid tests showed the Morgan to tend toward hypothyroidism, and BSP clearance after a glucose load indicated some degree of hepatic impairment. Each of the metabolic parameters studied are discussed in relation to currently known etiologic factors in laminitis and fatty liver. It is proposed that the Morgan horse is metabolically predisposed to laminitis and the associated fatty liver compared to the Thoroughbred.
INTRODUCTION

Laminitis, especially the chronic form, occurs with greater frequency among obese, crestnecked horses, commonly designated as "easy keepers," which can be maintained in a near obese condition on minimal quantities of feed (10). A variety of physiological conditions which alter carbohydrate and lipid metabolism (obesity (16), hypothyroidism (29), insulin insensitivity (13), and prolonged administration of certain medications (20, 58) (such as glucocorticoids and ACTH) have been implicated as risk factors in laminitis. Animals which develop chronic laminitis have been found to exhibit hypercholesteremia, elevated serum glutamic oxalacetic transaminase (SGOT) levels and a fatty liver (12). During the acute stage, Obel grade 3 laminitis (44), hyperglycemia is also evident (13). Laminitis and fatty liver are considered to be stress-related syndromes, but this tends to contradict the observations in certain equines, that the ability to form very low density lipoprotein (VLDL) is increased under stress and that the stressed animal will tend to develop fatty plasma rather than fatty liver (6). Stress and its accompanying hormonal changes are responsible for increased levels of plasma non-esterified fatty acids (NEFA), most probably mobilized from adipose tissue or possibly from hydrolysis of lipoprotein or chylomicron triglyceride by lipoprotein lipase. However, for fatty liver to result, other changes must be present. Both insulin and thyroid levels must be decreased below normal, and glucocorticoid levels increased (23, 27, 37). In addition to decreased energy intake, a high carbohydrate to protein ratio in
the diet is also usually evident (28). All these factors have been implicated in the laminitic syndrome as well.

Stress, however, is not the only factor that must be considered in the laminitic fatty liver syndrome. The etiology of laminitis is poorly understood at present, and, although various metabolic changes occur in the laminitic animal, few correlations between these changes and the symptoms of laminitis have been established. The etiology of fatty liver, on the other hand, although complex, is better understood (23, 27, 37), but it has not been determined if previous fatty liver contributes to chronic laminitis or if fatty liver appears as a secondary complication.

There are no formal studies at this time which designate any particular breed as being more susceptible to the disease, but surveys (19, 30) of horse populations and responses from equine practitioners (30) have led to the conclusion that the breed of horse at higher risk is a Quarter Horse, a Morgan, or one of mixed breed from one of these. A survey of 10,000 horses at New Bolton Center showed that 7 percent of clinic population were Morgans with laminitis, whereas 2 percent of the overall clinic population was affected (19). According to a survey of equine practitioners across the nation, it was estimated that approximately 11 percent of the Morgan horse population is afflicted with the disease (30). This is a relatively high percentage and hard to believe, since the incidence of laminitis in the general horse population has been estimated at 1 to 2 percent (19, 30).

In this study, glucose tolerance tests were utilized to assess the equine's ability to metabolize a large glucose load, since laminitis can occur after a carbohydrate overload (22), and is often
associated with obesity and overeating (1). Also, hyperglycemia has been observed during Obel grade 3 laminitis (41) (a very acute stage of the disease). During the glucose tolerance test, blood insulin levels were measured to detect possible insulin deficiency or resistance, since this is thought to be a symptom in both laminitis and fatty liver (27). Blood lipid levels, i.e., non-esterified fatty acids (NEFA), triglycerides (TG), and total cholesterol (CHOL), were also determined during the test. The etiology of fatty liver involves mobilization of large amounts of fatty acids from adipose tissue and decreased triglyceride release from the liver (27). Since hypercholesteremia is one of the metabolic alterations known to occur in laminitis (13), it was of interest to follow changes in blood levels throughout the glucose tolerance tests.

Bromsulfphthalein (BSP) clearance is a general screening test for overall liver function which measures the ability of liver cells to remove a dye introduced into the circulatory system. The rate of removal is influenced by hepatic blood flow and the functioning capacity of the polygonal cells of the liver (26, 56). Therefore, this test was performed immediately following the glucose tolerance test to determine the effect of such a large glucose load on liver function.

Insulin tolerance tests were conducted to study the effect of exogenous insulin on both glucose and lipid levels. This test can serve to verify insulin resistance when suspected from results of a glucose tolerance test. However, the effect of exogenous insulin on lipid metabolism is also of importance since insulin has been described as a treatment for both laminitis (13, 30) and fatty liver (38). (Insulin inhibits NEFA mobilization). Insulin tolerance tests can
demonstrate the animal's ability to maintain blood glucose levels by initiating secretion of growth hormone and glucocorticoids which promote gluconeogenesis (60). The animal which can initiate gluconeogenesis more easily should be more resistant to hypoglycemic shock.

In order to assess liver and muscle glycogen reserves and to observe blood NEFA, TG and CHOL responses to stress, epinephrine tolerance tests were also conducted. These are important determinations because the laminitis-fatty liver syndrome is thought to be stress related (30). The hyperglycemia observed in the later stages of acute laminitis has been hypothesized to originate from gluconeogenesis during stress (13). Therefore, to test the effect of stress on the liver, serum SGOT levels were measured. This enzyme is found primarily in liver and muscle tissue, but following injury or death of physiologically active cells, or a change in permeability in the cell membrane, the enzyme is released into the circulation (26, 56). Thus, the amount of circulating SGOT is in direct proportion to the number of cells damaged.

Since the effects of exogenously supplied glucagon have never been assessed in the horse, and since its action is usually associated with insulin in a tandem relationship (36), studies of its activity were undertaken. Although the main function of glucagon is to maintain normal blood glucose between meals by inducing glycogenolysis in the liver and activating gluconeogenic mechanisms, glucagon has also been shown to be a potent stimulator of NEFA mobilization in some animals (57). Both the gluconeogenic and lipolytic effects would be interesting to observe since both are increased in the blood during the onset of fatty liver.
Propionate infusion was also undertaken to determine the role that volatile fatty acids (VFA) might play in the energy metabolism of the horse, particularly in stimulating insulin release. In tests with ponies, it was found that the equine can utilize VFA resulting from crude fiber fermentation through absorption in the large intestine (35,55). It has been proposed (49) that the equine may rely on VFA when glucose substrates are low. The exact capacity for utilization, however, has never been clearly established.

Tri-iodothyronine uptake (T-3) and thyroxine (T-4) tests were conducted to identify those animals that might be hypothyroid, since this hormonal imbalance is associated with laminitis and may be responsible for both the obesity and hypercholesteremia that precede or accompany the condition (36). Hypothyroidism is often associated with insulin deficiency (26, 53) which is thought to accompany both laminitis and fatty liver.
MATERIALS AND METHODS

Experimental Animals - In all studies, four gelded Morgan horses and three gelded Thoroughbred horses were used, all of which were clinically healthy. Care and maintenance of the animals has been described previously (47). All trials for each set of experiments were duplicated with the animals given a two-week rest between trials.

Blood Samples - Feed was withheld from all animals for 16 to 18 hours before any experiments were begun, but access to water was permitted. Blood samples were obtained at the times specified in each particular experiment by jugular vein catheter to minimize excitement. Samples were placed in capped tubes which were left undisturbed at ambient temperature for 2-4 hours to allow clotting. The serum was decanted, centrifuged at 200xg for 10 minutes to sediment any erythrocytes, placed in capped tubes and refrigerated at 4°C until analysis. All analyses were performed within 48 hours of obtaining serum.

Glucose Tolerance - Treatments consisted of intravenous infusions of 3.5 mM glucose/kg body weight in a total volume of 1000 ml of physiological saline. All infusions were completed within a five minute period. Blood samples were collected prior to infusion and at 5, 10, 15, 30, 60, 90, 120, and 180 minutes post infusion. In addition to glucose, insulin and lipid levels were also determined in order to observe changes during the glucose tolerance test. The half time ($T_{1/2}$) for glucose clearance was calculated.

BSP clearance utilized an aqueous solution of sodium sulfobromophthalein containing 50 mg/ml. The intravenously injected dosage was
5 mg/kg of body weight, and blood samples were taken at 2, 4, 6, 8, 10, 12, 13, and 16 minutes post-injection. Spectrophotometric determinations of serum BSP were performed according to the method described by Seligson, Marion and Dodson (52). Calculation of $T_{1/2}$ was done according to the method described by Cornelius (14).

**Insulin Tolerance** - After obtaining a fasting blood sample, 0.1 unit of crystalline zinc insulin (in 1.6% glycerin with 0.2% phenol as preservative) /kg body weight was injected intramuscularly in the trapezius muscle (neck) area. Blood samples were obtained at 15, 20, 45, 60, 75, 90, 105, 120, and 135 minutes post-injection for insulin, glucose and lipid determinations.

**Epinephrine Tolerance** - After obtaining a pre-injection fasting blood sample, 5 ml of 1:1000 epinephrine hydrochloride in physiological saline was administered intramuscularly in the deltoid area. Blood samples were obtained at 5, 10, 15, 20, 30, 60, and 90 minutes post-injection to evaluate changes in serum glucose, lipids and SGOT in response to the epinephrine.

**Glucagon Test** - A fasting blood sample was obtained before intravenously administering a test dose of 5 mg glucagon dissolved in 5 ml of 1.6% glycerin with 0.2% phenol as a preservative. Blood samples were obtained at 5, 10, 15, 20, 60, and 90 minutes post-injection and glucose, insulin, and lipid levels determined in each sample.

**Propionate Test** - A solution containing 5.0 mM sodium propionate /kg of body weight dissolved in a total of 1000 ml physiological

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aEli Lily, Indianapolis, Indiana
saline was infused intravenously. The infusion was completed within 5 minutes. Samples were withdrawn prior to infusion and at 10, 15, 30, 45, 60, 90, and 120 minutes post-infusion for glucose and insulin determinations.

Thyroid Hormone and Insulin Baselines - In order to establish normal baseline values for serum insulin and thyroid hormone levels, (this had not been done in the earlier study (34) when normal baseline values for serum glucose and lipid levels were determined) insulin and thyroid function determinations were also conducted on an additional population of 6 Morgan and 4 Thoroughbred horses. Examination of a larger animal population was deemed necessary.

Serum Analyses - All glucose and lipid determinations were performed by colorimetric methods. b

Triglycerides were determined by a procedure based on the Hantzsh (9, 21) reaction with a triglyceride test kit. c

Non-esterified fatty acids were determined by Duncombe's method (17) with an NEFA test kit. d

Total cholesterol was determined by Watson's method (62, 63) with a cholesterol test kit. d To obtain total cholesterol, values were multiplied by 1.25 (47).

Glucose was determined by the glucose oxidase method (59) with a glucostat test kit. e

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b Spectronic 20 Colorimeter, Bausch & Lomb, Inc., Rochester, NY

c Oxford Tri-Chol Test Kit, Oxford Laboratories, Foster City, CA

d Test Kits from Boehringer Manheim Corporation, New York, NY

e Worthington Glucostat Test Kit, Worthington Biochemical Co., Freehold, NJ
SGOT determinations were done with an SGOT test kit\(^d\) according to a method by Reitman and Frankel (46).

All radioimmunoassays were carried out in a Packard Auto-gamma spectrometer.\(^f\)

Insulin was determined by solid phase radioimmunoassay (25) with a Phedebas Insulin Test kit.\(^g\)

T-4 radioimmunoassays were conducted with a Curtis Nuclear TT-4 test kit \(^h\) based on the Murphy-Pattee procedure (40) of competitive protein binding on an anion exchange membrane.

T-3 uptake was done with the Tri-Ionex test kit \(^h\) which uses a modified Scholer procedure (51).

Statistical Analyses - Statistical examination of data obtained was performed by least squares analyses of variance (61) to determine differences between breeds for T\(_1/2\) of glucose tolerance and T\(_1/2\) for BSP clearance. This procedure was also utilized to identify differences between breeds in T-4 levels and T-3 uptakes, as well as in fasting levels of immunoreactive insulin.

Analyses of variance for covariates (42, 54), a multiregressional statistic tool, was utilized to determine differences in breed response to the various treatments over the time spans studied.

Significant differences (p < .05) were visualized by graphical presentations. Areas individual under curves were determined by planimetry with the baseline as zero concentration, and analysis of

\(^{f}\) Packard Nuclear, Downers Grove, Illinois

\(^{g}\) Phedebas Insulin Test, Pharmacia, Uppsala, Sweded

\(^{h}\) Curtis Nuclear Corporation, Three Westchester Plaza, Elmsford, NY
Correlation coefficients (62) were computed to establish the relationship between peak insulin levels and \( T_{1/2} \) levels during glucose tolerance and between T-4 and T-3 uptake and \( T_{1/2} \) of glucose tolerance.

Calculations and graphical representations were made using mean values for the two trials in each case.

RESULTS

Glucose Tolerance - The mean absolute serum glucose values for the two breeds of horses at the various time intervals are shown in Figure 1. \( T_{1/2} \) values (time at which one can find one-half the original injected level in the blood) were calculated from the lines of best fit from each regression between serum glucose values and time on a semi-logarithmic plot of the utilization component of the curve, or that portion of the curve which represents the rate at which the infused glucose leaves a uniformly mixed pool (4, 44). Absolute glucose values were used in the computations since excess glucose responses would have yielded negative numbers which could not have been plotted logarithmically. Also, lines of best fit had to be calculated using the means of regressions from several exponential utilization curves since more than one was evident in these studies. \( T_{1/2} \) values were then calculated from the formula (45):

\[
T_{1/2} = \ln \left( \frac{1}{\lambda} \right),
\]

where \( \ln2 \) is the natural log of 2 or 0.693, and \( \lambda \) is the slope of the line. The slope of the line can be calculated from the following formula:

\[
\lambda = \ln \left( \frac{y_1/y_2}{\Delta^*} \right)
\]

where \( y_1 \) and \( y_2 \) are the absolute glucose concentrations at times 1 and 2 on the exponential component of the utilization curve, and \( \Delta^* \) is the difference between
The rate of disappearance is equal to the mean of the computed slopes of the utilization component exponential curves. Table 1 shows the $T_{1/2}$ values for the two breed groups along with the disappearance rates of glucose, or the amount cleared per unit time from the circulation. One can also express the disappearance rate on the basis of metabolic body weight expressed in kilograms$^{0.75}$, so that the effect of body composition can also be taken into consideration (31). The mean $T_{1/2}$, $K/hr$ and $K/hr/W^{0.75}$ are all significantly different ($p < .05$) between breeds. $T_{1/2}$'s vary between animals of the same breed, and when these differences are calculated as a fraction of glucose cleared/hr/W$^{0.75}$, these differences were still apparent. This indicated that body composition did not account for this variability. There were no significant differences between weights within each breed. The early drop and subsequent rise in the serum glucose which occurred immediately after infusion in the Thoroughbred is an atypical glucose response and cannot be fully explained with the data available. What is evident, however, is the Morgan horse's reduced capacity to clear a glucose load when compared with the Thoroughbred. This is evident in the latter stages of the test.

Figure 2 illustrates the difference in insulin response between the two breeds during the glucose tolerance test. The Morgan shows a delayed and reduced insulin response to the glucose load. When one examines the pre-injection fasting levels of immunoreactive insulin, the Morgan horse has a concentration of 20.25 uU/100 ml and the Thoroughbred 25.67 uU/100 ml. When a larger population sample from each breed was examined, the mean fasting values were 23.1 uU/100 ml and 34.8 uU/100 ml for the Morgan and Thoroughbred respectively, and
this difference was found to be significant \( (p < .01) \). Correlation of the rise in immunoreactive insulin concentration with the \( T_{1/2} \) values obtained in Table 1 gave correlation values of \( r = -.73 \) and \( r = -.90 \) for the Morgan and Thoroughbred respectively. This indicates an inverse correlation between parameters.

The mean \( T-4 \) and \( T-3 \) uptake values presented in Table 2 show a significant difference between breeds \( (p < .05) \). The \( T-3 \) uptake values were also correlated with the \( T_{1/2} \) values in Table 1, the Morgan having a correlation value of \( r = -.87 \) and the Thoroughbred \( r = -.93 \). Thus, thyroid transport capability appears inversely correlated with the glucose \( T_{1/2} \) values, with the Thoroughbred having a slightly stronger correlation. \( T-3 \) uptake values were used in the correlation since these have been shown to give more accurate indices of thyroid function in the horse (8).

The serum lipid responses during glucose tolerance are represented in Figure 3. Comparison of the curves showed a significantly different pattern in NEFA changes between breeds during the test. During the first five minutes the Morgan shows a moderate rise in NEFA, whereas the Thoroughbred shows a slight decrease. The most striking difference occurs between 5 and 15 minutes in the test. While the Morgan has a steady decrease in NEFA, the Thoroughbred exhibits a steep increase until the values between the two breeds become nearly identical at 15 minutes. At this point, the Thoroughbred begins to stabilize its NEFA level, whereas the Morgan continues to decrease its NEFA until it stabilizes at about 90 minutes. Total triglyceride release was less in the Morgan, and 60 minutes elapsed before release into the circulation. This was a time lag of 30
minutes compared to the Thoroughbred. There were no significant differences in the cholesterol response to a glucose load between breeds although mobilization of cholesterol appeared slightly greater in the Morgan.

BSP clearance tests resulted in $T_{1/2}$ values of 4.53 and 3.99 minutes for the Morgan and Thoroughbred horses respectively, as calculated from the curves shown in Figure 4. These values show no statistically significant breed differences; however, the value for the Morgan lies outside the normal range reported for the horse (14). Correlation values between $T_{1/2}$ values for BSP clearance and glucose tolerance were $r = +.94$ for the Morgan and $r = +.41$ for the Thoroughbred. This means that there was a strong, direct correlation between BSP clearance half-times and glucose tolerance half-times in the Morgan horse. No correlation between these two parameters was seen in the Thoroughbred. These results are summarized in Table 3.

Epinephrine Tolerance - Statistically significant differences between breeds ($p < .05$) were seen in the glucose response to epinephrine administration. The Morgan serum glucose level rose to less than half the highest level seen in the Thoroughbred and peaked later, but the disappearance rate of the glucose was delayed in this breed. These curves appear in Figure 5.

The lipid response to epinephrine administration is represented in Figure 6. A statistically significant ($p < .01$) difference was obtained between breeds in the total amount of NEFA mobilized.

The ability of the Morgan to mobilize fatty acids is dramatic. Triglyceride responses were similar between breeds with the Morgan showing a slightly higher level. An interesting point is the
secondary rise in triglyceride levels at 90 minutes in the Morgan. It is unfortunate that values were not obtained to follow this tendency further. Significant differences between breeds (p < .05) were seen in the cholesterol levels although responses were similar.

SGOT responses to epinephrine administration (Figure 7) show no statistically significant differences between breeds; however, the two breeds appear to show significant differences (p < .05) in the initial values. Thus, there are no differences in the patterns of the curve, but the two breeds differ in their normal circulating SGOT levels. Table 4 summarizes these differences in response to epinephrine.

Insulin Tolerance - Glucose and insulin responses to an insulin injection are represented in Figure 8. Although the relative rates of glucose disappearance are not significantly different, it is noteworthy that all tests in the Thoroughbred were terminated by 140 minutes or shortly thereafter since these animals suffered insulin (hypoglycemic) shock and had to receive intravenous glucose supplementation to counteract this effect. Insulin shock was not observed in the Morgan horses, although all tests in this breed were terminated at 150 minutes as a precaution. However, even at as low serum glucose concentrations as in the Thoroughbreds, the Morgans did not show any symptoms of impending insulin shock. The insulin level shows a marked rise in the Thoroughbred from the exogenous insulin given. This difference in response throughout the test between breeds is significant at the p < .05 level. The lipid responses to exogenous insulin can be seen in Figure 9. Cholesterol and triglyceride responses do not differ appreciably between breeds; however, the rate of mobilization of NEFA from the circulation was significantly different (p < .05)
between breeds. When exogenous insulin was given, the Morgan horse cleared its NEFA more rapidly than did the Thoroughbred. Table 5 summarizes the major similarities and differences when insulin is administered.

**Glucagon Test** - Figure 10 represents the glucose and insulin responses which occurred during the test. Although the amount of glucose liberated by the Morgan appears to be less than that of the Thoroughbred, the difference is not statistically significant. A statistically significant difference (p < .05) is seen in the insulin response. The Thoroughbred elicits a markedly higher level of insulin in response to the glucagon administration.

The lipid responses appear in Figure 11. The NEFA mobilized by the Morgan is significantly greater (p < .05) than that of the Thoroughbred. No difference between breeds in triglyceride response to glucagon was observed. Cholesterol levels during the test were significantly different between breeds (p < .05). Both breeds showed a decrease in cholesterol during the first 5 minutes, although the Thoroughbred response is appreciably greater. The Thoroughbred continues a precipitous decline and more or less stabilizes at a level 35mg/100ml lower than its initial value. On the other hand, cholesterol in the Morgan begins a gradual and continual increase after 30 minutes to attain a level 13mg/100ml above the initial value by the end of the test. Table 6 summarizes the principal similarities and differences observed during the glucagon tolerance tests.

**Propionate Test** - Figure 12 depicts the insulin and glucose response to the propionate infusion. Neither the insulin nor the glucose responses showed statistically significant differences between
breeds. The Thoroughbred did show a slightly faster response to attain maximal glucose levels but the small changes in glucose concentration were not significant. The Thoroughbred did reach a slightly higher peak insulin value than the Morgan and also attained it sooner. It must be kept in mind that the concentration of propionate infused far exceeded the physiological level normally found in the horse (.092-.189mM) (35).

DISCUSSION

It is evident that the Morgan and Thoroughbred horse differ in various metabolic features and that these differences involve two general systems:

1) The Morgan horse's lesser ability to secrete insulin and to metabolize an exogenous glucose load; and

2) The Morgan horse's greater ability to mobilize and metabolize NEFA.

Glucose Tolerance - The Morgan's lesser ability to metabolize an intravenous glucose load appears somewhat analogous to chemical diabetes, that is, the fasting blood glucose levels appear normal but the disappearance rates of a glucose load are slow. This slow rate of disappearance may be the result of a lesser insulin secreting capability in the Morgan horse. In this respect the Morgan horse, although a monogastric herbivore, resembles the ruminant more than does the Thoroughbred (7, 53). Like the human, both breeds exhibit biphasic insulin curves during glucose clearance (44). The first rise in insulin represents that pool which is available for rapid release, and the second rise indicates the insulin available for sustained action and is more closely related to insulin synthesis. The Morgan
shows a lower response in both components when compared with the Thoroughbred. Although the early glucose response of the Thoroughbred is atypical of glucose tolerance curves in general, a plausible explanation may be derived by examining the two compartment insulin curve. The rise in insulin is substantial in the first component; therefore, the glucose influx could be reduced rather quickly by the insulin present. The subsequent increase in glucose could be caused by release of glucose from glycogenolyses in the liver in response to such a rapid glucose drop. Then, the second compartment insulin release gradually decreases the secondary glucose load. The Thoroughbred is primarily a short distance racer, and therefore may be adapted to releasing a relatively large amount of insulin to quickly move glucose into the cells for intensive work of short duration. On the other hand, the Morgan's insulin releasing capabilities may be more reflective of its less intense but sustained working capabilities. During prolonged aerobic exercise, NEFA is the favored fuel. Therefore, since glucagon mobilizes NEFA (insulin inhibits), glucagon rather than insulin would be of greater importance (11, 24).

With reduced insulin secreting ability, it seems strange that the Morgan should show a tendency towards obesity since decreased ability of cells to take up glucose in insulin insufficiency usually leads to lipolyses and a decrease in body weight due to oxidation of the fat metabolized. The Morgan horses used in this study were exercised regularly, and their diet was carefully adjusted to prevent obesity. Perhaps the overnight fast in the Morgan stimulates a greater secretion of anti-insulinogenic hormones, such as glucagon which would result in less insulin available. Or it may be that the Morgan has a higher
glucagon to insulin ratio than the Thoroughbred, thus maintaining normal blood glucose by a different mechanism. The Morgan may also have a higher level of insulinase and thus destroys insulin more rapidly. Another possibility is that the Morgan horse has a higher circulating level of adrenocorticoids. It has been shown that chronically elevated levels of adrenocortical hormones can result in a form of diabetes which is nonketotic but which is characterized by reduced glucose tolerance (18). Peripheral uptake of glucose, as well as phosphorylation of glucose within the cell, is diminished in the presence of corticosteroids (18).

In addition to the different insulin response, low hepatic uptake of glucose might also explain the lesser glucose tolerance in the Morgan horse. It has become increasingly clear that normal glucose tolerance is achieved largely by the hepatic response of increased glycogenesis and possibly increased glycolysis (53). The BSP clearance in this animal did suggest a lesser ability to clear materials. The high positive correlation obtained also indicates that when the T1/2 of the BSP clearance is high in the Morgan so is the T1/2 glucose tolerance. Although insulin is not needed for glucose uptake by hepatic cells the presence of insulin is thought to be necessary to activate the synthetases for glycogen formation. Therefore, it appears that insulin may have an indirect effect on the functional state of the liver during glucose overloads in the Morgan. Little correlation between T1/2 of BSP clearance and glucose tolerance T1/2 is observed in the Thoroughbred.

The NEFA reaction to the glucose load was very different in both breeds. Events which occurred early in the test in both breeds are
not the expected responses usually seen in most mammals. It is known that increasing quantities of insulin inhibit NEFA mobilization (5, 36); nevertheless, the Morgan increases its NEFA immediately following glucose infusion. The rise of NEFA may be partially explained by the delayed insulin response early in the test. When the insulin level begins to rise, the NEFA begins to decrease and continues to do so until it stabilizes at a level considerably below the pre-injection level. This decrease in NEFA may be the result of a combination of factors, primarily inhibition of lipolyses from adipose cells by insulin and increased NEFA oxidation.

The Thoroughbred, on the other hand, showed essentially the reverse. The precipitous drop in NEFA in the beginning of the test may also be due to the large influx of insulin and which occurs at that time, as well as increased oxidation. The subsequent rise in NEFA is not so easily explained. It is possible that the Thoroughbred's adipose cells are not as sensitive to insulin as those of the Morgan. The NEFA level reached by the Thoroughbred, however, was essentially the same as the initial value prior to infusion; therefore, it may be that insulin secretion in the Thoroughbred tends to maintain fasting levels of NEFA.

Release of hepatic triglycerides also appears different between the two breeds. The Morgan horse is much slower in the formation and/or release of triglyceride from the liver. Two factors may be responsible for this decrease and delay: (1) influx of NEFA into the liver is much greater and more rapid in the Morgan and overwhelms the triglyceride synthesizing mechanism; (2) disproportionate conversion of fatty acids (derived either from glucose transformation or mobilized
from adipose stores) to triglyceride rather than to phospholipids due to low levels of choline or other lipotrophs in the liver. This would thereby decrease the ratio of phospholipids to triglycerides in the lipoproteins for transport from the liver.

Another factor which might explain the Morgan's lesser ability to metabolize a glucose load is its relative hypothyroidism. This is evident in both T-3 uptake and T-4 values. Although an uptake of 40% in horses is not considered an overt hypothyroid condition (39), it does represent the lower side of the normal range for horses in general. Since this represents a mean value, it is obvious that some animals exhibit values less than 40%. Examination of correlation values show inverse relationships between thyroid function and glucose tolerance for both animals, but glucose tolerance in the Thoroughbred is more strongly correlated with thyroid function. That is, a higher T-3 uptake is almost always found along with a low T\(_4\) of glucose tolerance. On the other hand, in the Morgan a low T-3 uptake correlation with a high T\(_4\) value of glucose tolerance, or lower glucose tolerance. It has been demonstrated in humans (53) that hypothyroid individuals are much less sensitive to insulin than normal individuals. In tests where hypothyroid individuals were given glucose \(^{14}\)C, both glucose turnover and amount of glucose metabolized was reduced. It is hypothesized that this effect may be related to differences in end organ response or to the rate of insulin destruction. Therefore, it is possible that the relative hypothyroid tendency of the Morgan might contribute to the lower glucose tolerance.

**Insulin Tolerance** - Even when equivalent doses of insulin were given to both breeds, the Morgan exhibited a slightly slower rate of
glucose mobilization than the Thoroughbred. When exogenous insulin was administered, a considerably lower level of insulin was found circulating in the bloodstream of the Morgan. This may account for the slower rate of glucose removal, but it is not known why this level should be low. Perhaps the Morgan horse has a higher level of insulinase (which hydrolyzes insulin and inactivates it) in its hepatic cells as evidenced by the rapid disappearance rate.

When the glucose available to the brain reaches dangerously low levels a hypoglycemic reaction occurs. The Morgan did not show any symptoms whatsoever of impending insulin shock; therefore, the low level of glucose must have been adequate to supply the brain. The difference seen between the two breeds may be related to relative amounts of musculature and also to different insulin sensitivities of various tissues between the breeds. It has been shown that the greater the muscle mass of an organism, the larger the glucose uptake (53). It is agreed among veterinarians that the Morgan horse tends to be more obese than the Thoroughbred (30). Another possibility may be that the Morgan has an increased transport capacity in the membranes separating the cerebral interstitial fluid from the site of glucose phosphorylation in the brain. Therefore, transportation of glucose from cerebral capillary plasma through the blood-brain barrier to the brain interstitial fluid may be more efficient. Other possibilities are that the Morgan may utilize noncarbohydrate substances derived from the blood or utilize lipid stored in the brain or that there is a difference in the Km of hexokinase in this breed. Such possibilities have been hypothesized to explain the sheep's increased tolerance to hypoglycemia (43).
The insulin tolerance test also measures an organism's ability to stimulate secretion of growth hormone in response to hypoglycemia (60). Growth hormone inhibits further uptake of glucose from the blood by peripheral tissues and acts as a protective and supportive factor by mobilizing lipid, a more expendable fuel for the organism (26). In view of the Thoroughbred's acute hypoglycemia, it appears doubtful that this animal is secreting appreciable amounts of growth hormone. The Morgan, however, late in the test begins to show a rise in the NEFA level (indicating that lipolysis is being activated) which could conceivably be metabolized for energy to spare glucose.

It seems that exogenous insulin injection has a greater effect on inhibiting fat mobilization from adipose tissue in the Morgan than the Thoroughbred. Adipose cells of the Morgan may be more sensitive to insulin than the Thoroughbred, or exogenous insulin may cause a greater change in the glucagon to insulin ratio in the Morgan than the Thoroughbred. Thus, the insulin inhibits the lipolytic action of glucagon.

Epinephrine Tolerance - This test can be used to measure liver glycogen stores, hepatic function and the animal's response to stress. From the amount of glucose liberated by the Morgan, it would seem that this breed has a smaller glycogen reserve than the Thoroughbred. The relatively low level of insulin in the Morgan may prevent optimal glycogen synthesis. It is possible, too, that the high circulating glucocorticoid levels previously hypothesized in the Morgan horse could be stimulating hepatic phosphorylase phosphatase, thus inhibiting glycogen breakdown (18).

It is possible that glucose liberated by the Morgan may not be derived entirely from liver glycogenolyses since the time to reach
maximal level is rather prolonged, and the rate of glucose release appears too gradual. It would seem that much of the glucose liberated by the Morgan could have arisen from an indirect action of epinephrine on gluconeogenesis by activation of the Cori cycle (33), and that this glucose might be the result of lactate transformation in the liver. It is possible also that glucose levels are prevented from increasing by prior release of high NEFA levels from epinephrine-stimulated lipoysis. This latter effect may also be responsible for the difference between breeds in the utilization of the glucose during the test. The Morgan's slower rate, therefore, may be the result of high circulating concentrations of NEFA that affect plasma membranes of many cell types and decrease their ability to take up glucose (56). The total increase in glucose over fasting levels is just about 20mg%. A rise of less than 35-40mg% of glucose is indicative of hepatic dysfunction in most animals (6). Therefore, during stress, as simulated by the administration of epinephrine, glucose does not appear to be as important an energy source for muscle in the Morgan as it appears to be in the Thoroughbred. It has been shown that the horse can rely on other substrates for energy, especially during exercise (11, 24). The horse can mobilize NEFA during exercise, and this substrate can be utilized effectively by muscle for energy. The Morgan releases four times as much NEFA as the Thoroughbred in response to epinephrine administration. It may be that the Thoroughbred is exhibiting metabolic responses similar to the ruminant, which reacts very weakly in its lipolytic response to epinephrine. On the other hand, the Morgan reacts more like the monogastric or the fasted ruminant in its response (32, 37).
It is known that in many animals under stress the level of VLDL rises (39). Since triglyceride accounts for 50-80% of the lipid in the VLDL of the equine (48), it is not surprising to see a rise in serum triglyceride. One would, however, expect a much greater amount of triglyceride to be formed and liberated after such a large NEFA output as seen in the Morgan. It is not known from the data available whether the Morgan horses in this test oxidized the NEFA in the muscle or whether NEFA were taken up and stored in the liver since so little was released. It is possible also that the gluconeogenic effect of epinephrine might increase catabolism of amino acids necessary for lipoprotein formation.

The Morgan also showed a threefold greater output of cholesterol than the Thoroughbred. Cholesterol levels are often elevated in stress reactions in response to epinephrine secretion (26). The abundance of NEFA liberated can be catabolized eventually to HMG-CoA in the liver which is an important intermediate in cholesterol biosynthesis. It is possible that the Morgan normally has lower circulating levels of epinephrine than the Thoroughbred and that the test dose caused a greater impact on the Morgan.

SGOT levels in both breeds were within the normal range for the horse (breed not specified) as reported in the literature (15, 61) (81-195 uM/100 ml) and, although the level in the Morgan is considerably higher than in the Thoroughbred, it is difficult to assign a reason for this difference. SGOT levels can increase with a change in the permeability of membranes such as could occur in electrolyte imbalance of stressful reactions (26, 56). Therefore, the early slight increase seen in the Morgan may be related to the epinephrine administration
and the stress reaction it elicits. It has also been shown that adrenocortical steroids can elevate the activity of several transaminase enzymes (18). Therefore, if the Morgan does have higher circulating levels of these steroids, SGOT levels could be normally elevated.

Glucagon Test - Little is reported concerning glucagon metabolism in the horse, and very little is known about its effects on lipid metabolism on mammals in general. Glucagon regulates carbohydrate metabolism by inducing glycogenolysis in the liver and, most of all, by promoting gluconeogenesis. It also facilitates the uptake of amino acids by the liver. Unlike the gluconeogenesis stimulated by epinephrine, the action of glucagon is more sustained so that the glucose formed from amino acid catabolism is liberated over a longer period of time (57). Glucagon is also liberated during stress. In addition, glucagon stimulates insulin production (50). This may account for the more "normal" removal of the glucose load by the Morgan when glucagon is administered. Although the levels of glucose liberated were lower in the Morgan than the Thoroughbred, the insulin (probably stimulated by glucagon) aided the removal of glucose from the circulation so that removal rates were similar in both breeds. Glucagon also stimulates adipose and hepatic lipases and accelerates fatty acid oxidation (57). The physiological significance of this activity is not known, but glucagon has been shown to accelerate the breakdown of depot fat in obese subjects (34) and to reduce the concentration of cholesterol in patients with this hyperlipemic condition (36). By mobilizing lipid the hormone may indirectly contribute to blood glucose elevation since the supply of non-carbohydrate
fuels to tissues with flexible requirements is increased. Again, the Thoroughbred reacts more like the ruminant in its weak lipolytic response to the glucagon injection whereas the Morgan reacts more like a monogastric (53). Glucagon does not seem to have as great an effect in reducing cholesterol levels in the Morgan as it does in the Thoroughbred. It has been observed in insulin-deficient rats that the level of enzymes which control cholesterol synthesis are elevated (26). The lower insulin level in the Morgan, therefore, could be a factor contributing to higher cholesterol levels. Cholesterol is regulated by many factors, and with combinations of factors working jointly, it is difficult to single out any one factor as causing the effect.

**Propionate Test** - It may be assumed from the established dependence on microbial fermentation for the digestion of crude fiber, that the equine utilizes some FVA as a source of energy (55). However, the exact capacity for utilization at the tissue level has not been well established. Propionate was observed to affect glucose and insulin levels in the horse (3). Ruminants can carboxylate propionate to succinate, and, therefore, it is a precursor of glucose in the liver (26). In these animals neither breed showed marked increases in either glucose or insulin levels. It was shown by Argenzio (3) that the fasted animal (72 hrs.) begins to show a more pronounced effect. This is most likely because the fasted animal has shifted to gluconeogenesis and may be able to utilize these short chain fatty acids. Horino, et al (28), suggested that a species may evolve an insulin secretory mechanism capable of regulating the nutrient which is the primary metabolic or energetic substrate. Since the insulin
response to the propionate infusion was minimal, it is doubtful that this particular VFA contributes much to the energy pattern of the short-term fasted (18 hrs.) Morgans and Thoroughbreds.

General Correlations with Laminitis - The laminitic attack is often precipitated by stress. A typical example would be the insulin-deficient or -resistant horse which during the winter months is fed a diet low in energy, such as hay which cannot provide for the equine's energy needs (1). Another example might be a horse exhibiting the metabolic characteristics described above which, instead of being subjected to a nutritional stress, is subjected to stress from sudden removal of extended corticosteroid therapy (20). In both cases the stress could raise the levels of catecholamines and glucocorticoids above normal levels. NEFA liberated by epinephrine during the stress period could easily cause triglyceride saturation of the liver. The glucocorticoids, however, also promote increased metabolism of endogenous protein and, thereby could inhibit lipid mobilization from the liver by decreasing lipoprotein formation and promoting catabolism of the amino acids needed for their lipotropic action as components of VLDL. Since some laminitic horses respond dramatically to lipotropic compounds (30), a possible deficiency of choline could also contribute to the lowered triglyceride release from the liver. Also, there appears to be an unusual peak present in the HDL lipoprotein fractions. Since this same feature appears in the laminitic non-Morgan horse, it might suggest reduced lipid removal from the liver.
The laminitic horse is also sometimes hypothyroid or has hypothyroid tendencies. Low thyroid activity has been associated with decreased insulin levels and observed in patients with fatty liver. Hypothyroidism has also been reported to cause edema or mucopolysaccharide infiltration of the dermis and predispose the animals to the effects of subtle compartmental fluid shifts which occur in laminitis (13).

Finally, hypercholesteremia is often associated with the laminitis-fatty liver syndrome. This elevation of cholesterol could be the result of prolonged, elevated epinephrine and glucagon levels and low insulin levels. This would result in the flux of NEFA to the liver. Since the liver accumulates acetoacetate and other ketones during B-oxidation and lacks the thiokinase to convert it to the CoA ester, much of the acetoacetate is transformed to HMG-CoA, an important intermediate in cholesterol biosynthesis.

If one examines the therapy utilized to treat the laminitic horse, one can now see the rationale for the major components in the treatment and why they would be useful in treating the Morgan horse. Insulin and glucose, methionine and other lipotropic agents, amino acid infusions and thyroid extract are often used (30). Insulin would reduce the flow of NEFA from peripheral fat stores, promote movement of glucose into the cell to provide energy for metabolic functions, promote a braking effect on protein catabolism and, therefore, favor the formation of lipoprotein and needed lipotropic agents. Thus the animal could better cope with the toxic products generated during the laminitic episode.

In summary, the fatty liver in chronic laminitis may occur more
readily and have a more pronounced effect in those animals or breeds that exhibit low concentrations of thyroid hormone and either show insulin deficiency, accelerated inactivation of insulin or insulin resistance and have increased gluconeogenesis. These metabolic patterns can result from poor nutrition or from prolonged physiological stress.

**General Metabolic Conclusions** - Morgans and Thoroughbreds exhibit different metabolic patterns as discussed. Comparing breeds, the following trends are apparent:

1) The Morgan tends to show a higher rate of insulin destruction. This is evidenced by the lower levels of circulating immunoreactive insulin in the Morgan both under normal overnight fasting conditions, as well as after insulin injection. It is hypothesized that either the relative hypothyroid tendency which has been related to the rate of insulin destruction or a high level of insulinase may be responsible.

2) The Morgan tends to show greater adipose sensitivity to insulin. When the insulin increases in the Morgan (both during glucose tolerance and as a result of insulin injection) a decrease in NEFA (perhaps by inhibition of lipolyses from adipose cells and increased oxidation NEFA) was much more pronounced than in the Thoroughbred.

3) The Thoroughbred reacts metabolically more like the ruminant whereas the Morgan exhibits more metabolic features of the pre-ketotic ruminant. The Thoroughbred has insulin levels comparable to the ruminant and also exhibits a much reduced lipolytic response to injections of epinephrine and glucagon. The Morgan, on the other hand, like the pre-ketotic ruminant, has much greater lipolytic response to
these hormones.

4) The Morgan appears to rely less on glucose as a source of energy as evidenced by its relatively lower circulating insulin levels, its abnormal glucose tolerance curve, its lower glycogenolytic activities, its relative resistance to hypoglycemic shock and the high NEFA levels.

5) The Morgan may have higher adrenocortical hormone levels than the Thoroughbred. Although these levels were not measured, the abnormal glucose tolerance exhibited by the Morgan could be caused by decreased peripheral uptake of glucose as well as phosphorylation of glucose within the cell which occurs in the presence of corticosteroids. Elevated glucocorticoid levels could also account for the higher SGOT levels, as well as decreasing the amounts of available amino acids needed for VLDL synthesis to remove triglycerides from the liver. This aspect should be examined in detail in future studies. The role of ACTH and cortisol has been questioned, especially in relation to the effect of adrenal androgens (2) in the etiology of laminitis. Perhaps the circulating level of ACTH may be useful in determining the animal's response to stress and susceptibility to laminitis.

These differences between breeds may explain (at least in part) the differences in susceptibility between the two breeds to the laminitis-fatty liver syndrome.
REFERENCES


TABLE 1 - RATE OF DISAPPEARANCE OF GLUCOSE FROM THE CIRCULATION FOLLOWING AN INTRAVENOUS INFUSION IN MORGAN AND THOROUGHBRED HORSES

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>$T_1^2$</th>
<th>WEIGHT (in kg)</th>
<th>$W^{.75}$</th>
<th>K/hr</th>
<th>K/hr/$W^{.75}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORGAN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>119.0*</td>
<td>490</td>
<td>104.15</td>
<td>.0058</td>
<td>5.569 x 10^{-5}</td>
</tr>
<tr>
<td>2</td>
<td>109.0</td>
<td>484</td>
<td>102.19</td>
<td>.0064</td>
<td>6.202 x 10^{-5}</td>
</tr>
<tr>
<td>3</td>
<td>92.1</td>
<td>430</td>
<td>94.43</td>
<td>.0075</td>
<td>7.942 x 10^{-5}</td>
</tr>
<tr>
<td>4</td>
<td>92.4</td>
<td>427</td>
<td>93.93</td>
<td>.0075</td>
<td>7.985 x 10^{-5}</td>
</tr>
<tr>
<td>MEAN</td>
<td>103.13 ± 22.87**</td>
<td>457.75 ± 29.35</td>
<td>98.93 ± 4.76</td>
<td>.0068**</td>
<td>6.925 x 10^{-5}**</td>
</tr>
<tr>
<td>THOROUGHBRED</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>60.4</td>
<td>500</td>
<td>105.74</td>
<td>.0115</td>
<td>1.087 x 10^{-4}</td>
</tr>
<tr>
<td>2</td>
<td>63.5</td>
<td>538</td>
<td>111.71</td>
<td>.0109</td>
<td>9.757 x 10^{-5}</td>
</tr>
<tr>
<td>3</td>
<td>67.7</td>
<td>593</td>
<td>120.17</td>
<td>.0102</td>
<td>8.488 x 10^{-5}</td>
</tr>
<tr>
<td>MEAN</td>
<td>63.87 ± 5.18**</td>
<td>543 ± 38.18</td>
<td>112.54 ± 5.92</td>
<td>.0109**</td>
<td>9.444 x 10^{-5}**</td>
</tr>
</tbody>
</table>

$T_1^2$ - half life of infused glucose; $W^{.75}$ - metabolic weight; K/hr - fraction (mg/100 ml) cleared per unit time; K/hr/$W^{.75}$ - effect of body composition on fraction cleared per unit time.

* Each value is the arithmetic mean of two values.

** Difference between breeds significant (p < .05)
### TABLE 2 - SERUM THYROID HORMONE LEVELS

<table>
<thead>
<tr>
<th>BREED</th>
<th>T-4</th>
<th>T-3% Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgan</td>
<td>1.42 ± .68*</td>
<td>40.31 ± 5.50*</td>
</tr>
<tr>
<td>Thoroughbred</td>
<td>2.68 ± .92*</td>
<td>45.83 ± 3.32*</td>
</tr>
</tbody>
</table>

Each value is the arithmetic mean for either ten Morgan or seven Thoroughbred horses.

*Differences between breeds statistically significant (p < .05)*
TABLE 3 - SUMMARY OF RESULTS FROM GLUCOSE TOLERANCE TEST

<table>
<thead>
<tr>
<th></th>
<th>MORGAN</th>
<th>THOROUGHBRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Clears glucose at a slower rate</td>
<td>Clears glucose at a faster rate</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insulin release slower, less secretion</td>
<td>Insulin release faster, greater secretion</td>
</tr>
<tr>
<td>NEFA</td>
<td>Increases quickly early, then steady decline - stabilized at lower level by 90 minutes</td>
<td>Slight decrease very early, then steady increase - stabilized at a high level by 30 minutes</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Peak value lower - peak appears 30 minutes later than Thoroughbred</td>
<td>Peak value higher - peak appears 30 minutes earlier than Morgan</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Differences Not Significant</td>
<td></td>
</tr>
<tr>
<td>BSP</td>
<td>No Differences in Values Between Breeds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T½ value shows liver malfunction.</td>
<td>T½ within normal range.</td>
</tr>
<tr>
<td></td>
<td>Correlates strongly with T½ of glucose clearance</td>
<td>Little correlation with T½ of glucose clearance</td>
</tr>
<tr>
<td>T-3</td>
<td>Value lower. Inverse correlation with T½ of glucose clearance</td>
<td>Value higher. Inverse correlation with T½ of glucose clearance</td>
</tr>
</tbody>
</table>
**TABLE 4 - SUMMARY OF RESULTS FROM EPINEPHRINE TOLERANCE TEST**

<table>
<thead>
<tr>
<th></th>
<th>MORGAN</th>
<th>THOROUGHBRED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose</strong></td>
<td>Rise gradual - very slow to reach maximal level; sustains maximal level 20mg% above initial level</td>
<td>Reaches maximal level rapidly, then falls rapidly to near initial level. Maximal level 35mg% above initial value.</td>
</tr>
<tr>
<td><strong>NEFA</strong></td>
<td>Dramatic rise - nearly four-fold increase above initial value</td>
<td>Slight rise</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>Slightly higher level throughout test; higher level at end.</td>
<td>Slightly lower level throughout test; stabilizes at initial level early.</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td>Higher initial values; maximal value 40mg% higher than initial value.</td>
<td>Lower initial values; maximal value 10mg% higher than initial value.</td>
</tr>
<tr>
<td><strong>SGOT</strong></td>
<td>Higher initial value</td>
<td>Lower initial value</td>
</tr>
</tbody>
</table>

No Difference in Trends
TABLE 5 - SUMMARY OF RESULTS FROM INSULIN TOLERANCE TEST

<table>
<thead>
<tr>
<th></th>
<th>MORGAN</th>
<th>THOROUGHBRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Decline in glucose, slightly slower.</td>
<td>Decline in glucose, slightly more rapid.</td>
</tr>
<tr>
<td></td>
<td>Did not exhibit insulin shock.</td>
<td>Exhibited insulin shock.</td>
</tr>
<tr>
<td></td>
<td>Glucose levels at end of test equal</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Moderate increase by end of test; double initial value.</td>
<td>Substantial increase at end of test; about seven-fold increase from initial value.</td>
</tr>
<tr>
<td>NEFA</td>
<td>Decrease quite rapid with a substantial decrease from initial level.</td>
<td>Decrease very gradual with a moderate decrease from initial level.</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Essentially no difference</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Essentially no difference</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 6 - SUMMARY OF RESULTS FROM GLUCAGON TOLERANCE TEST

<table>
<thead>
<tr>
<th></th>
<th>MORGAN</th>
<th>THOROUGHBRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Lower level reached</td>
<td>Two-fold higher level reached.</td>
</tr>
<tr>
<td>Insulin</td>
<td>Lower level reached, gradual decrease during last 75 minutes.</td>
<td>Higher level reached, high level maintained for 60 minutes, then slight decrease.</td>
</tr>
<tr>
<td>NEFA</td>
<td>Two-fold higher maximal level reached.</td>
<td>Lower maximal level reached.</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Essentially no difference</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Slight decrease early, then rise, fall, and continued rise - finally attained value 18mg% above initial value.</td>
<td>Rapid decrease early in the test; plateaued at level 35mg% below initial value.</td>
</tr>
</tbody>
</table>
Fig. 1 - Absolute serum glucose concentration after intravenous glucose infusion in Morgan (●) and Thoroughbred (■) horses. Each time point represents the mean ± SEM of two trials with four Morgan or three Thoroughbred horses.
Fig. 2 - Serum immunoreactive insulin after intravenous glucose infusion in Morgan (●) and Thoroughbred (■) horses. Each time point represents the mean ± SEM of two trials with four Morgan or three Thoroughbred horses.
IN S U L I N

TIME (MIN)

INSULIN µU/100
Fig. 3 - Serum nonesterified fatty acids (NEFA), cholesterol, and triglycerides following intravenous glucose infusion in Morgan (●) and Thoroughbred (■) horses. Each time point represents the mean ± SEM of two trials with four Morgan or three Thoroughbred horses.
Fig. 4 - Bromsulfphthalein clearance (BSP) in Morgan (●) and Thoroughbred (■) horses. Each point represents the least squares mean of two trials with four Morgan or three Thoroughbred horses.
Fig. 5 - Serum glucose in Morgan (●) and Thoroughbred (■) horses in response to epinephrine administration. Each time point represents the mean ± SEM of two trials with four Morgan or three Thoroughbred horses.
Fig. 6 – Serum triglycerides, cholesterol, and non-esterified fatty acids (NEFA) of Morgan (○) and Thoroughbred (■) horses in response to epinephrine administration. Each time point represents the mean ± SEM of two trials with four Morgan and three Thoroughbred horses.
Fig. 7 - Serum glutamic-oxalacetic transaminase (SGOT) in Morgan (●) and Thoroughbred (■) horses in response to epinephrine administration. Each time point represents the mean ± SEM of two trials with four Morgan or three Thoroughbred horses.
Fig. 8 - Serum immunoreactive insulin and glucose of Morgan (●) and Thoroughbred (■) horses in response to insulin administration. Each time point represents the mean ± SEM of two trials with four Morgan or three Thoroughbred horses.
Fig. 9 - Serum cholesterol, non-esterified fatty acids (NEFA), and triglycerides in Morgan (●) and Thoroughbred (■) horses in response to insulin administration. Each time point represents the mean ± SEM of two trials with four Morgan or three Thoroughbred horses.
Fig. 10 - Immunoreactive insulin and glucose in Morgan (●) and Thoroughbred (■) horses in response to intravenously administered glucagon. Each time point represents the mean ± SEM of two trials with four Morgan and three Thoroughbred horses.
Fig. 11 - Serum non-esterified fatty acids (NEFA), triglycerides, and cholesterol in Morgan (●) and Thoroughbred (■) horses in response to intravenously administered glucagon. Each time point represents the mean of two trials with either four Morgan or three Thoroughbred horses.
Fig. 12 - Serum glucose and immunoreactive insulin in Morgan (•) and Thoroughbred (■) horses in response to an intravenous infusion of sodium propionate. Each time point represents the mean ± SEM of two analyses of either four Morgan or three Thoroughbred horses.
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