**Insulin resistance (IR)** is a component of certain metabolic conditions and a risk factor for the development of several diseases of humans and domestic animals, including *Equus caballus* (horses and ponies).

In humans, those conditions and diseases include diabetes mellitus type 2, obesity, dyslipidemia, hypertension and stroke, surgery or injury, stress, sepsis, aging and longevity, coronary heart disease, polycystic ovary syndrome, cancer, inflammation, oxidative stress, and endotoxemia. Insulin resistance is a component of several of the same conditions and diseases in horses (Table 1).15-29,a

Insulin resistance is regarded generally as a decrease in tissue responses to insulin and more specifically as a decrease in insulin-mediated uptake of glucose by the liver, muscles, and adipose tissues. These responses to insulin are usually measured as insulin sensitivity, so IR may simply be regarded as the inverse of low sensitivity of insulin receptors on the cell surface. In addition to glucose transport into a cell, however, IR may involve ineffectiveness as a result of various disruptions of intracellular glucose metabolism.

Controversy about IR has been provoked by the hypothesis that genetic predispositions are exacerbated by diets high in carbohydrate content. Notable examples are the high-carbohydrate, low-fat diets recommended to prevent coronary heart disease in humans and grain-molasses concentrates for horses.30

Allusions to IR in the medical literature on horses have been based on various kinds of evidence, ranging from speculative analogies via common associations to various ambiguous indications on the basis of plasma concentrations of glucose and insulin and to specific quantitative measurements that separate function of pancreatic β-cells from peripheral actions of insulin. Our objective was to evaluate types of evidence that have been used to document IR in horses and ponies and thereby identify opportunities for improvement in the assessment of IR, especially as it relates to nutritional recommendations for the treatment and prevention of clinical conditions, the avoidance of nutritional risk factors, and the promotion of production and performance.

**Analogy with Conditions in Humans**

The expectation that IR contributes to certain diseases in horses has been based on analogy with disor-

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**Table 1—Metabolic conditions and disorders involving insulin resistance as a component or risk factor in horses.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Method*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withholding of food</td>
<td>OG, IG, IT</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>IT</td>
<td>16</td>
</tr>
<tr>
<td>Laminitis</td>
<td>IT</td>
<td>17</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>OG, IT</td>
<td>18</td>
</tr>
<tr>
<td>Hyperlipemia</td>
<td>FI, IT</td>
<td>19</td>
</tr>
<tr>
<td>Pituitary gland adenoma</td>
<td>FG, IG, FI</td>
<td>21</td>
</tr>
<tr>
<td>Obesity</td>
<td>OG</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>OG</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>FI</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>FI, GC</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>MM</td>
<td>26</td>
</tr>
<tr>
<td>Feed restriction or leanness</td>
<td>FI, GC</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>FI, GC</td>
<td>25</td>
</tr>
<tr>
<td>Osteochondritis dissecans</td>
<td>OG</td>
<td>27</td>
</tr>
<tr>
<td>Adaptation to sweet feed</td>
<td>MM</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>MM</td>
<td>a</td>
</tr>
<tr>
<td>Ovarian functions</td>
<td>GC</td>
<td>28</td>
</tr>
<tr>
<td>Endotoxemia or inflammation</td>
<td>GC</td>
<td>29</td>
</tr>
</tbody>
</table>

*Method used to assess insulin resistance.
OG = Oral glucose tolerance test. IG = Intravenous glucose tolerance test. IT = Insulin tolerance test. FG = Measurement of fasting glucose concentrations. GC = Glycemic clamp method. MM = Minimal model of glucose-insulin dynamics.
ders in humans, despite the lack of published, directly relevant data in horses.

**Pregnancy loss**—Gestational diabetes is a major risk factor for pregnancy loss in women. It involves IR and probably anti-insulin hormones (such as growth hormone or progesterone). By analogy, IR was proposed as a rule-out for *mare reproductive loss syndrome* (MRLS). However, we are not aware of any data pertaining to IR for pregnant mares with MRLS. The need to cast a wider net for possible causes of MRLS was prompted by anecdotal reports that mares do not voluntarily consume caterpillars.

**Metabolic syndrome**—It has been suggested that a metabolic syndrome exists that results in mature, obese horses developing mild or moderate laminitis. This clinical entity has been proposed on the basis of anecdotal claims without substantiating evidence of illustrative clinical cases or descriptive statistics of groups of affected horses. Numerous nutritional means of treating and preventing this laminitic syndrome have been recommended without appropriate evidence from clinical intervention trials. Instead, these recommendations rely on an alleged analogy of this form of laminitis with a metabolic syndrome of risk factors for diabetes mellitus type 2 in healthy people, as defined by the World Health Organization (WHO). The WHO definition requires finding at least 3 of 6 risk factors that fit into 2 requirements to establish a diagnosis. The first requirement is the identification of at least 1 of 2 risk factors (IR documented by use of the euglycemic clamp or impaired glucose tolerance or diabetes mellitus type 2). The second requirement is the identification of at least 2 of 4 other risk factors (abdominal obesity, dyslipidemia [high serum triglyceride and high-density lipoprotein cholesterol concentrations], microalbuminuria, or hypertension).

Relevant anecdotal claims for the metabolic syndrome in horses include consistent fasting hyperglycemia in combination with hypertriglyceridemia and obesity in most but not all clinical cases. These claims do not meet the WHO requirements; thus, the analogy remains unsubstantiated by the use of data from horses.

**Association with Other Risk Factors**

In public health, IR is often associated with other risk factors to form syndromes, such as syndrome X, metabolic syndrome X, and 2 metabolic syndromes defined by the WHO and the National Cholesterol Education Program. Separate findings of abdominal obesity, high plasma triglyceride concentrations, microalbuminemia, or hypertension are suggestive but not direct evidence of the coexistence of IR, which is the central feature of preclinical metabolic syndromes. Similarly, high plasma concentrations of anti-insulin hormones (such as cortisol or growth hormone) or changes in tissue activities of key enzymes (eg, 11β-hydroxysteroid dehydrogenase) may be used to qualify the nature of IR, but they do not by themselves establish the coexistence of IR when there is a lack of more direct evidence.

**Non-specific Indications of IR**

Observations on plasma concentrations of glucose and insulin may indicate the possibility of IR but are not conclusive. Their value as diagnostic or prognostic screening tests depends on statistical and pathophysiologic relationships. Involvement of IR in diseases and disorders of horses remains mainly dependent on non-specific indications.

**Basal hyperglycemia**—Measurement of fasting plasma glucose concentrations is the most common screening test used for diabetes mellitus. However, the finding of basal hyperglycemia does not discriminate between inadequate secretion of insulin by pancreatic β-cells and a decrease in insulin sensitivity of tissues. Basal hyperglycemia was considered to be an indication of IR in old horses and ponies with pituitary adenoma, albeit in conjunction with more convincing evidence of IR.

**Glucose tolerance**—Glucose tolerance is assessed by the plasma glucose response (the time-integral of the incremental area under the curve) to the oral or IV administration of a specified dose of glucose. Glucose intolerance may but does not necessarily coexist with IR, and the results are open to interpretation. Exaggerated glucose responses can be attributable to a primary inadequacy of β-cell secretion of insulin, impaired disposal of glucose (glucose- or insulin-mediated), or fat adaptation that spares glucose utilization without decreasing insulin sensitivity.

Compared with the IV glucose tolerance test, the oral glucose tolerance test is complicated by factors such as rate of consumption (or administration), gastric emptying, and intestinal absorption. The IV glucose tolerance test avoids gastrointestinal complications associated with the oral glucose tolerance test, but it cannot avoid the possibilities that the primary impairment involves β-cell secretion of insulin or glucose-mediated disposal of glucose.

Results of the IV glucose tolerance test have been used to indicate IR in ponies from which food has been withheld and horses and ponies with pituitary gland adenoma. In the latter, a more convincing indication of IR was hyperinsulinemia after withholding of food in affected horses and ponies. Despite its ambiguities, intolerance after oral administration of glucose has been considered evidence of IR in ponies from which food was withheld for 72 hours, mature obese ponies, and especially laminitic obese ponies.

A standard meal of grain was used as a glucose challenge in 11 healthy young horses and 4 horses with radiographic evidence of osteochondritis dissecans. The maximal increments of plasma glucose and insulin in affected horses were more than twice those of the healthy horses, but the glucose-to-insulin ratio was normal in affected osteochondritis dissecans-affected or healthy horses. The author of that study concluded that oral tests did not determine whether postprandial hyperglycemia and hyperinsulinemia were attributable to insulin resistance or to changes in rates of glucose digestion or absorption.

An increase in serum triglyceride concentrations is commonly associated with IR in humans and horses.
Saturated animal fats increase serum triglyceride content and IR, but polyunsaturated vegetable oils decrease serum triglyceride concentrations and IR. In a study in ponies, a ration high in polyunsaturated fat (13% soybean oil, by weight) decreased hepatic synthesis of fatty acids and plasma triglyceride concentration but increased muscle triglyceride concentration and activities of oxidative enzymes. In another study in ponies, plasma glucose and insulin responses to oral administration of glucose were higher in ponies fed a diet supplemented with soybean oil (approx 23% digestible energy) than in control ponies fed a nonsupplemented diet (approx 2% digestible energy). The authors of that study concluded that feeding fat caused glucose intolerance and IR. This conclusion is inconsistent with their observed decrease in serum triglyceride concentration. An alternative explanation for the glucose intolerance is a decrease in glucose clearance rate associated with glucose sparing by fats. It has been suggested that glucose sparing accounts for the lower glucose clearance rate of pregnant mares adapted to feeds high in fat and fiber that avoid the decrease in insulin sensitivity induced by feeds rich in starch and sugar (grain and molasses).

**Insulin tolerance**—The concept of insulin insensitivity was introduced in 1936. Two oral glucose tolerance tests are performed (with and without concurrent administration of insulin). The glucose response (area under the glycemic curve) is decreased in patients sensitive to insulin but not in insulin-insensitive patients.

Most investigators have simply used the decrease in plasma glucose concentration following IV administration of insulin to assess insulin tolerance. Fitting an exponential curve yields a rate constant. However, glycemic responses to exogenous insulin are also affected by responses of endogenous insulin and hormones that are counter-regulatory for hypoglycemia (a hazard for subjects is clinical hypoglycemia).

Plasma glucose concentration decreased 72% and 30% within 30 minutes after IV administration of insulin in fed and nonfed (food withheld for 72 hours) ponies, respectively. Similar results have been found in fed and nonfed donkeys. In addition, plasma cortisol concentration increased in 3 of 6 fed donkeys and 6 of 6 nonfed donkeys in that study. This anti-insulin hormone presumably contributed to the diminished response after withholding of food. It has been suggested that hypercortisolemia is a cause of hyperlipemia and laminitis.

Blood glucose concentration decreased 71% and 41% within 120 minutes after administration of insulin in control and laminitic ponies, respectively. Laminitis also exaggerates decreases in mean, systolic, and diastolic blood pressures following IV administration of insulin. Blood glucose concentration decreased 66% in clinically normal Standardbreds and ponies, 42% in obese ponies, and 30% in obese laminitic ponies after IV administration of insulin.

In 4 mares, each of which was >270 days of gestation, plasma glucose concentrations decreased by 57% during a 6-hour insulin infusion. This response compares with a decrease of 75% to 80% in nonpregnant mares. The authors of the study suggested that there is peripheral antagonism or tissue resistance to the action of insulin during late gestation in mares. This decrease in insulin sensitivity has been observed in several species, and it is usually considered to be a physiologic mechanism that partitions nutrients to the fetus.

**Basal hyperinsulinemia**—Once specific assays for measurement of plasma insulin concentrations became available, basal hyperinsulinemia was initially used as a certain sign of IR. Hyperinsulinemia persists when insulin insensitivity is compensated for by insulin secretion, but it declines when compensation becomes inadequate. Thus, a false-negative response may develop during impending diabetes mellitus type 2, a decompensation that is common in humans but rare in horses.

Enhanced β-cell sensitivity to glucose has been proposed as another interpretation for basal hyperinsulinemia in pregnant mares (<270 days of gestation). This extra secretion would likely compensate for concurrent IR. The subsequent abatement of basal hyperinsulinemia after 270 days of gestation in mares may indicate decompensation, a decrease in insulin secretion by β-cells, or alleviation of IR. However, the data are not conclusive.

The plasma insulin concentration during withholding of food was consistently 2 to 4 times higher during a 52-week period in mature obese mares, compared with the concentration in young lean mares. It was 3 to 4 times higher in obese mares (body condition score, 8 to 9), compared with the concentration in lean mares (body condition score, 4 to 5), and it was not changed by 7 days of light exercise (30 minutes of lunging while trotting) or another 9 days without exercise.

Hyperinsulinemia during withholding of food (values 6 times the values in control horses) was found in 10 horses with pituitary gland adenoma. The anecdotal claim of consistent hyperinsulinemia during withholding of food, when it is confirmed by the publication of relevant data, would be the strongest evidence of IR in a form of mild laminitis in mature, obese horses that has been termed the equine metabolic syndrome. However, it would not be conclusive evidence for IR. Moreover, the interpretation of IR in obese, inactive laminitic horses in the future will have to account for currently quantified IR in obese, inactive, healthy horses.

**Glucose-to-insulin and insulin-to-glucose ratios**—Simple screening tests or surrogate estimates of insulin sensitivity and secretion have been validated by comparison with quantitative methods in humans. The glucose-to-insulin ratio correlates positively with insulin sensitivity, and the insulin-to-glucose ratio correlates positively with insulin secretion; this difference has determined use of these ratios. In a test of 156 youths, fasting glucose-to-insulin ratio was correlated (r = 0.92) with insulin sensitivity measured by use of the euglycemic clamp, and fasting insulin-to-glucose ratio was correlated (r = 0.79 for the first phase and r = 0.86 for the second phase) with insulin secretion measured by use of the hyperglycemic clamp. A decrease in
plasma insulin-to-glucose ratio from 0 to 15 minutes after IV administration of glucose was considered to indicate a deficiency of insulin secretion in horses and ponies affected with pituitary adenoma.21

Surrogate tests—Other simple tests or surrogates for quantitative methods have been developed for screening IR in humans. Fasting plasma concentrations of glucose and insulin concentrations have been used in equations for screening tests identified by acronyms41,42; screening test 1 (ie, the HOMA-IS) = 22.5/(G × I) and screening test 2 (ie, the QUICKI) = 1/(log G + log I), where G is the glucose concentration and I is the insulin concentration. In the aforementioned study of 156 youths, insulin sensitivity was measured by use of the euglycemic-hyperglycemic clamp and it was correlated with insulin concentration (r = −0.92), glucose-to-insulin ratio (r = 0.92), results for test 1 (r = 0.91), and results for test 2 (r = 0.91).

Surrogate tests for horses have been identified in a preliminary analysis of data from 34 healthy horses evaluated by use of the minimal model of glucose-insulin dynamics.3 The 2 best predictive surrogate tests are the logarithm of the reciprocal of basal insulin concentration for insulin sensitivity and a function of basal glucose with the reciprocal of basal insulin concentration for acute insulin response. The combined use of both surrogate tests should eliminate ambiguity in interpretation of a decreasing insulinemia after withholding of food attributable to β-cell decompensation following a period of compensated hyperinsulinemia during the nonfed state.

Quantitative Methods

Three quantitative and specific methods for measuring insulin sensitivity have been developed on the basis of glucose and insulin assays for a series of blood samples collected under specified conditions. The insulin suppression test assumes that insulin sensitivity is negatively correlated with the steady-state plasma glucose concentration. The euglycemic-hyperinsulinemic clamp technique measures glucose concentration, which is assumed to be equal to glucose disposal rate, during a period of induced hyperinsulinemia, and it offers the simplest concept among these 3 quantitative methods. The minimal model of glucose-insulin dynamics calculates insulin sensitivity in the form of glucose clearance per unit of insulin from data generated by use of a frequent-sampling IV tolerance test. Because these methods are not measuring exactly the same variable and their primary units are not the same, comparisons are more empirical than physiologic. For example, correlation coefficients for glucose disposal rate and insulin sensitivity ranged from 0.41 to 0.92 (median, 0.70),14 but this correlation does not explain how the 2 variables are related mechanistically, nor does it cast light on their respective values.

Insulin suppression test—The insulin suppression test measures the ability of a fixed-rate infusion of insulin to dispose of a glucose load. Somatostatin or octreotide are used to suppress endogenous insulin concentrations. Infusion rates are controlled to yield fairly consistent or steady-state concentrations of plasma glucose and insulin during the last 60 minutes of the 150-minute infusions of glucose and insulin.43 The steady-state plasma glucose concentration is the mean for 6 samples obtained during the 60-minute period and reflects insulin-mediated glucose disposal, which is directly related to IR. Difficulties include adverse effects of the insulin suppressant drugs, inconsistency of the steady-state, and a steady-state plasma glucose concentration that tends to exceed the renal threshold.44 Overall technical difficulty of determining the steady-state plasma glucose concentration is between that for the euglycemic-hyperinsulinemic clamp and the minimal model of glucose-insulin dynamics.

Euglycemic-hyperinsulinemic clamp technique—The euglycemic-hyperinsulinemic clamp technique and minimal model of glucose-insulin dynamics were introduced at the same time,45,46 and the euglycemic-hyperinsulinemic clamp technique initially gained wider acceptance as a reference method for quantifying IR. The principle of the euglycemic-hyperinsulinemic clamp technique is to maintain constant plasma glucose concentrations for a controlled state of induced hyperinsulinemia that stimulates glucose disposal. Exogenous insulin is administered as a priming dose, which is followed by an infusion of insulin designed to achieve a desired hyperinsulinemic plateau.47 Plasma glucose concentration is maintained (ie, clamped) at a predetermined plateau, which is usually the typical fasting glucose concentration of 5 mmol/L, by means of repeated frequent collection and analysis of samples combined with a variable infusion rate (Figure 1). Endogenous glucose production is largely suppressed by the insulin infusion during a period of 60 minutes, and the glucose disposal rate is calculated as the mean glucose infusion rate during the last 60 minutes of a 120- or 180-minute test.

The euglycemic-hyperinsulinemic clamp technique requires special equipment and trained personnel. It is labor intensive and requires skill to obtain a stable glucose concentration. Technical difficulties include the need for 2 catheters (1 for infusion of insulin and the other for collection of samples). Arterial blood samples are preferred because insulin infusion increases the arteriovenous difference in glucose concentration, thereby introducing a time delay when venous blood samples are used.48 The glucose infusion pump must be capable of rapid and fine adjustment (0.05 mL/min).

It has been argued49 that the experimental constraints of the euglycemic-hyperinsulinemic clamp technique are nonphysiologic. The measured glucose disposal rate relates to an arbitrarily high plasma insulin concentration. Plasma glucose clearance relates to plasma concentrations of glucose and insulin in a complex fashion. Thus, comparisons of data obtained by the use of the euglycemic-hyperinsulinemic clamp technique for various conditions should be approached with caution, and correlations of clamp data with data or results obtained by use of other methods may be expected to be highly variable.50

Insulin infusion rate is based on body weight or preferably body surface area. Also, glucose disposal
rate may be indexed for specific purposes (per kilogram of body weight, per kilogram of fat-free mass, per kilojoule of metabolic rate, or per mean plasma insulin concentration during the last 40 minutes of a test). Moreover, glucose disposal rate can be divided by the plateau of plasma glucose concentration to yield the glucose clearance rate from plasma. This plateau is the plateau of plasma glucose concentration to yield the glucose disposal rate [M] reflects insulin-mediated glucose disposal during the euglycemic-hyperinsulinemic clamp procedure. Notice the substantial decrease in glucose disposal rate (decrease in insulin sensitivity) from approximately 2.2 mg/kg/min per mU/L when horses were fed forage to 1.5 mg/kg/min per mU/L after horses were fed the starch-sugar diet for 7 weeks. (To convert to mg/lb/min per mU/L, divide by 2.2)

e especially appropriate for applications of the euglycemic-hyperinsulinemic clamp technique in horses because 3 of 6 curves in 1 study had glucose infusion rates that were still increasing at the end of the 120-minute test. In another study, the mean (± SD) intra-subject variability for glucose disposal rate was 8.8 ± 1.5% for 6 horses.

In horses, use of the euglycemic-hyperinsulinemic clamp technique has revealed increases in glucose disposal rate of 93% and 119% in lean and obese mares, respectively, when horses were lightly exercised for 7 days; glucose disposal rate returned to preexercise values after another 9 days without exercise. Remarkably, this increase in insulin sensitivity with activity and decrease with inactivity were not evident in plasma insulin concentrations determined during the nonfed state, which further reduces confidence in plasma insulin concentration as an indicator of insulin sensitivity.

In another study involving use of the euglycemic-hyperinsulinemic clamp technique by the same laboratory group, glucose disposal rate was 43% lower in obese mature mares than in recently feed-restricted mature mares or young lean mares in November. A right shift in all of the increasing glucose infusion curves in February reflected a decrease in insulin sensitivity through the winter. At that time, glucose disposal rate for obese mature mares approached the rate for young mares, whereas glucose disposal rate in the chronically feed-restricted group (which now had body condition scores of 3) was 38% lower. If this singular result is repeatable, then both extremes of body condition will be associated with IR.

Administration of bacterial endotoxin has been used to induce a mild inflammatory condition in horses. Within 24 hours after administration, results for the euglycemic-hyperinsulinemic clamp technique revealed a remarkable decrease in glucose disposal rate. This IR is purportedly mediated by the release of cytokines, such as tumor necrosis factor-α, from adipose tissue (as has been documented in other species), and it may be involved in some forms of laminitis.

The euglycemic-hyperinsulinemic clamp technique has been used to document mean glucose disposal rates of 96, 19, 7, and 1 μmol/kg/min in pigs, sheep, ponies, and camels, respectively. It has also been used to determine the reference ranges for glucose disposal rate, but this involved only 5 Dutch Warmbloods and 4 ponies. These numbers of animals are insufficient to test for a normal distribution in the populations from which these small sample sizes were selected, so these should be regarded as tentative reference ranges. Nevertheless, the mean for the ponies was 7 μmol/kg/min (95% confidence interval [CI] 3 to 11 μmol/kg/min). The corresponding value for the Dutch Warmbloods of 14 μmol/kg/min (95% CI 3 to 25 μmol/kg/min) was significantly higher, which reinforces the suggestion, determined on the basis of non-specific indications, that ponies are susceptible to IR and hence hyperlipemia and laminitis.

In another study of various breeds of horses, glucose disposal rate was 7.2 μmol/kg/min (95% CI, 3.9 to 10.5 μmol/kg/min) in lean mares (body condition...
scores of approx 4.5) and 4.5 µmol/kg/min (95% CI, 0 to 14.5 µmol/kg/min) in obese mares (body condition scores of approx 8.5); these data have been converted from the original values of glucose disposal rate expressed as milligrams per kilogram of body weight per minute. The discrepancies between studies conducted in the Netherlands and Kentucky confirm the need to standardize euglycemic-hyperinsulinemic clamp methods in horses and determine reference ranges with greater numbers of horses.

**Minimal model of glucose-insulin dynamics—**
The minimal model of glucose-insulin dynamics partitions glucose disposal into 2 parts (ie, glucose- and insulin-mediated disposal). It is a nonlinear regulatory model that is fitted to data obtained by use of a frequent-sampling IV glucose tolerance test. This test is technically simpler than the euglycemic-hyperinsulinemic clamp technique. It requires placement of a catheter in a jugular vein and collection of a series of blood samples (Figure 2).

The minimal model of glucose-insulin dynamics describes the glucose-time curve as 2 differential equations. One represents glucose-mediated glucose disposal by use of a single-rate constant, whereas the other represents insulin-mediated glucose disposal by use of another rate constant with insulin sensitivity included on the right side of the equation. The nonlinear mathematics of any regulatory model are accessible only to experts, and most users of the minimal model of glucose-insulin dynamics must trust the underlying mathematical procedures. Use of a highly evolved minimal model of glucose-insulin dynamics has been facilitated by the availability of that model on a compact disc.

The frequent-sampling IV glucose tolerance test usually requires 180 to 360 minutes. The response of endogenous insulin to an exogenous glucose bolus is sometimes inadequate. Tolbutamide has been used to stimulate the insulin response. Another approach is to administer a dose of insulin IV 20 minutes after administration of the glucose bolus.

The minimal model of glucose-insulin dynamics generates calculated variables that call for physiologic interpretations. Glucose effectiveness is the preferred term for glucose-mediated disposal by use of a single-rate constant, which is a measure of the effect of glucose to enhance its own disappearance at basal insulin concentrations. Insulin sensitivity represents the ability of insulin to enhance total net glucose disappearance from the extracellular fluid via decreases in endogenous glucose production and augmentation of glucose use.

Theoretical criticisms of the minimal model of glucose-insulin dynamics mainly concern glucose-mediated disposal by use of a single-rate constant, which may not be entirely devoid of influence from insulin. A single-rate constant is sometimes inadequate to describe the glucose component of the model. Difficulties with insulin sensitivity are mainly related to the dose of insulin, which can be adjusted. For example, the insulin dose for sensitive weanlings was one twentieth of the dose for less sensitive mature geldings.

The minimal model of glucose-insulin dynamics has been successfully applied to horses. It has been used to document IR in mature obese horses. It can differentiate between compensated and decompensated IR and has revealed a compensated decrease of insulin sensitivity in weanlings chronically adapted to a sweet feed that has a high glycemic index, which can be avoided by feeding a fat-and-fiber feed with a moderate or low glycemic index.

**Conclusions and Recommendations**

Our main conclusions are that the application of specific quantitative methods of assessing IR has lagged in studies of horses and too much reliance has been placed on nonspecific indications. Quantitative methods have documented IR in all of the aforementioned conditions in humans but less than half of the aforementioned conditions in horses (Table 1). The technical difficulty and expense of the quantitative methods limits their use in population studies or monitoring of clinical cases. Thus, a need exists for the development of statistically validated surrogate tests for insulin sensitivity in equids.

Evidence-based medicine emphasizes controlled intervention studies. These clinical studies are essen-
tial to support claims for the nutritional treatment or prevention of disease. As a preliminary requirement to controlled intervention studies on IR syndromes, which require much effort and expense, we suggest that there is a need to establish evidence for IR by the use of quantitative methods. However, during the course of such studies, surrogate tests may enable the use of larger numbers of subjects and observations.

Evidence-based nutrition has 2 other aspects. One is the avoidance of risk factors by healthy subjects. This practice was developed in the 1988 Surgeon Generals Report on Nutrition and Health.5 Two types of evidence are required (population studies to establish association and mechanistic studies to explain causation). The recommendations were for humans to avoid excessive intake of saturated fats, salt, and sugar. An example of avoidance in horses would be dietetic measures to replace grain and molasses with fats and fibers in the diets of healthy horses.25 Replacement is a standard procedure in dietetics, and an adequate database for feed energy exchanges is available for most nutritional purposes in healthy horses.52,53 In establishing recommendations of avoidance, surrogate tests would enable the use of more subjects in population studies but quantitative methods of assessing IR would be more definitive in mechanistic experiments.

A third field of scientifically based nutrition is the promotion of buoyant health, production, and performance. Supporting studies are performed on healthy subjects and usually involve nutritional constraints and production or performance outcomes. Insulin sensitivity and compensation of the subjects could be characterized by quantitative methods or surrogate tests, depending partly on the number of subjects and observations in the experimental design. Insulin sensitivity has been associated with superior fitness in human athletes,34 and metabolic and behavioral advantages for exercise have been documented in horses adapted to fat-and-fiber diets,26 which reportedly can avoid IR associated with adaptation to sweet feeds.29,30

Studies of IR can be used to guide 3 types of nutritional recommendations: prevention of disease, avoidance of nutritional risk factors, and promotion of performance. Each type of recommendation requires a different kind of supporting evidence. In contrast, establishing any involvement of IR requires the same kinds of evidence (ie, validated surrogate tests or more compelling specific quantitative measurements).

References

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