

# Evaluation of a continuous glucose monitoring system for use in dogs, cats, and horses

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**Objective**—To evaluate a continuous glucose monitoring system (CGMS) for use in dogs, cats, and horses.

**Design**—Prospective clinical study.

**Animals**—7 horses, 3 cats, and 4 dogs that were clinically normal and 1 horse, 2 cats, and 3 dogs with diabetes mellitus.

**Procedure**—Interstitial glucose concentrations were monitored and recorded every 5 minutes by use of a CGMS. Interstitial glucose concentrations were compared with whole blood glucose concentrations as determined by a point-of-care glucose meter. Interstitial glucose concentrations were also monitored in 2 clinically normal horses after oral and IV administration of glucose.

**Results**—There was a positive correlation between interstitial and whole blood glucose concentrations for clinically normal dogs, cats, and horses and those with diabetes mellitus. Events such as feeding, glucose or insulin administration, restraint, and transport to the clinic were recorded by the owner or clinician and could be identified on the graph and associated with time of occurrence.

**Conclusions and Clinical Relevance**—Our data indicate that use of CGMS is valid for dogs, cats, and horses. This system alleviated the need for multiple blood samples and the stress associated with obtaining those samples. Because hospitalization was not required, information obtained from the CGMS provided a more accurate assessment of the animal's glucose concentrations for an extended period, compared with measurement of blood glucose concentrations. Use of the CGMS will promote the diagnostic and research potential of serial glucose monitoring. (*J Am Vet Med Assoc* 2003;223:987–992)

Serial monitoring of blood glucose concentrations is a common diagnostic procedure used in animals. In dogs and cats with diabetes mellitus, serial blood glucose concentration curves are used to determine proper insulin type, dosage, and frequency of administration necessary to maintain appropriate blood glucose concentrations.<sup>1,2</sup> Glucose tolerance testing requires administration of an oral or IV bolus of glucose and subsequent serial monitoring of blood glucose concentrations and may be used as a research tool and to diagnose small intestinal malabsorptive diseases, detect

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hyperinsulinism, and differentiate type I from type II diabetes mellitus.<sup>3,6</sup> Although these tests are useful, there are several potentially confounding effects associated with the procedures that must be considered when data are being reviewed.

Monitoring blood glucose concentrations requires obtaining multiple blood samples during a defined period of time. This is usually done by repeated venipuncture or by use of an indwelling venous catheter. These procedures require handling or restraint of the animal, which may result in stress-induced hyperglycemia, thereby altering the blood glucose concentration. It has been found that a sudden stressful incident will result in transient hyperglycemia in cats.<sup>7</sup> Besides the stress of restraint and catheter placement, these procedures usually require hospitalization of the animal, which amplifies stress and removes the animal from its normal environment.<sup>8</sup> New techniques have been introduced in which small amounts of capillary blood are rapidly analyzed for glucose concentration and the blood samples can be obtained within the animal's natural environment.<sup>9,10</sup> However, these techniques require animal handling and restraint and are performed primarily by owners with limited blood sampling skills.

Various assays provide the clinician with an assessment of the glycemic state of an animal.<sup>11,12</sup> In a persistent hyperglycemic state, serum fructosamine and glycosylated hemoglobin increase, and measurement of these substances may provide the clinician with a decision-making tool regarding therapy.<sup>13-16</sup> Although these are excellent assays to determine the glycemic state of an animal, they have not been validated for use in all species, and false-positive and false-negative results have been reported.<sup>14,17</sup> Also, these assays do not provide information regarding glucose nadirs or change in glucose concentration in response to insulin administration. An alternative to measuring blood glucose concentrations is measurement of glucose concentrations in the interstitial space within the subcutaneous tissue. Accurate measurement of glucose concentrations from the interstitial space is more advantageous than measurement of blood glucose concentrations, because it alleviates the need for repeated venipuncture or placement of an indwelling catheter within a vessel to obtain multiple blood samples. Measurements of glucose concentrations in the interstitial space are comparable to measurements of whole blood glucose concentrations in humans and dogs.<sup>18,19</sup> An ideal system for serially measuring interstitial glucose concentrations in animals should be easy to apply, correlate well with blood glucose concentrations, and alleviate stress associated with serial blood sampling and hospitalization.

The purpose of the study reported here was to evaluate a **continuous glucose monitoring system (CGMS)** for use in dogs, cats, and horses. This system has been validated and approved for use in humans.<sup>20,21</sup> The CGMS uses a novel sensor and calibration method for measuring glucose concentrations in the interstitial space within the subcutaneous tissue. Interstitial glucose passes through a semipermeable membrane and reacts with the enzyme glucose oxidase, which converts glucose into gluconic acid and hydrogen peroxide. This reaction generates an electric signal proportional to the glucose concentration that is recorded by the system and converted into an interstitial glucose concentration in milligrams per deciliter. This system does not require placement of a catheter within a blood vessel and can monitor interstitial glucose concentrations for an extended period of time.

### Materials and Methods

**Animals**—Seven horses, 3 cats, and 4 dogs that were clinically normal and 1 horse, 2 cats, and 3 dogs with diabetes mellitus were included in the study. Owners of each animal provided informed consent for use of the CGMS.

**Placement of the CGMS**—The CGMS<sup>a</sup> consists of a recording device with an attached cord and a flexible sensor (Fig 1). The sensor is a small, flexible electrode that measures glucose concentrations in the interstitial fluid after insertion into the subcutaneous tissue. Glucose values are stored in the recording device, which can record up to 288 readings (1 reading every 5 minutes) during a 24-hour period. For sensor placement, a small patch of hair was shaved on the lateral thoracic region (cats and dogs) or over the masseter muscle (horses). The skin was cleaned of excess hair and wiped with an alcohol swab. The sensor and attached stylet were inserted into the skin, and the stylet was removed once placement of the sensor was completed. The sensor was secured on the skin by use of a cyanoacrylate adhesive. Once the sensor was securely placed, the cord from the recording device was attached to the sensor, and the end of the cord was also secured to the skin with adhesive. The recording device was attached to the animal by taping the device to a halter or harness (horses and dogs) or held in place with bandage (cats). The recording device measures 9.0 × 6.5 × 2.0 cm and weighs approximately 170 g. After the system was attached, the manufacturer's procedures were followed for initialization and calibration. This involved a 1-hour initialization period immediately following attachment of the device and 3 separate whole blood glucose determinations



Figure 1—Continuous glucose monitoring system (CGMS) with sensor.

during a 24-hour monitoring period. Typically, following attachment and acquisition of 1 or 2 whole blood glucose determinations for calibration of the instrument, dogs and cats were returned to their home environments overnight. Dogs and cats returned to the clinic the following day for the remainder of whole blood glucose determinations necessary to properly calibrate the instrument and remained in the clinic until the 24-hour monitoring period was complete. Following the 24-hour period of monitoring, the instrument was removed from the animal, and the site of sensor attachment was examined for any signs of redness or irritation. Horses were kept in the clinic for the entire period of monitoring for observation. Owners of dogs and cats were instructed to periodically check for signs of discomfort or irritation at the site of sensor attachment or for abnormal behavior (ie, rolling, rubbing, or biting at the area of sensor attachment). Horses were monitored periodically for the same signs by the clinical staff and students. Time of events, such as feeding, insulin administration, and transport to the clinic, were recorded by the owners, clinicians, or attending staff monitoring the animals.

**Calibration of the CGMS**—After a 60-minute initialization period, a minimum of 3 separate whole blood glucose determinations was required for calibration of the system during a 24-hour monitoring period. According to manufacturer's instructions, it was not necessary to evenly space the blood samplings used for calibration. The only requirement was that at least 3 blood glucose determinations, and more if desired, were performed within the 24-hour monitoring period. For this study, blood samples for calibration were obtained at various times throughout the 24-hour period without a regimented time between samplings. When convenient, more than the required 3 blood samples were obtained from individual animals for calibration of the system. Approximately 0.2 to 2.0 mL of whole blood was obtained from the jugular, cephalic, or medial tarsal veins of each animal and placed in a heparinized tube. The glucose concentration in whole blood was immediately determined by use of a portable chemistry analyzer.<sup>b</sup> When the glucose concentration had been determined, the information was promptly entered into the CGMS recording device.

**Correlation of glucose results**—All whole blood glucose concentrations obtained from dogs (n = 23 samples), cats (16), and horses (36) in this study and used for CGMS calibration were compared with interstitial glucose concentrations recorded by the CGMS for each species. Each whole blood glucose reading entered into the CGMS recording device was paired with the corresponding sensor value recorded by the system at that time point. The calibration system used by the CGMS permits for this type of calibration and has been determined to be a valid method for calibration of blood glucose and interstitial glucose concentrations.<sup>18,20,21</sup> Studies have found that blood glucose concentrations obtained by the portable chemistry analyzer correlate well with serum glucose concentrations determined by use of a standard, dry, chemistry, automated analyzer<sup>c</sup> for dogs,<sup>22</sup> cats,<sup>d</sup> and horses.<sup>e</sup> Therefore, measurement of blood glucose concentrations by use of the portable chemistry analyzer was believed to be a valid method for determining whole blood glucose concentrations for this study.

**Oral and IV glucose tolerance tests**—Oral and IV glucose tolerance tests (OGTT and IVGTT, respectively) were performed on 2 clinically normal horses. For the OGTT, food was withheld overnight before attachment of the CGMS. After initialization and calibration, 1 horse was given an oral bolus of glucose (1.0 g of glucose/kg [0.45 g/lb] as a 20% aqueous solution) through a nasogastric tube. The CGMS recorded interstitial glucose concentrations for > 12 hours following the glucose bolus. The IVGTT was performed similarly on another

er horse, except that a bolus of glucose (0.5 g of glucose/kg [0.23 g/lb] as a 50% aqueous solution) was administered IV.<sup>25</sup>

**Statistical analyses**—Whole blood glucose concentrations were compared with interstitial glucose concentrations obtained from the CGMS for each species by use of simple linear regression. For each model, the regression coefficient or slope and the correlation coefficient ( $r$ ) were reported.

## Results

Placement of the CGMS sensor within the subcutaneous tissue caused minimal discomfort and did not appear to result in irritation or inflammation at the sensor attachment site in all dogs, cats, and horses as reported by the owners or clinical staff. Owners and clinical staff reported no abnormal behaviors, such as rolling, biting at or rubbing the site of sensor placement, or chewing. Removal of the sensor from the skin resulted in mild discomfort, and examination of the site revealed slight redness with no swelling.

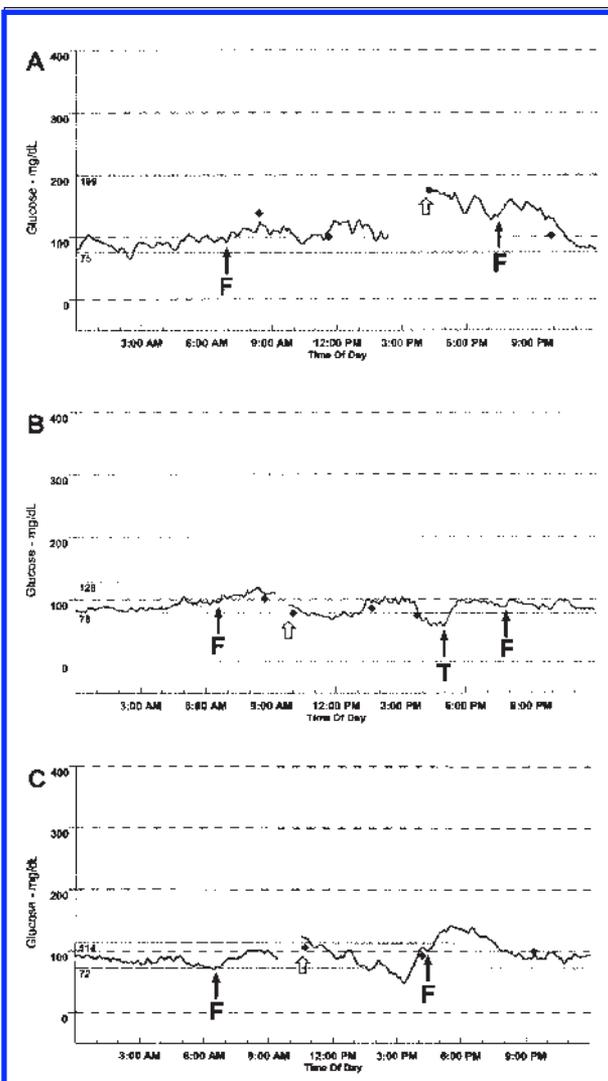


Figure 2—Serial interstitial glucose concentrations recorded by a CGMS (open arrow indicates beginning of glucose monitoring) from a clinically normal cat (A), dog (B), and horse (C). F = Feeding. T = Transport to the clinic. ♦ = Blood withdrawn for blood glucose determination. Values inside the graphs are the reference ranges for serum glucose concentrations for each species.

A typical graphic representation of data obtained from the CGMS for clinically normal dogs, cats, and horses is depicted (Fig 2). Events such as feeding, transport to the clinic, or blood sampling are recorded on several of the graphs.

Interstitial glucose concentrations from the horse with diabetes mellitus measured by the CGMS for approximately 12 hours revealed values markedly higher than the laboratory's established reference range for serum glucose (72 to 114 mg/dL) at all time points (Fig 3). Times of blood sampling and feeding in this horse were recorded.

Interstitial glucose concentrations from 2 cats and 3 dogs with diabetes mellitus were measured for approximately 24 hours by the CGMS. Times of insulin administration, feeding, travel to the clinic, and blood sampling were recorded by the owner or attending clinician. Glucose concentrations determined by the

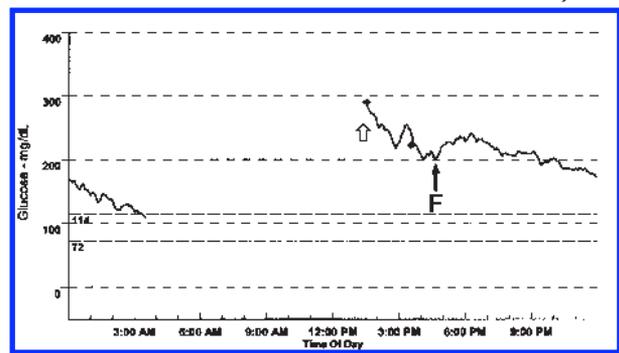


Figure 3—Serial interstitial glucose concentrations recorded by a CGMS for approximately 15 hours in a horse with diabetes mellitus. See Figure 2 for key.

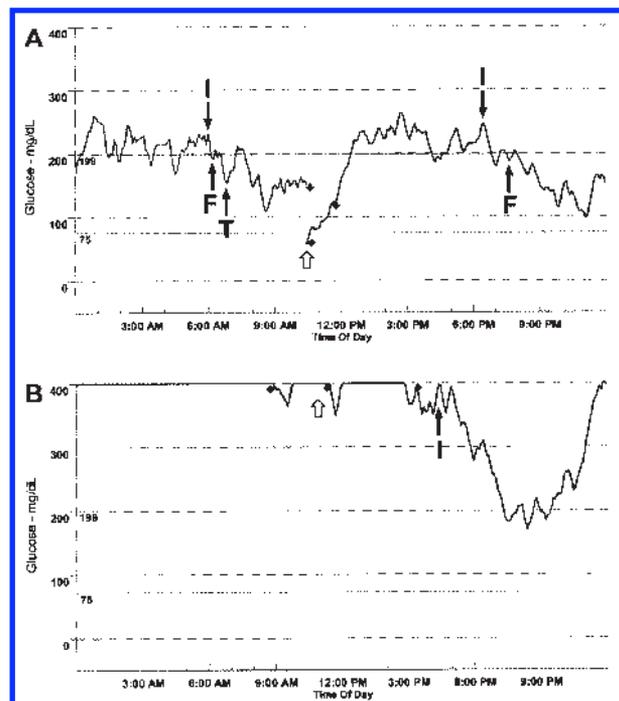


Figure 4—Serial interstitial glucose concentrations recorded by a CGMS during a 24-hour period from 2 cats with well controlled (A) and uncontrolled (B) diabetes mellitus. I = Insulin administration. See Figure 2 for remainder of key.

CGMS suggested that the diabetes mellitus in 1 cat was well controlled by the administered insulin, and this finding was supported by a history and lack of clinical signs of diabetes mellitus (Fig 4). This cat was hypoglycemic at the beginning of the monitoring period on the basis of values obtained from the CGMS and whole blood glucose concentration. The owner reported that the cat had not eaten after insulin administration just before transport to the clinic. Results from the morning of the second day of monitoring were more representative of the cat's normal routine.

Interstitial glucose concentrations measured from the CGMS revealed that the diabetes mellitus in 1 cat and 1 dog was uncontrolled by their present insulin regimen (Fig 5). The cat had received a single dose of insulin in the afternoon. Interstitial glucose concentrations measured from the CGMS revealed that the dia-

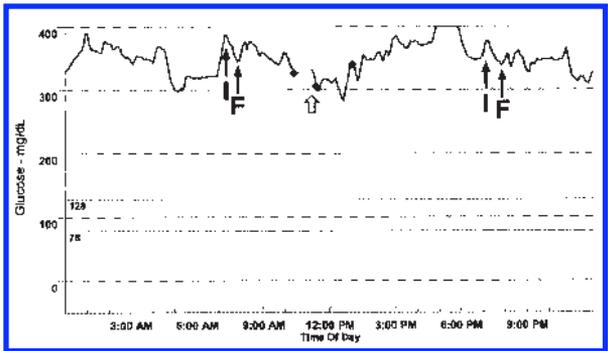


Figure 5—Serial interstitial glucose concentrations recorded by a CGMS during a 24-hour period from a dog with uncontrolled diabetes mellitus. I = Insulin administration. See Figure 2 for remainder of key.

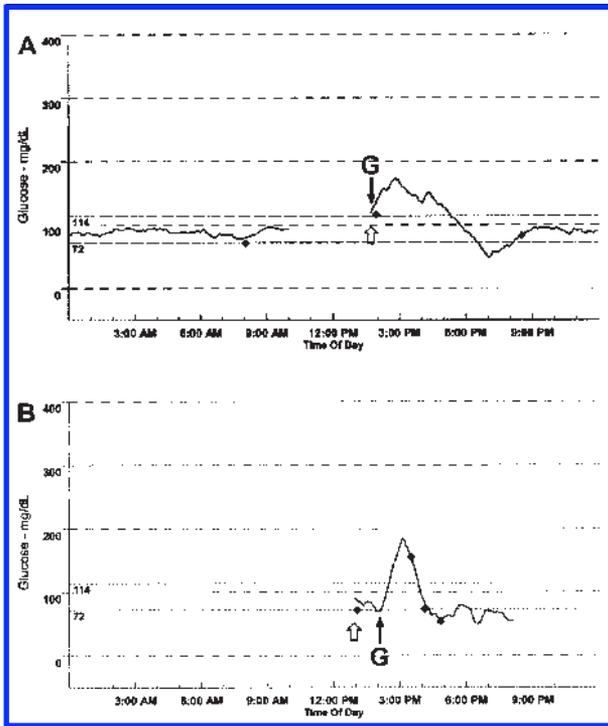


Figure 6—Serial interstitial glucose concentrations recorded by a CGMS from 2 horses after oral (A) and IV (B) glucose tolerance tests. G = Glucose administration. See Figure 2 for remainder of key.

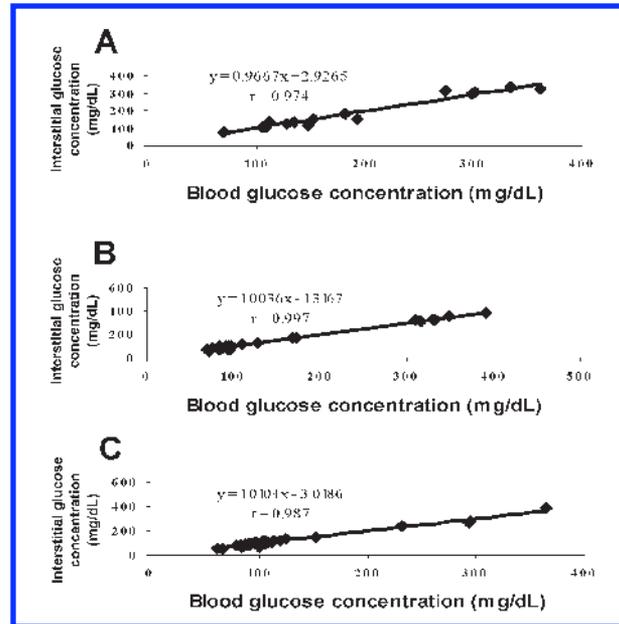


Figure 7—Correlation between whole blood and interstitial glucose concentrations from 5 cats (A), 7 dogs (B), and 8 horses (C).

betes mellitus in the other 2 dogs was also uncontrolled.

Shortly after administration of an oral or IV bolus of glucose for the OGTT and IVGTT, there was an increase in the interstitial glucose concentration in both horses. Glucose concentration peaked approximately 2 hours after administration and rapidly returned to baseline values (Fig 6).

There was a positive correlation between interstitial and whole blood glucose concentrations in all dogs ( $r = 0.997$ ), cats ( $r = 0.974$ ), and horses ( $r = 0.987$ ; Fig 7) used in the study.

## Discussion

To the author's knowledge, this is the first report of the use of a CGMS in dogs, cats, and horses. Results of this study indicate that interstitial glucose concentrations measured by CGMS correlated well with whole blood glucose concentrations, were sensitive to abrupt changes in glucose concentration, and provided a detailed representation of an animal's glucose concentrations for an extended time period. The CGMS was found to be valid for use in 3 veterinary species and has the versatility to be applied to many diagnostic and research situations.

The sensor was placed within the subcutaneous tissue on the lateral thoracic region of dogs and cats or over the masseter muscle in horses. These sites were selected for their accessibility and because they were considered unlikely to be disturbed by the animal. However, other sites may provide comparable data and should be investigated.

The relationship between blood glucose and the glucose concentration within the interstitial space has been studied in multiple species.<sup>18,19,24,25</sup> The dynamic relationship between blood and interstitial glucose concentrations has been examined by use of several models and can be described mathematically.<sup>19,26</sup>

Basically, if the capillary is not a barrier to glucose diffusion, then changes in interstitial glucose concentrations will be related to changes in blood glucose concentrations and by the rate of glucose clearance from the interstitial fluid surrounding the subcutaneous sensor. In dogs, it was found that there was a 5- to 12-minute delay between changes in blood and interstitial glucose concentrations.<sup>19</sup> In humans, this delay has been determined to be < 5 minutes.<sup>1</sup> To compensate for this delay, the CGMS is equipped with digital filtering techniques that can correctly assess the interstitial glucose concentration and how it relates to blood glucose. However, it is believed that correction is not necessary for slower glucose dynamic changes observed in day-to-day human use.<sup>18,19</sup> Also, it has been found that changes in interstitial glucose concentrations are not affected by physiologic changes in insulin concentration.<sup>19</sup> This information becomes important for the assessment of glycemic control in animals with diabetes mellitus. In this study, we found that rapid changes in blood and interstitial glucose concentrations occur in response to insulin administration, as well as to administration of an oral or IV bolus of glucose. Because of this and findings from other published studies,<sup>18-20</sup> we are confident that the CGMS can accurately assess glucose status in horses, dogs, and cats.

For proper calibration of the CGMS, at least 3 blood samples must be analyzed for glucose concentration over a 24-hour period. Most routine assays and measuring devices use a 1-point calibration for calculation of an accurate value. With 1-point calibration, a calibration constant is determined for the calibration point, and subsequent reported values are calculated by use of that constant until the next calibration is entered. The CGMS estimates glucose concentrations in the interstitial fluid compartment of the skin rather than in the blood, and the CGMS sensor converts this interstitial glucose into gluconic acid and hydrogen peroxide through a reaction that generates an electric current, which is applied to an algorithm that is used to convert the electric current (nanoamperes) into a glucose concentration. The sensor's electric signal is calibrated to blood glucose values by use of linear regression with a fixed intercept. This calibration process uses all of the capillary blood glucose readings entered into the instrument within a 24-hour moving window to generate an accurate calibration factor, as opposed to a single point calibration, which can result in errors because of inherent meter inaccuracy. Independent meter readings not used for calibration have been evaluated to validate this calibration approach.<sup>18,20</sup>

Assessing an animal's blood glucose profile through a standard glucose concentration curve may result in complications that interfere with an accurate interpretation. Stress produced by transport, restraint, struggling, or blood sampling can result in hyperglycemia in cats.<sup>7,8</sup> For standard blood glucose concentration curves, restraint of the animal is necessary for multiple blood sampling. It is usually required that the animal be hospitalized for these procedures, which further contributes to stress. Therefore, procedures associated with performance of a blood glucose concentra-

tion curve can affect the blood glucose concentration and result in misleading values and inaccurate conclusions. Techniques using a small amount of capillary blood from the ear and a handheld glucose meter can be performed by the owner with the animal in its natural environment and reduce the need for hospitalization.<sup>9,10</sup> These techniques are useful for reducing stress; however, they do not provide a complete blood glucose profile of the animal. Use of a valid, in-home technique for measurement of blood glucose concentrations in conjunction with the CGMS may reduce stress associated with standard techniques and provide a more accurate assessment of the animal's glucose profile.

Serial glucose monitoring of animals with diabetes mellitus is the most accepted monitoring procedure to determine the adequacy of insulin administration.<sup>1,2</sup> Goals of insulin administration in diabetic patients include avoidance of hypoglycemia and maintenance of blood serum glucose concentrations within a mild to moderately hyperglycemic range.<sup>1,2</sup> Data from the CGMS obtained from 2 cats and 3 dogs with diabetes mellitus in this study found that the diabetes mellitus in 1 cat was well controlled, whereas diabetes in another cat and the dogs was unregulated according to the target principles of insulin administration. A standard glucose concentration curve was not performed on these animals for comparison. However, it is likely that a standard glucose concentration curve performed on these animals would have resulted in the same diagnostic conclusions.

The OGTT and IVGTT can be used for diagnosis of small intestinal absorptive diseases and diabetes mellitus, respectively.<sup>3,5,6,27</sup> In the same manner that glucose concentration curves are used to monitor a response to insulin administration, glucose tolerance tests require serial monitoring of blood glucose concentrations after administration of a bolus of glucose. The same complications associated with performance of a glucose concentration curve may interfere with interpretation of the glucose tolerance test results. In our study, we examined data generated by the CGMS in horses in response to an oral or IV bolus of glucose. As expected, the interstitial glucose concentrations increased after a certain period of time and then rapidly returned to baseline values. Blood glucose concentrations were not obtained according to a standard glucose tolerance test for comparison with interstitial glucose concentrations. However, a wide range of blood glucose concentrations was obtained during these studies, and those values were positively correlated with the interstitial glucose values as measured by the CGMS. Therefore, we are confident that the CGMS can be used effectively for glucose tolerance tests and will provide accurate and comprehensive data.

Assays that measure glycated proteins, such as glycosylated hemoglobin or fructosamine, have been useful as an assessment of glycemic control in animals.<sup>15,16,28</sup> Assays measuring fructosamine and glycosylated hemoglobin have been found to be valuable in distinguishing between stress-induced hyperglycemia and glucose control in certain diabetic animals.<sup>14,15</sup> Despite a correlation between glycated proteins and glucose homeostasis, these assays may give false-posi-

tive results.<sup>14,17</sup> Therefore, fructosamine and glycosylated hemoglobin assays should not be relied on as the sole indicator of response to insulin administration in animals with diabetes mellitus. We suggest that fructosamine and glycosylated hemoglobin assays be used in conjunction with the CGMS to correctly evaluate the response to insulin treatment in animals with diabetes mellitus.

Use of the CGMS for veterinary species does have limitations. If the sensor detaches from the skin, the system can no longer record glucose concentrations and provides incomplete data. The system has a working glucose range of 40 to 400 mg/dL. Interstitial glucose values > 400 mg/dL are not recorded at their true concentration. Therefore, data recorded by the CGMS may not accurately reflect the glucose profile in certain animals. However, persistent glucose concentrations > 400 mg/dL likely represent insufficient control of diabetes mellitus.

<sup>a</sup>Medtronic Minimed, Los Angeles, Calif.

<sup>b</sup>I-Stat portable chemistry analyzer, Heska Corp, Fort Collins, Colo.

<sup>c</sup>Vitros 500, Ortho-Clinical Diagnostics, Rochester, NY.

<sup>d</sup>Cohn LA, McCaw DL, Tate D. Comparison of glucose measuring devices in cats (abstr), in *Proceedings. Annu Forum Am Coll Vet Intern Med* 2001;309.

<sup>e</sup>Curtis K. Clinical Pathology Laboratory, College of Veterinary Medicine, University of Missouri, Columbia, Mo: Personal communication, 2002.

<sup>f</sup>Steil GM, Bernaba B, Saad M, et al. Accurate determination of plasma glucose during hyper- and hypoglycemia with a subcutaneous glucose sensor (abstr). *Diabetes* 2000;49:A510.

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