The Evolution of Insulin Therapy

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ABSTRACT: Commercial insulin has evolved over the years as a result of efforts to find the most effective product with the fewest number of side effects for humans with diabetes mellitus. Veterinarians have had to base their insulin choices on the availability of human insulin products. The original insulins were animal based, but technologic advances, along with the goal of avoiding antiinsulin antibody production in humans, led to the development of human recombinant insulins. The recent advent of insulin analogues has shifted human insulin market demands, and veterinarians have been forced to follow suit. This article is a guide to the insulin products available for veterinary use.

Diabetes mellitus (DM) is one of the most common endocrinopathies diagnosed in dogs and cats. It results from absolute or relative insulin deficiency secondary to impaired insulin secretion by the beta cells. The three main goals of treatment of DM are:

- To reduce the clinical signs (polyuria, polydipsia, polyphagia) associated with the disorder
- To achieve glycemic control without inducing hypoglycemia
- To reduce the development of long-term complications (cataracts and diabetic neuropathies)

Insulin therapy is the mainstay of treatment of DM in dogs and cats because it offers the most reliable means of achieving glycemic control. Insulin lowers blood glucose levels by stimulating peripheral glucose uptake and inhibiting hepatic glucose production. Insulin also inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis. Insulin inhibits the progression of beta cell destruction by reducing glucose toxicity to the cells. In cats, insulin appears to prevent formation of amyloid deposits derived from islet amyloid polypeptide. Therefore, it is clear that insulin is the most effective therapy in managing canine and feline DM.

HISTORY OF INSULIN PREPARATIONS

Insulin was introduced in the 1920s and was originally manufactured from bovine and porcine pancreata. In January 1922, Fred Banting and Charles Best administered 15 ml of a slightly acidic alcohol solution described as “a thick, brown muck” to a diabetic patient. The solution was exogenous insulin, and the patient’s blood glucose level dropped from 440 to 320 mg/dl. Later, a sterile abscess developed at the
injection site. By 1923, the extraction process had been improved, and insulin was commercially available in North America. Banting and associates at the University of Toronto were awarded the Nobel Prize in Medicine for their achievement, and animal-based insulins were the mainstay of insulin therapy for the next 60 years.4

Animal-based insulins are useful in treating DM in humans because all mammalian insulin is structurally similar and is composed of 51 amino acids in two linked polypeptide chains (A and B). Porcine insulin is very similar to human insulin and identical to canine insulin. Bovine insulin is most similar to feline insulin (Table 1). Eli Lilly and Novo Nordisk are the two largest manufacturers of commercial insulin in the United States. Insulin preparations were originally available as bovine–porcine combinations (Iletin I, Eli Lilly; PZI VET [protamine zinc insulin], IDEXX) and purified bovine or porcine insulin (Iletin II, Eli Lilly). The bovine–porcine combinations contain a mixture of approximately 90% bovine and 10% porcine insulin due to the greater availability of bovine pancreata from the beef industry.5

In the 1980s, biosynthetic insulins made with human DNA (Humulin, Eli Lilly; Novolin, Novo Nordisk) became commercially available. In humans with diabetes, the use of human insulin is preferred to reduce the development of antiinsulin antibodies to animal-derived insulins. In recent years, more than 95% of humans with diabetes requiring insulin therapy have been treated with recombinant human insulin preparations.6 Production of the animal-derived insulin preparations has fallen dramatically as a result of human market demands. Fortunately, human insulin has proven to control hyperglycemia in dogs and cats, and the incidence of antiinsulin antibody development in these species is not a major problem. Human insulin differs from canine insulin by one amino acid and from feline insulin by four amino acids. Antiinsulin antibody formation following long-term administration of recombinant human insulin to diabetic dogs appears to be uncommon.7

Recently, the use of insulin analogues has gained popularity in humans with diabetes. Analogues are produced by amino acid alterations in the insulin molecule that reduce the typical hexamer association of regular human insulins.8 This allows them to exhibit monomeric behavior in solution, resulting in rapid absorption, faster onset of action, and shorter duration of effect than short-acting regular crys-

<table>
<thead>
<tr>
<th>Amino Acid Position</th>
<th>Human</th>
<th>Bovine</th>
<th>Porcine</th>
<th>Canine</th>
<th>Feline</th>
<th>Lispro</th>
<th>Aspart</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A8</td>
<td>Threonine</td>
<td>Alanine</td>
<td>Threonine</td>
<td>Threonine</td>
<td>Alanine</td>
<td>Threonine</td>
<td>Threonine</td>
<td>Threonine</td>
</tr>
<tr>
<td>A10</td>
<td>Isoleucine</td>
<td>Valine</td>
<td>Isoleucine</td>
<td>Isoleucine</td>
<td>Valine</td>
<td>Isoleucine</td>
<td>Isoleucine</td>
<td>Isoleucine</td>
</tr>
<tr>
<td>A18</td>
<td>Asparagine</td>
<td>—</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Histidine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
</tr>
<tr>
<td>A21</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
</tr>
<tr>
<td>B3</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>Asparagine</td>
<td>—</td>
</tr>
<tr>
<td>B28</td>
<td>Proline</td>
<td>Proline</td>
<td>Proline</td>
<td>Proline</td>
<td>Proline</td>
<td>Lysine</td>
<td>Aspartic acid</td>
<td>Proline</td>
</tr>
<tr>
<td>B29</td>
<td>Lysine</td>
<td>Lysine</td>
<td>Lysine</td>
<td>Lysine</td>
<td>Lysine</td>
<td>Proline</td>
<td>Lysine</td>
<td>Lysine</td>
</tr>
<tr>
<td>B30</td>
<td>Threonine</td>
<td>Alanine</td>
<td>Alanine</td>
<td>Alanine</td>
<td>Alanine</td>
<td>Threonine</td>
<td>Threonine</td>
<td>Threonine</td>
</tr>
<tr>
<td>B31</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Arginine</td>
</tr>
<tr>
<td>B32</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Arginine</td>
</tr>
</tbody>
</table>

Because insulin analogues have more appropriate pharmacokinetic profiles in humans with diabetes, they are replacing animal-derived insulins and early human biosynthetic insulins.
talline insulin. Insulin analogues are designed to overcome the limitations of the earlier human insulins. The newer insulin analogues, both rapid- and long-acting, have more appropriate pharmacokinetic profiles in humans with diabetes and have replaced many of the earlier human recombinant insulins. In July 1996, the FDA approved the first recombinant DNA human insulin analogue, lispro (Humalog, Eli Lilly). Since then, many other analogues have been developed and evaluated in humans with diabetes.

As a result of the changing insulin market, Eli Lilly announced on July 6, 2005, the discontinuation of US sales of four insulin products, including its remaining animal-derived insulins; as a result, Humulin L Lente insulin, Humulin U Ultralente insulin, Iletin II regular porcine insulin, and Iletin II neutral protamine Hagedorn (NPH) porcine insulin are no longer available to US veterinarians.

Therefore, it became necessary to convert veterinary patients receiving these insulins to comparable insulin preparations and to begin administering available products to newly diagnosed diabetic cats and dogs.

CHOOSING INSULIN

Insulin is typically characterized by its species of origin and its onset, duration, and intensity of action after parenteral administration. Table 2 lists several parenteral insulins according to manufacturer, type, concentration, and cost of 10-ml bottles. More potent insulins have a shorter duration of action than less potent insulins. Short-acting insulins are typically reserved for unstable diabetic patients or patients in a diabetic ketoacidotic crisis, whereas intermediate- and long-acting insulin preparations are generally used for long-term control of stable diabetes. Theoretically, insulin of porcine origin should be best suited for diabetic dogs, and insulin of bovine origin should be most suitable for diabetic cats. Controlled clinical trials evaluating the newer insulin preparations in veterinary medicine are lacking; therefore, some recommendations are extrapolated from studies in humans with diabetes.

**Short-Acting Insulins**

Three short-acting insulins are available:

- Regular human insulin (Humulin R, Eli Lilly; Novolin R, Novo Nordisk)
- Lispro (Humalog, Eli Lilly)
- Aspart (Novolog, Novo Nordisk)

**Regular human insulin** has a strong affinity for self-association and contains hexamers of insulin crystallized during manufacture. 

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**Table 2. Parenteral Insulin Preparations**

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Species</th>
<th>Strength</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin R</td>
<td>Eli Lilly</td>
<td>Regular</td>
<td>Human</td>
<td>U-100</td>
<td>$20–$36</td>
</tr>
<tr>
<td>Novolin R</td>
<td>Novo Nordisk</td>
<td>Regular</td>
<td>Human</td>
<td>U-100</td>
<td>$30–$35</td>
</tr>
<tr>
<td>Humalog</td>
<td>Eli Lilly</td>
<td>Lispro</td>
<td>Human analogue</td>
<td>U-100</td>
<td>$30–$80</td>
</tr>
<tr>
<td>Novolog</td>
<td>Novo Nordisk</td>
<td>Aspart</td>
<td>Human analogue</td>
<td>U-100</td>
<td>$40–$80</td>
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<tr>
<td><strong>Intermediate acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin N</td>
<td>Eli Lilly</td>
<td>NPH</td>
<td>Human</td>
<td>U-100</td>
<td>$20–$36</td>
</tr>
<tr>
<td>Novolin N</td>
<td>Novo Nordisk</td>
<td>NPH</td>
<td>Human</td>
<td>U-100</td>
<td>$30–$35</td>
</tr>
<tr>
<td>Vetsulin/Caninsulin</td>
<td>Intervet</td>
<td>Lente</td>
<td>Porcine</td>
<td>U-40</td>
<td>$15–$30</td>
</tr>
<tr>
<td>PZI VET</td>
<td>IDEXX</td>
<td>PZI</td>
<td>Bovine–porcine</td>
<td>U-40</td>
<td>$70–$105</td>
</tr>
<tr>
<td><strong>Long acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lantus</td>
<td>Sanofi-Aventis</td>
<td>Glargine</td>
<td>Human analogue</td>
<td>U-100</td>
<td>$60–$85</td>
</tr>
<tr>
<td>Levemir</td>
<td>Novo Nordisk</td>
<td>Detemir</td>
<td>Human analogue</td>
<td>U-100</td>
<td></td>
</tr>
</tbody>
</table>

**PZI VET and Vetsulin/Caninsulin are currently the only animal-derived insulins available for use in veterinary medicine.**
The hexamers cannot be absorbed into the bloodstream until they are dissociated into dimers and then monomers. Dissociation occurs by dilution as the insulin diffuses from the injection site. The rate-limiting step in the absorption of regular insulin is dissociation to the monomeric form.

Regular human insulin may be administered intravenously, intramuscularly, or subcutaneously in dogs and cats. In veterinary medicine, regular insulin is used mainly to treat diabetic ketoacidosis. Its onset of action is approximately 10 to 30 minutes, and its duration of effect is approximately 3 to 10 hours, depending on the route of administration. It may be given as a constant-rate infusion or dosed intermittently IM every hour or q4–6h IM or SC. The box on this page contains a brief overview of regular insulin administration, but the details of treating diabetic ketoacidosis are beyond the scope of this article.

Intermediate-Acting Insulins

Three intermediate-acting insulins are available:

- NPH (Humulin N, Eli Lilly; Novolin N, Novo Nordisk)
- Purified porcine-origin Lente (Vetsulin/Caninsulin, Intervet)
- PZI (PZI VET, IDEXX)

NPH and PZI VET contain the fish protein protamine and zinc to further delay the absorption of the insulin, thereby prolonging their duration of effect. Lente does not contain any foreign protein but does contain zinc. Alterations in the zinc content and the size of zinc insulin crystals result in differences in the duration of effect. Larger crystals are absorbed more slowly, leading to a longer duration of effect. Intermediate-acting insulin is preferred for initially establishing glycemic control in diabetic dogs.

Recombinant human-origin NPH insulins are still available for use in cats and dogs. NPH is produced by recombinant DNA technology using a nonpathogenic strain of *Escherichia coli*. NPH recombinant human-source insulin is useful in preventing the development of antiinsulin antibodies. A starting dose in cats and dogs is 0.25 to 0.5 U/kg q12h. The concentration of human NPH is 100 U/ml; therefore, U-100 insulin syringes should be used for administration.
More than 90% of diabetic dogs require recombinant human NPH twice daily, so it is best to begin with twice-daily therapy. This improves glycemic control and decreases the number of problems related to hypoglycemia and the Somogyi effect. The duration of effect of NPH appears to be considerably shorter in cats than in dogs, resulting in inadequate glycemic control despite twice-daily administration in some diabetic cats.

Although human-origin Lente is no longer available, porcine-origin Lente (Vetsulin/Caninsulin, Intervet) is available and is the first FDA-approved veterinary product to treat DM in dogs. Canine and porcine insulin have an identical amino acid sequence; therefore, the theoretical complication of antiinsulin antibodies and their effect on glycemic control is eliminated. Vetsulin/Caninsulin is a mixed insulin zinc suspension containing 30% amorphous zinc insulin (which is rapidly absorbed and has a short duration of activity) and 70% crystalline zinc insulin (which is absorbed more slowly and has a longer duration of activity). The amorphous fraction reaches its maximum effect approximately 4 hours after subcutaneous administration, and its effects last for approximately 8 hours. The crystalline fraction reaches its peak effect approximately 11 hours after injection, and its effects gradually decline over 24 hours after administration. Therefore, many diabetic dogs receiving porcine insulin zinc suspension appear to have two peaks of insulin activity. According to the manufacturer of Vetsulin/Caninsulin, these kinetics may allow once-daily dosing in some dogs. However, one study demonstrated that most dogs require twice-daily administration for adequate glycemic control.

The manufacturer’s recommended initial dose of Vetsulin/Caninsulin is 1 U/kg plus a supplemental dose of 1 to 4 U, depending on optimal body weight, once daily (Table 3). If twice-daily treatment is initiated, the manufacturer recommends that each of the two doses be reduced by 25% of the once-daily dose. Despite these recommendations, a practical starting dose to avoid potential hypoglycemia is 0.5 U/kg q12h. Vetsulin/Caninsulin is available at a concentration of 40 U/ml, so U-40 insulin syringes should be used for administration. In addition, it is available in 2.5-ml bottles for cats and small dogs.

**PZI VET** is a currently available bovine–porcine insulin (90% bovine; 10% porcine) that had previously been considered long acting. PZI VET is longer acting and is more consistently absorbed than Ultralente (no longer available) and has a longer duration of effect than NPH in diabetic cats. It has not been shown to be more effective than other intermediate-acting insulins in controlling clinical signs of diabetes in dogs. In addition, bovine insulin has been shown to stimulate development of antiinsulin antibodies in 40% to 65% of diabetic dogs in which it was used. Therefore, use of bovine and bovine–porcine combination insulins should be avoided in diabetic dogs.

A clinical trial including 67 diabetic cats showed that PZI VET was very effective in significantly improving glycemic control in newly diagnosed diabetic cats and in previously treated, poorly controlled diabetic cats based on owner observation and serum fructosamine levels. However, the absorption kinetics, glucose nadir, and duration of action of PZI VET are variable. The glucose nadir occurred within 9 hours of PZI VET administration in more than 80% of treated diabetic cats in the study. Twice-daily administration is recommended, but once-daily administration may be effective in controlling hyperglycemia in some diabetic cats.

### Table 3. Manufacturer-Recommended Dosing of Vetsulin/Caninsulin

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Dose +</th>
<th>Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 kg (≤22 lb)</td>
<td>(Weight in kg) × 1 U/kg + 1 U</td>
<td>1 U/kg + 1 U</td>
</tr>
<tr>
<td>10–11 kg (22–24.2 lb)</td>
<td>(Weight in kg) × 1 U/kg + 2 U</td>
<td>1 U/kg + 2 U</td>
</tr>
<tr>
<td>12–20 kg (26.4–44 lb)</td>
<td>(Weight in kg) × 1 U/kg + 3 U</td>
<td>1 U/kg + 3 U</td>
</tr>
<tr>
<td>&gt;20 kg (&gt;44 lb)</td>
<td>(Weight in kg) × 1 U/kg + 4 U</td>
<td>1 U/kg + 4 U</td>
</tr>
</tbody>
</table>

Glargine is a long-acting insulin analogue that has been associated with high remission rates in diabetic cats.
The initial recommended dose is approximately 1 U/cat q12h. The concentration of PZI VET is 40 U/ml; therefore, U-40 insulin syringes should be used for administration.

**Long-Acting Insulins**

Glargine (Lantus, Sanofi-Aventis Pharmaceuticals) and detemir (Levemir, Novo Nordisk) are the only long-acting insulins available in the United States.

Glargine insulin is produced by recombinant DNA technology using *E. coli*. It differs from human insulin in that the amino acid asparagine at position A21 is substituted with glycine, and two arginines are added to the terminal B chain. Glargine has a pH of approximately 4, is poorly soluble at physiologic pH, and forms microprecipitates when it is injected into subcutaneous tissue, from which small amounts of the insulin analogue are slowly released. These aggregates result in delayed, prolonged, and relatively constant absorption of insulin from the subcutaneous injection site. Glargine gained FDA approval for use in humans in June 2000 and is marketed as a very long-acting "peakless" insulin. It is designed to provide a basal or background insulin concentration in humans after administration once daily at bedtime, while other short-acting insulins are administered at mealtimes to maintain glycemic control. In humans, the onset of action of glargine is 2 to 4 hours after subcutaneous injection, and the duration of action is 20 to 24 hours. Rapid- and short-acting insulins, such as lispro or aspart, are typically administered with meals.

Veterinary studies evaluating the pharmacokinetics and pharmacodynamics of glargine have shown that there are definite peaks in insulin concentration and glucose-lowering effects in healthy cats. Once-daily and twice-daily administration of glargine has also been compared in healthy cats and diabetic cats. Although once-daily administration of glargine at 0.5 U/kg provided a significant blood glucose lowering effect, a longer effect was achieved by administering 0.25 U/kg q12h. There was no statistical difference in onset of

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**Figure 1. Recommendations for glargine insulin use.**
action, nadir glucose, or mean daily glucose.\textsuperscript{24}

Glargine has been evaluated in a small number of diabetic cats with some encouraging results. Glargine combined with a low-carbohydrate, high-protein diet has been associated with high remission rates in 14 newly diagnosed diabetic cats.\textsuperscript{25} Based on the initial studies, some guidelines for glargine therapy in cats have been developed (Figure 1).

The dose of glargine should not be increased during the first week of therapy because cats often have negligible glucose lowering in the first 3 days. However, if biochemical or clinical hypoglycemia occurs, the dose should be decreased. Cats should be reevaluated weekly for the first month. Dose changes should be made based on preinsulin glucose concentration, nadir glucose concentration, daily water intake, and urine glucose concentration. Urine glucose in well-controlled cats is often 0 or 1+. A urine glucose of 2+ or greater indicates that an increase in dose is required. Insulin therapy should be continued for a minimum of 2 weeks from the time of diagnosis to give the beta cells a better chance to recover from glucose toxicity.\textsuperscript{26}

Unopened glargine should be stored in a refrigerator and away from direct heat and light. Once a vial is opened, it may be stored at room temperature for 28 days. The concentration of glargine is 100 U/ml; therefore, U-100 insulin syringes should be used for administration. To date, not enough information is available about glargine use in dogs. Other, more cost-effective insulin options are available for use in dogs.

Detemir is a soluble long-acting human insulin analogue acylated with a 14-carbon fatty acid. The fatty acid modification allows detemir to reversibly bind to albumin, providing slow absorption and a prolonged, consistent metabolic effect of up to 24 hours in humans with diabetes.\textsuperscript{27} To date, no clinical trials of detemir use in diabetic dogs and cats have been conducted.

**CONCLUSION**

Advances in human medicine have forced veterinarians to change the management of diabetes in cats and dogs. New insulins with novel mechanisms of action, pharmacokinetic parameters, and dosing regimens will likely continue to affect veterinary medicine for years to come. Insulin choices should be made on an individual basis with a focus on species differences and proven scientific data substantiating effectiveness.

**REFERENCES**

The Evolution of Insulin Therapy


1. Which statement regarding DM is correct?
   a. It is a disorder of the delta cells.
   b. Oral hypoglycemic agents are the mainstays of therapy.
   c. A goal of therapy is to reduce signs of polyuria and polydipsia.
   d. It is an uncommon problem in veterinary medicine.

2. Which is not a mechanism of action of insulin?
   a. inhibition of lipolysis in the adipocyte
   b. inhibition of protein synthesis
   c. stimulation of peripheral glucose uptake
   d. inhibition of hepatic glucose production
3. Which statement comparing types of insulins is correct?
   a. Human insulin differs from porcine insulin by one amino acid.
   b. Bovine insulin is most similar to canine insulin.
   c. Porcine insulin is identical to feline insulin.
   d. Human insulin differs from canine insulin by four amino acids.

4. Which statement regarding insulin analogues is incorrect?
   a. Insulin analogues exhibit monomeric behavior in solution.
   b. Rapid-acting insulin analogues include lispro and aspart.
   c. Insulin analogues are produced by amino acid alterations in the insulin molecule.
   d. The first FDA-approved insulin analogue was aspart.

5. Which statement regarding insulin is correct?
   a. Short-acting insulins are less potent than long-acting insulins.
   b. Regular insulin may be given as a constant-rate infusion.
   c. Aspart and lispro are not potent enough for use in veterinary medicine.
   d. Lispro is suitable for once-daily administration in veterinary patients.

6. Which statement regarding NPH is correct?
   a. The duration of effect of NPH is longer in cats than in dogs.
   b. NPH is produced by recombinant DNA technology using S. cerevisiae (baker’s yeast).
   c. Twice-daily administration of NPH is often required in diabetic dogs.
   d. NPH contains zinc but no foreign protein to prolong its duration of effect.

7. Which statement regarding Vetsulin/Caninsulin is incorrect?
   a. Vetsulin/Caninsulin contains 30% crystalline zinc and 70% amorphous zinc in suspension.
   b. Vetsulin/Caninsulin is a porcine-origin Lente insulin.
   c. The concentration of Vetsulin/Caninsulin is 40 U/ml.
   d. Vetsulin/Caninsulin is FDA approved for treating dogs with diabetes.

8. Which statement regarding PZI VET is correct?
   a. The initial recommended dose of PZI VET in cats is 1 U/kg q12h.
   b. Twice-daily administration is likely to provide better glycemic control in cats than once-daily administration.
   c. The absorption kinetics, glucose nadir, and duration of activity of PZI VET in cats are constant.
   d. PZI VET is not likely to stimulate the development of anti-insulin antibodies in dogs.

9. Which statement regarding glargine is incorrect?
   a. Glargine insulin is typically administered once daily at bedtime in humans with diabetes.
   b. It is long acting and may be given once or twice daily.
   c. It should not be mixed or diluted.
   d. It has been associated with high remission rates in newly diagnosed diabetic cats when combined with a high-carbohydrate, low-protein diet.

10. Detemir insulin
    a. irreversibly binds to albumin.
    b. is created through amino acid alterations similar to other insulin analogues.
    c. is a long-acting insulin analogue and is available in the United States.
    d. is rapidly absorbed and produces a prolonged effect in humans with diabetes.