FELINE DIABETES MELLITUS

A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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INTRODUCTION

The diagnosis and therapy of diabetes mellitus in cats is a challenging, complex and often frustrating experience for veterinarians. Although the tendency has been to manage this disease in cats as if they were small dogs, such an approach can lead to disaster. Certain aspects of this disorder are quite different in cats compared to dogs and must be appreciated for a consistently successful outcome. The precise incidence of diabetes mellitus in cats is not known, although it has been suggested to occur at a rate of 1:800. It occurs less commonly than in dogs (canine incidence 1:200). Reported cases range in age from 1 to 15 years with over 50% diagnosed after the age of 9. Males have predominated in all recent feline case studies and one author suggested a male to female ratio of 4:1 exists. The only breed suggested to be at increased risk is the Siamese.

ETIOLOGY

The etiology of feline diabetes mellitus is multifactorial. Lesions identified include insular amyloid, with or without prominent islet cell vacuolation, reduced numbers of islet cells (secondary to chronic inflammatory pancreatic disease), rare peri-insular lymphoid deposits and occasional cases where the islets appear histologically normal.

The most common lesion identified in the islet cells of feline diabetics is insular amyloidosis. Although 50% of normal aged cats have evidence of islet cell amyloid deposits, this lesion is present in 65% of diabetic cats. In addition, when aged matched control cats are compared to cats with diabetes, many more islets are involved and the severity of these deposits is significantly more severe, suggesting a causal relationship. The pathogenesis of insular amyloid leading to diabetes is unknown.

Vacuolation (hydropic degeneration) of feline pancreatic islets is also a frequently observed lesion. The cause of this degenerative change is unknown. It has been observed in some diabetic cats receiving medroxyprogesterone acetate. Whether this lesion was induced by the drug is unknown. Occasional cats with islet cell vacuolation and insulin dependent diabetes will return to clinical normalcy.

The potential for the induction of diabetes mellitus in cats by the use of progestational compounds is well documented. Every veterinarian must be aware of the potentially severe side effects to the therapeutic use of these compounds. Published reports of such drug induced diabetes in cats have been limited at present to 11 cases. Information regarding drug dosage (megestrol acetate), duration of therapy, use of other diabetogenic drugs (glucocorticoids) etc. is too limited to draw meaningful conclusions. However, it is clear, diabetes can develop within 10 to 14 days of initiation of progestational therapy at dosages currently recommended for control of non-specific feline dermatoses i.e. "miliary eczema", linear granuloma, eosinophilic ulcer complex. Fortunately, clinical evidence of diabetes regressed in 8 of 11 cats. Nearly all these animals required therapy with insulin for weeks to months. Three of the 11 cats died due to complications of diabetes.

The pathogenesis of progesterone induced diabetes is incompletely understood. Progesterone alone has diabetogenic potential in both dogs and cats. This effect produces only mild carbohydrate intolerance, however. The most significant effect is due to progesterone stimulated growth hormone release from the anterior pituitary gland, although this effect only occurs in dogs and not cats. Growth hormone is a potent diabetogenic agent in cats and dogs. Growth hormone induces severe insulin resistance of major insulin dependent tissues (muscle and fat). This initially leads to hyperglycemia, and in a normal animal, compensatory hyperinsulinemia. Ultimately, prolonged growth hormone excess leads to beta cell exhaustion and overt diabetes mellitus. A recent report of severe insulin resistant diabetes and growth hormone excess in a megestrol acetate treated cat has appeared. It was subsequently learned that the cat had a growth hormone secreting tumor of the pituitary in addition to it receiving megestrol acetate. Although the incidence of megestrol acetate induced diabetes in cats appears to be low, veterinarians should inform owners of cats being given this drug of its potential adverse effects.

A few cats, primarily aged males, have been identified with profound insulin resistance secondary to pituitary neoplasms secreting growth hormone. The only way to identify the neoplasm is through a CT of the brain.

HISTORY/PHYSICAL EXAM

Historical findings in feline diabetes are similar to those seen in dogs. Depression, anorexia, weight loss and weakness are most commonly observed. Polyuria, polydipsia and polyphagia, although common, are not as frequently mentioned by owners as the other signs. Polyuria is particularly difficult for many owners to document due to the micturition habits of most cats. The duration of clinical signs varies from one day to 6 months, with most cats being symptomsomatic for approximately one month.

Recently, we as well as others, have observed diabetic cats presented with a primary complaint of gait abnormalities, particularly noticeable in the rear limbs. These cats walk in a severe plantigrade posture. Their hocks are consistently flat to the floor. Preliminary results suggest these cats are suffering from distal symmetric diabetic polyneuropathy. These cats have hind and forelimb muscle atrophy, hypotonic tarsi and absent patellar reflexes. Withdrawal responses and pain perception are normal. Electromyography indicated there were decreased motor nerve conduction velocities in both sciatic and ulnar nerves. Denervation potentials were present in all limb muscles.

Physical findings are non-specific in most cases. In one series of 13 cats, obesity, hepatomegaly, renomegaly, seborrhea sicca, muscle wasting and dehydration were frequent findings. Another large series found hypothermia and icterus to be frequent physical abnormalities. Cataract formation, a common occurrence in dogs, is very uncommon in cats. Two of 19 diabetic cats surveyed from the author's practice had cataracts. No other similar observations were found in literature reports.

DIAGNOSIS

The diagnosis of diabetes mellitus in cats is relatively straight forward. The single major caution is to be sure the animal has <u>persistent</u> hyperglycemia and glucosuria. Cats are very prone to stress induced hyperglycemia and it is often accompanied by glucosuria. Non-sick hyperglycemic or glucosuric cats should always have a second fasting blood glucose and repeat urinalysis 24 to 36 hours after the initial abnormal samples to insure the hyperglycemia was not a transient event. If ketonuria and glucosuria are present, however, the diagnosis is certain.

Significantly abnormal laboratory parameters, in addition to hyperglycemia and glucosuria, often include anemia, increased liver enzymes, hyperbilirubinemia, azotemia, hypercholesterolemia, altered electrolytes, elevated serum amylase or lipase, ketonemia, and ketonuria. Anemia (PCV = < 30%) is relatively infrequent. Only 1 of 13 diabetic cats was found to be anemic in one study while 7 of 30 were mildly to moderately anemic in a second survey (< 26%).

Blood glucose concentrations in diabetic cats range from 200 to 800 mg/dl. The mean blood glucose at presentation of 19 diabetics studied by the author was 350 mg/dl.

Hepatic abnormalities are nearly always detected. Serum concentrations of alanine aminotransferase are increased in approximately 80% of patients. The magnitude of rise is usually mild to moderate (2 to 4 times normal). Although serum alkaline phosphatase is infrequently elevated in feline liver diseases, this enzyme was significantly increased in 21 of 47 (47%) diabetic cats. Maximal increases were 3 1/2 times normal. Total serum bilirubin concentrations are elevated in approximately 56% of cases. Values range from 1.4 to 8.1 mg/dl. Serum cholesterol concentrations are nearly always increased.

Varying degrees of azotemia exist in a significant number of feline diabetics. Twenty-six of 57 cases had increases in blood urea nitrogen on admission. Most were prerenal in origin due to severe dehydration. Adequate fluid therapy resulted in correction of the azotemia in most cases. When prerenal uremia was present, the urine specific gravity was greater than 1.030. In diabetic cats with concomitant primary renal failure, the urine is usually isosthenuric in spite of the large quantity of glucose present. Urinary tract inflammation was present in 7 of 13 cats in one report. These cats had significant quantities of pyuria, proteinuria and hematuria.

Electrolyte abnormalities are common in diabetic cats and are particularly severe in ketoacidotic animals. Varying combinations of hyponatremia, hypokalemia, and hypophosphatemia or hyperphosphatemia may be present. Since these changes are unpredictable in their development or magnitude, it is important for optimal patient management that electrolytes be determined, whenever possible.

Pancreatitis is a relatively uncommon clinical entity in cats. However, it has been documented both biochemically (amylase or lipase values) and/or pathologically in a number of cats with diabetes mellitus. The magnitude of rise in amylase and lipase are often only 2-3x the upper limit of normal.

Ketoacidosis is present in roughly 58% of diabetic cats. Unfortunately, reports of blood gas analyses from these patients to determine the severity of systemic acidosis are virtually nonexistent. Ketoacidotic cats require intensive care and in-depth monitoring for the greatest success.

Abdominal radiography of diabetic cats is characterized by 3 major lesions, emphysematous cystitis, hepatomegaly and nephromegaly. Emphysematous cystitis is caused by urinary tract infections with glucose fermenting organisms that produce gas within the wall of the urinary bladder.

THERAPY

Therapy of feline diabetes mellitus, except for a few important differences, is similar to that of the dog. Cats are quite sensitive to insulin and wide swings in blood glucose concentrations can occur with small dosage adjustments. Iatrogenic hypoglycemia is much more common in cats than dogs. Additionally, the kinetics of insulin metabolism are unpredictable in cats. Each cats' response to different forms of insulin (Lente or NPH vs Ultralente) is highly variable between patients. Recent clinical studies in diabetic cats indicate that NPH/Lente insulin has its maximal glucose lowering effects 4 to 8 hours following administration. Ultralente was found to have a more prolonged maximal glucose lowering effect (range 6 to 12 hours) post insulin administration. It appears that approximately 20% of cats will have poor absorption of Ultralente insulin, even when dosages of 8 to 10 units are given BID. When this occurs a switch to NPH or Lente insulins, at 2 to 3 units given BID is indicated. Feline diabetics also have a tendency to revert to a non-insulin requiring state at unpredictable intervals post diagnosis. This is especially true in megestrol acetate induced diabetes, but can also occur in cases of undefined etiology, particularly those with initialy mild diabetes. It is particularly important that owners monitor their cat's urine for glucose and veterinarians monitor fasting blood glucose values at least weekly to prevent continued insulin administration to cats whose diabetes has gone into remission.

REGULATION OF NON-KETOTIC DIABETICS

This discussion applies to non-sick, non-anorectic cats who will require little in therapy except insulin and possibly fluids, coupled with dietary adjustment and weight control. The watch word for insulin dosing in diabetic cats is start low and go slow. It is much safer and easier on the cat to slowly correct for hyperglycemia than to be constantly giving 50% dextrose to seizuring cats in insulin shock. Start with 0.2 to 1 unit/kg, up to a maximum of 3 units of either intermediate acting insulins (Lente or NPH) or long acting preparations (Ultralente) administered at 8:00 AM. Long acting preparations generally are preferred. The majority of cats (75%) require BID administrations of insulin for good control. The cat should be fed approximately half of its total food requirement at this time. Blood glucose concentrations should be taken prior to when insulin is given and every two hours until the time of maximal insulin response is detected i.e. the lowest blood glucose value is observed and a rise noted. The goal is to attain a blood glucose between 100 to 175 mg/dl. Once this time of peak insulin effect has been determined, the cat should be fed approximately 30 minutes prior to this time on subsequent days. This will prevent hypoglycemic attacks and allow most of its dietary carbohydrates to be available when the insulin peaks. It is easy to obtain frequent blood glucose measurements using chemical reagent strips with or without an inexpensive colorimetric.[a,b] glucose reader. With Lente or NPH insulin, this peak is often between 4 and 8 hours after administration. For cats peaking very early in the day, very little, if any, insulin activity will remain for the remainder of the day. These cats will require twice daily Lente or NPH insulin administration or a change to Ultralente insulin. Ultralente insulin usually has its peak hypoglycemic effect 6 to 12 hours after administration and is often better than Lente or NPH in cats for once daily insulin therapy. However, most cats will still require BID administration for good glycemic control even with long acting insulins. Insulin dosages should be adjusted up or down by 1/2 to 1 unit per day based on the lowest blood glucose values obtained and the duration of activity. The average maintenance dose for 19 diabetic cats regulated at the University of Minnesota Veterinary Teaching Hospital was 1.3 units/kg, while that from a recently published survey of 13 cats was 1 unit/kg.

Utilizing morning urine sugar concentrations to regulate diabetic cats is difficult and often unreliable. Cats rarely cooperate in the timing of their micturition and due to the early insulin peak in cats, frequently have 3+ to 4+ AM urine glucose while their blood glucose at peak insulin time is as low as practicable. The primary value in owners checking their cats morning urine glucose is to be sure that the cat is still diabetic and has not recovered spontaneously. Placing clear plastic wrap over the litter or using plastic aquarium gravel as litter will usually allow a small quantity to be salvaged for glucose determinations. Owners should be instructed to return their cats once weekly for a recheck blood glucose at the time it is calculated to be the lowest of the day. The cat should not be fed its PM meal on the days it is rechecked until after the blood sample is taken. After 2 to 3 weeks, if the cat remains stable, rechecks can be schedule every 3 to 4 months.

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[a] Dextrostix: Ames Co., Miles Lab., Inc., P.O. Box 70, Elkhart, IN 46515.
[b] Chemstrip - BG: Biodynamics, 9115 Hague Rd., Indianapolis, IN 46250.

Dietary management of diabetic cats is often not as easily managed as in dogs. Cats often have selective appetites and eating habits which are very hard to change. Where possible, overweight cats should be put on a weight reduction program and fed high fiber diets (Table-2). Reducing weight and altering the diet to contain higher quantities of fiber significantly reduces insulin demands and may result in reversal of the diabetes. We recommend Hill's r/d diet initially, and once ideal weight is attained, switch the cats to w/d diets. If cats can be fed two or three times daily their food is divided up into 3 equal sized meals. If they prefer to nibble throughout the day, no attempt is made to change their eating pattern. Many cats receiving insulin twice daily are fed 50% of their caloric intake just prior to each insulin injuction and do very well clinically.

ORAL HYPOGLYCEMIC AGENTS IN FELINE DIABETES MELLITUS

From 20% to 60% of diabetic cats are potentially non-insulin dependent, and may respond to oral hypoglycemic agents, at least for a time. These cats usually have mild diabetes, lack ketoacidosis, and are often obese.

DIAGNOSIS:

No pre-therapy evaluation consistently determines which cats will respond to oral hypoglycemic agents. In occasional animals, either a fasting serum insulin concentration, or an IV glucose tolerance test may provide evidence that a response is likely. For the IV glucose tolerance test, the cat is given 500 mg/kg of 50% destrose IV over 30 sec, blood glucose and serum insulin values are obtained at 5,15, 30, 45, and 60 minutes. In IDDM serum insulin values remain near baseline throughout the test (< 20 μU/ml) while some cats with NIDDM have one or more serum values > 20 μU/ml. Not all cats with NIDDM can be diagnosed with this test. Ultimately, response to therapy often establishes the diagnosis following a therapeutic trial with oral hypoglycemics, high fiber diets and weight loss.

THERAPY:

Oral hypoglycemics should only be used in cats that have mild signs of diabetes, without overt ketoacidosis. Sulfonylureas are the only approved oral hypoglycemic drugs in the United States. They stimulate insulin secretion of preformed insulin from the pancreas. Glipizide (Glucotrol, Pfizer Inc.) is the drug for which there is the most information. Following oral dosages, insulin secretion increases within 10 minutes. Sulfonylureas do not increase synthesis of insulin. A number of extrahepatic efects of these drugs have also been identified. Over time, they decrease hepatic glucose production, increase hepatic glucose utilization and decrease hepatic insulin extraction. They also partially reverse a post receptor binding defect in insulin handling, and increase the number of insulin receptors. Some of these effects may be due to enhanced insulin secretion rather than an effect of the sulfonylureas themselves.

The initial dosage of glipizide is 2.5 mg BID for two weeks to monitor for signs of toxicity. If the cat tolerates the medication, then the dosage is increased to 5 mg two times/day in conjunction with a meal. The drug will need to be given for one to two months to determine if the cat is capable of responding. Responses to glucotrol are variable. Some cats respond well with mean blood glucose values being maintained below 200 mg/dl and clinical signs resolve (approximately 25%). Some of these good responders may be taken off all medication and their diabetes resolves. Others need lower dosages of glucotrol (2.5 mg BID) to maintain them in a euglycemic state and prevent signs of hypoglycemia. Some cats have a partial response in that clinical signs are lessened but fasting blood glucose values are consistently over 200 mg/dl.

However, owners are pleased with the condition of their cat and do not want other therapy instituted (approximately 40%). Other cats fail to respond, clinical signs worsen, and they must be given parenteral insulin (approximately 35%).

Significant side effects have been infrequent to date. Vomiting has been seen in approximately 10% of cats given the drug and may decrease if the dosage is decreased (2.5 mg BID). Occasional cats have also had increases in hepatic enzymes (ALT & ALP), or may develop icterus. Increases in liver enzymes can be dramatic. These cats may not have other signs of active hepatic disease(15% of cases). Stopping the drug has resulted in return to normal of hepatic enzymes. Hypoglycemia has been observed in approximately 15% of cats and requires modifications in dosages (2.5 mg BID or stop the drug for a week). Some of the cats developing hypoglycemia may eventually be taken off all mediation.

Most cats with NIDDM will respond to oral therapy within one to two months, although one reported case required 5 months before adequate glycemic control was obtained. Owners can check the cats urine occasionally for glucose and ketones using aquarium gravel as litter, to be sure that glycosuria is present, at least some of the time. During initial drug evaluation cats are returned weekly for a fasting blood glucose concentration, and several "post-pill glucose measurements, as well as a weight and physical exam. These evaluations need to be performed during initial therapy to monitor the cat's clinical response.

Spontaneous resolution of the diabetes may occur in up to 20% of cats. If the cat becomes hypoglycemic, the dosage is reduced or discontinued and the cat's blood glucose is reevaluated in one week to see if reinstitution of glipizide at a lower dosage is indicated.

Insulin is begun if the cats signs worsen, they develop neuropathy, their blood glucose is consistently > 350 mg/dl, or owners become unhappy with the cat's clinical signs.

The duration of effective control in cats that respond is variable, lasting from a few weeks to over a year. Oral hypoglycemics offer owners of diabetic cats a reasonable alternative to insulin by injection in a significant number of cats.

REGULATION OF THE KETOACIDOTIC DIABETIC CAT

The sick ketoacidotic diabetic cat is an extremely fragile patient. The highest degree of patient response is going to be obtained only when full laboratory and constant care facilities are available. Initial laboratory work should include a CBC, blood glucose, serum concentrations of alanine aminotransferase, alkaline phosphatase, bilirubin, amylase or lipase, sodium, potassium, chloride, calcium and phosphorus. Blood gas analysis, or at least total CO_2 estimations, are the only way of determining the severity of any acidosis present and are useful for calculating if alkalinization therapy should be employed. An intravenous catheter should be sterilely placed as soon as a decision to treat is made. Jugular catheters are useful as they allow fairly large fluid volumes to be administered over short time intervals and are an easy access to blood for frequent monitoring. We usually use intravenous lactated Ringer's solution for immediate fluid replacement in these cats. Volumes to be used are calculated from the cats maintenance needs, the degree of dehydration present and the volume of any contemporary losses (polyuria, vomiting, etc). Cats with normal renal and cardiovascular function will tolerate fluid administration rates of 30 to 35 ml/lb/hr i.e. sufficient to replace their blood volume in 60 minutes. Rapid rehydration in diabetic cats is not recommended, however, as it may aggravate any hyperosmolarity present. Replacing maintenance and deficit amounts of fluid over 18 to 24 hours is usually quite adequate.

Regular insulin should be used in all cases. Several methods of insulin administration can be used successfully. Choices include intermittent I.V. boluses, continuous low dose intravenous infusions or intermittent low dose intramuscular injections. Traditionally, ketotic diabetic cats have received approximately 0.5 units/kg of regular insulin as an immediate I.V. bolus. Blood glucose concentrations are measured every 2 hours and additional regular insulin is given subcutaneously 4 hours after the initial I.V. bolus. These subsequent doses are on the order of 0.25 to 0.5 u/kg and will be repeated every 6 to 8 hours. Blood glucose determinations are made 2 to 4 hours after each subcutaneous injection. Once the blood glucose reaches 200 mg/dl, dextrose should be added to the I.V. fluids to prevent hypoglycemia. Adding 100 ml of 50% glucose to one liter of lactated Ringer's solution will produce a 5% dextrose in lactated Ringer's solution. The patient is usually switched from regular insulin to either Lente/NPH or Ultralente insulin within 24 to 36 hours. Regulation will then proceed as with the non-ketotic cat.

Low dose, constant infusions of insulin are also useful for rapid correction of ketoacidosis. To date, published reports of success with this technique have only been on its use in dogs. Five units of regular insulin are added to 500 ml of lactated Ringer's solution. This produces a resultant concentration of 0.01 units/ml. This dilute insulin solution is administered intravenously at a rate of 0.5 to 1 unit per hour (50 to 100 ml/hr). The insulin is administered with a pediatric infusion set through a separate fluid line than that used for rehydration and maintenance fluids. Blood glucose is checked every 1 to 2 hours and when it reaches 200 mg/dl or less, the cat is switched to NPH or Ultralente insulin subcutaneously. In dogs, most reached euglycemia in 8 hours or less. In man, this method of insulin administration is associated with fewer of the complications associated with intermittent bolus therapy i.e. hypoglycemia and hypokalemia.

A third potential method for rapid correction of diabetic ketoacidosis is low dose regular insulin given intramuscularly at frequent intervals. Cats are given 2 units IM immediately. Subsequently, they are given 0.5 to 1 unit intramuscularly every hour until their blood glucose is less than 250 mg/dl. Again, this protocol has only had limited testing in dogs, but has worked well in that species. Mean time to attain the desired blood glucose was 4 hours. Once the hyperglycemia is controlled, the cats should be given subcutaneous regular insulin every 6 to 8 hours until they can be switched over to either intermediate or long acting preparations. When on maintenance subcutaneous regular insulin, try to maintain the blood glucose at 100 to 200 mg/dl 2 to 4 hours post insulin administration.

Electrolyte abnormalities are common in ketoacidotic cats. Hyponatremia, hypochloremia, hypokalemia and hypophosphatemia are of particular importance. Rehydration with 0.9% sodium chloride or lactated Ringer's solution will usually correct the sodium and chloride deficits in 1 to 2 days. Hypokalemia and hypophosphatemia are more difficult to manage, since neither electrolyte is present in sufficient quantity in these two fluids to replace severe deficits. In non-azotemic cats with serum potassium concentrations less than 3.5 meq/L, we add 25 to 30 meq of potassium chloride to each liter of lactated Ringer's solution (resultant potassium concentration = 29 to 34 meq/L). The maximal safe rate of administration of this fluid will provide 0.5 meq/kg/hr of potassium (= 15 ml/kg/hr).

Hypophosphatemia is a challenging electrolyte disorder to manage. Based on our limited clinical experience with this disorder, we believe judicious phosphorous supplementation will benefit animals with serum phosphorous concentrations of < 1.5 mg/dl, and should be given if the serum phosphorous is < 1.0 mg/dl.

Both oral and parenteral phosphate preparations can be administered to animals with hypophosphatemia (Table 1). The safest and preferred method of phosphorous supplementation is the oral route if oral medications can be administered safely. If a balanced commercial diet is voluntarily consumed or can be force fed, it should prevent moderate hypophosphatemia from worsening and reverse severe hypophosphatemia. As an alternative to a balanced commercial diet, whole milk is a readily available source of phosphorous and contains 0.29 mmol/ml. Oral sodium phosphate solutions (Fleet's Phospho-Soda) contains 4.5 mmol/ml but may induce diarrhea if it is not given in small, frequent amounts. Oral doses used to supplement low phosphorous TPN solutions in man are 0.5 to 2 mmol/kg/day, and are probably a good starting dose for dogs and cats.

Parenteral phosphate supplementation is the most controversial route of phosphorous administration. This is because of the potential for serious complications to develop and the fact that neither the size of the phosphorous deficit nor dose to be given can be predicted with any certainty. Intravenous preparations of phosphorous may be given either as the sodium or potassium salt (Table 3). Dosages should always be converted to mmol/L since significant dosing errors can be made if mg/dl or meq available are used in dosing calculations (one mmol/l = 3.1 mg/dl = 1.7 meq/L). Most commercially available parenteral phosphate solutions contain 3.0 mmol/ml. Intravenous dosages which the authors have used successfully in dogs and cats range from 0.06 to 0.18 mmol/kg given over 6 hours (0.01 to 0.03 mmol/kg/hr). The serum phosphorous must be rechecked prior to readministering more phosphorous or complications related to overdosage may result. Parenteral phosphate should be added to fluids that do not contain calcium i.e., normal saline or dextrose and water, to avoid precipitation of calcium-phosphate salts. It is not necessary to administer phosphorous supplementation until the serum concentration normalizes. Generally, once the serum phosphorous reaches 2.0 mg/dl, supplementation can be stopped. Potential complications of parenteral phosphorous therapy include inducing hyperphosphatemia, hypocalcemia, soft tissue calcification, hypotension, and renal failure. Four of six hypophosphatemic cats treated at the authors hospital developed significant hypocalcemia (Ca^{++}= 5.5 to 8.1 mg/dl) and one had signs of mild tetany, weakness and depression which required treatment with calcium gluconate. Contraindications to the administration of phosphorous containing fluids include hypercalcemia of any cause, hyperphosphatemia, oliguria, renal failure, and evidence of tissue necrosis.

Daily serum electrolyte panels should be taken to assess the adequacy of your replacement therapy. Once insulin therapy is begun and the cat starts eating, these electrolyte alterations will revert to normal.

COMPLICATIONS (Table-3)

A number of complications can occur in diabetic cats both during initial stabilization and after the cats are home on maintenance therapy. Complications associated with initial therapy include renal failure, hyperadrenocorticism, non-ketotic hyperosmolar syndrome and pancreatitis. Primary renal failure is an infrequent complication of feline diabetes mellitus. Prerenal azotemia is very common, however, and must be managed aggressively during initial therapy. Hyperadrenocorticism, a common cause of diabetes in dogs, does occur in cats, but is rare. Another recently reported disorder leading to insulin resistance is growth hormone secreting tumors of the pituitary, particularly in aged male cats. Both hyperadrenocorticism and growth hormone secreting tumors in cats produce profound insulin resistance. Hyperosmolar non-ketotic coma has been described in one cat. Since this cat was also severely uremic and had pancreatitis, the contribution that hyperosmolarity played is questionable. The true incidence of severe hyperosmolarity in feline diabetes has yet to be defined. Pancreatitis is clinically recognized in occasional feline diabetics and appears to be responsible for initiation of the diabetic state. Symptomatic therapy and control of the diabetes will usually correct this complication.

A number of complaints may develop in previously regulated diabetic cats that are related to over or under regulation or development of coexisting diseases. Persistent polydipsia and polyuria in treated diabetic cats i.e. perceived "insulin resistance", or lack of effect, is a common complaint. This may be due to either too little or too much insulin. Some diabetic cats are well regulated for a time and then need more insulin due to ongoing destruction of their islets due to pancreatitis or insular amyloidosis. In order to diagnose this problem, these cats must be admitted and serial blood glucose curves obtained to determine the appropriate dosage and frequency of insulin injections. More commonly, owners have been slowly increasing insulin dosages because of apparent PU/PD but it has not alleviated the problem. Because of the short duration of action of insulin in many cats, PU/PD will persist and gradually increasing insulin dosages are given to correct the problem. Many of these cats have reasonable insulin effects early in the day, but the duration of action of Lente or NPH insulin is such that late afternoon or evening hyperglycemia develops. If owners continue to increase insulin in these cats they develop a phenomenon of insulin induced post-hypoglycemic, hyperglycemia (Samogyi reaction). Insulin induces hypoglycemia and counter-regulatory hormones respond, reversing the hypoglycemia and, in fact, produce a rebound hyperglycemia. The rebound hyperglycemia leads to more severe polydipsia and polyuria which causes the owner or veterinarian to increase the insulin still further. This phenomenon of insulin induced hyperglycemia has recently been described in the dog and cat. This problem also, can only be accurately diagnosed by determining a serial blood glucose curve on the cat and determining if and when inappropriately low blood glucose values develop. Correction of the Samogyi reaction is accomplished by reducing the insulin dosage by 30 to 50% if the duration is adequate but the glucose nadir is too low. If the glucose nadir is too low and duration of action too short, twice daily insulin injections are coupled with a decreased dosage. Another alternative is to switch to longer acting preparations i.e., changing from once daily Lente or NPH to once daily Ultralente, many of these cats will require BID Ultralente for good glycemic control.

True insulin resistance (over 2.0 units/kg/day or > 6 to 8 units/injection) does occur in cats (Table-3). Factors that should be looked for include infection anywhere in the body (abscesses, pyelonephritis, pyoderma, etc.), administration of diabetogenic drugs (glucocorticoids or progesterone), development of diestrus or pregnancy in intact females, hyperthyroidism, or the cat may have hyperadrenocorticism or a growth hormone secreting tumor of the pituitary. Anti-insulin antibodies have not been documented to be a problem in cats. If insulin resistance is documented and another cause cannot be found, a switch to pure beef insulins should help, as it is very similar to feline insulin.

Another uncommon complication is development of insulin shock. I have seen several "well regulated" feline diabetics present in severe insulin shock. In some cases, the owner was not checking the cats urine or having blood glucose concentrations monitored at a veterinarians and continued to give insulin injections. They may have been increasing insulin dosages based on urine sugar values or PU/PD. In some cases the cat ceased to eat its expected caloric intake yet standard daily dosages of insulin were continued. The hypoglycemic attacks are often profound and may persist for 2 to 3 days in spite of continuous intravenous glucose supplementation. Once these cats become hyperglycemic again, we usually re-regulate them using Ultralente insulin and thus tend to avoid mid-morning hypoglycemia and late day hyperglycemia. If none of the above problems can be identified as a cause for PU/PD, these cats must be evaluated for development of unrelated polydipsic-polyuria syndromes like renal failure of hyperthyroidism.

Table 1: Available oral and parenteral sources of phosphorus

Preparations	Phosphate mmol/ml	Dose
Oral		
Whole cow's milk	0.029	0.5-2 mmol/kg/day
Phospho-soda*	4.15	0.5-2 mmol/kg/day
Parenteral		
Sodium phosphate**	3.0	0.06-0.18 mmol/kg given over 6 hrs
Potassium phosphate**	3.0	0.06-0.18 mmol/kg given over 6 hrs

* Fleet Co. Inc. Lynchburg, VA 24505, ** Abbott Laboratories, North Chicago,IL 60064

Table - 2 Fiber and Digestible complex carbohydrate content of some commercially available high-fiber diets for cats

	Crude Fiber	Digestible complex carbohydrates
Prescription diet r/d		
Canned	28	24
Dry	19	30
Prescription diet w/d		
Canned	12	22
Dry	10	37
Science diet maintenance		
Light		
Canned	7	25
Dry	7	39
Iams less active-dry	2	41

Table -3 Causes for perceived "insulin "Resistance" in cats (greater than 6-8 units/injection). From Nelson & Feldman, CVT XI pp364-367

Problems in insulin administration
Inactive or outdated insulin
Post-Somogyi reaction (insulin induced hyperglycemia)
Diestrus or pregnancy
Hyperadrenocorticism
Acromegaly
Infection
Administration of diabetogenic drugs
Glucocorticoids
Megestrol acetate
Poor insulin absorption (esp. Ultralente)
Anti-insulin antibodies (?)