

THE EFFECT OF ACUTE STAPHYLOCOCCAL ALPHA-TOXIN
PANCREATITIS ON THE GLUCOSE TOLERANCE)
OF DOGS

by

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INTRODUCTION

Pancreatitis and diabetes mellitus commonly occur as two separate disease entities in dogs. However, pancreatitis is the main predisposing cause of diabetes mellitus. Diabetes may develop during the first episode of pancreatitis, or it may occur weeks or months after a recurrent episode. Pancreatitis damages both acinar and endocrine pancreatic tissue. It has been suggested that glucose tolerance is impaired during pancreatitis. Little work has been done in dogs concerning glucose tolerance during pancreatitis. Greve and Anderson (58) studied experimental pancreatitis with diabetes mellitus in dogs. Using the high-dose intravenous glucose tolerance test (H-IVGTT), they found that the glucose tolerance was markedly decreased after the induction of pancreatitis in dogs that were predisposed to diabetes by pre-treatment with diabetogenic hormones. The main objective of this study is to determine whether experimental acute pancreatitis reduces the glucose tolerance of dogs that are not pretreated before the induction of pancreatitis.

A practicing veterinarian is usually limited in the amount of time he can spend with an individual patient. For this reason, he might be reluctant to use the H-IVGTT to assess an animal's glucose tolerance. The standard H-IVGTT requires that six timed blood samples be drawn during an hour. If a practitioner were to perform this test, he would have little time for other activities between venipunctures. Therefore, it would be an advantage to the practitioner to decrease the time required to administer the test by decreasing the required number of venipunctures. That is the second objective of this study; i.e., to determine if a k-value calculated using fewer blood samples can closely approximate the k-value calculated using the standard number of samples.

REVIEW OF LITERATURE

Acute Pancreatitis In The Dog

Pritchett (1940) (1) described the clinical signs of acute pancreatitis in a 12-year-old male Fox Terrier. The dog was presented following the sudden onset of vomiting. It had clinical signs of thirst, dehydration, tachycardia, hyperemic oral mucous membranes, abdominal pain, a rigid abdomen with abdominal fluid, tenesmus, and a rectal temperature of 105° F. While the animal was under anesthesia, a disc-shaped mass was palpated in the extreme anterior portion of the abdomen just posterior to the xiphoid cartilage. An abdominal neoplasm was considered because the dog had a history of tumors; therefore, euthanasia was performed. On post-mortem examination, there was a large amount of blood-stained fluid in the abdomen and necrosis throughout the abdominal fat. The mass was an enlarged, firm, red and gray pancreas. The pancreas impinged on the duodenum causing duodenal stenosis. The histopathological diagnosis was acute hemorrhagic pancreatitis. Pritchett assumed that obstruction of the pancreatic duct due to an inflammatory process was the primary etiology of the pancreatitis.

Coffin and Thordal-Christensen (1953) (2) discussed the diagnosis, treatment, and the clinical signs of acute necrotic pancreatitis. Clinical signs consisted of sudden onset of abdominal pain and vomiting, bloody diarrhea, unwillingness to move, assuming a prayer position, increased heart rate, dehydration, and shallow respirations. A moderate leukocytosis might also be present. The authors attributed the necrotic changes in the pancreas to autodigestion by pancreatic enzymes.

Singleton and Rhodes (1957) (3) presented a case report of acute

pancreatic necrosis in a dog. The animal had a sudden onset of profuse emesis and anorexia. The anterior abdomen was very painful and the dog was quite unwilling to move. The dog died on the 12th day after onset, and necropsy examination revealed congested omentum and peritoneum around the pancreas. The pancreas was approximately three times its normal size. It was quite friable and contained numerous dark areas. The authors felt that either infection entering the gland or bile reflux into the pancreas might have been responsible for the pancreatitis.

Small et al. (1964) (4) made a comprehensive report on canine pancreatic diseases. Signs of acute pancreatitis were as follows: sudden onset of severe epigastric pain, vomiting, blood-tinged diarrhea, shock, and a rectal temperature of 104-105° F. The condition was said to occur most often in dogs of normal weight over 4 years of age. Typical laboratory findings were: PCV of 55-65%, moderate leukocytosis, glycosuria, hyperamylasemia from a few hours after onset lasting for 2-6 days, and an increase in serum lipase beginning several hours after the increase in amylase and remaining elevated from 5-15 days. Treatment consisted of corticosteroids, plasma and plasma expanders calcium lactate, large amounts of antimicrobial agents, meperidine HCl, atropine, and a kallikrein-trypsin inactivator. Three case reports of acute pancreatitis were presented.

Sragner (1965) (5) described a case of acute hemorrhagic pancreatitis associated with duodenal obstruction. The dog had repeated episodes of vomiting, a tense painful distended abdomen, a rectal temperature of 104° F, congested mucous membranes, and a weak, rapid pulse. Surgery was performed to relieve the obstruction, but the dog lived only a short time thereafter. After surgery, the serum amylase increased to 15,000 Somogyi units. Other clinico-pathologic

findings were PCV 58%, WBC 16,500 cells/mm³, BUN 120 mg./dl., and lipemia.

Anderson and Low (1965) (6) presented a comparative summary of 103 cases of canine pancreatic disease. Clinical signs and clinico-pathologic findings were described in detail.

Gage and Anderson (1967) (7) described acute pancreatitis as a disease occurring most frequently in older obese dogs. Clinical signs consisted of sudden onset of vomiting, restlessness, anorexia, polydipsia, anterior abdominal pain, weakness, and shock. Important clinico-pathologic findings were increased serum amylase and lipase, leukocytosis of 15,000-30,000 WBC/mm³, and a fasting hyperlipemia. A case history of a 7-year-old male Manchester Terrier with acute pancreatitis was presented. Treatments included antibiotics, atropine, meperidine HCl, lactated Ringer's solution, and B-complex vitamins.

Brobst (1970) (8) discussed the clinico-pathologic aspects of pancreatitis in dogs. He felt that the release of digestive enzymes into the parenchyma and interstitial tissue was a major cause of necrosis and inflammation in the pancreas.

Anderson and Strafuss (1971) (9) presented a survey of pancreatic disease that occurred in 32 dogs and 3 cats over an 8 year period. Acute or chronic pancreatitis was present in three-fourths of the animals. Of the 11 dogs with acute pancreatitis, 5 had fasting hyperlipemia.

Denny and Lucke (1972) (10) described a case of acute pancreatitis in an 8-year-old obese, spayed female Labrador dog. Clinical signs included frequent emesis, depression, marked abdominal pain, dehydration and rectal temperature of 104° F. Radiographically, a barium study showed delayed passage

of contrast medium through the duodenum and ventral displacement of the duodenum. A diagnosis of acute pancreatitis was made on the basis of clinical signs, radiographic findings, and a high serum amylase value. The dog deteriorated in condition under medical treatment; therefore, an exploratory laparotomy was performed. The affected portion of the pancreas was removed and the dog was fully recovered on the 12th day after admission to the clinic.

Anderson (1972) (11) wrote in detail about the clinical history, physical findings, clinico-pathologic findings, diagnosis, treatment, and prognosis of acute pancreatitis in animals. Serum amylase three times the upper limit of normal and serum lipase greater than one unit per milliliter were considered characteristic of pancreatitis.

Wolf and Gostlin (1973) (12) presented the case of a 10-week-old female mixed breed dog that suddenly began vomiting while being boarded. The animal went into shock within a short time after the onset of emesis. She was then treated with antihistamine, prednisone, and 5% dextrose solution. The dog responded to treatment, but relapsed the next morning and died. On necropsy examination the only pathologic lesion evident was a reddened pancreas. Histological diagnosis was hemorrhagic pancreatitis.

Fellenbaum (1974) (13) described the case of an obese, spayed 6-year-old Schnauzer that was admitted to his clinic for persistent vomiting of three days duration, polydipsia, anorexia, and lethargy. The dog had a temperature of 102° F., moderate dehydration, and abdominal pain. Abdominal radiographs showed a well-demarcated mass in the anterior abdomen. An exploratory laparotomy revealed an inflamed pancreas and a greatly distended gall bladder. Surgical correction consisting of gastrojejunostomy and cholecystogastrostomy

relieved the condition and the dog continued to recovery. The pancreas was not resected.

Spontaneous Diabetes Mellitus Associated

With Pancreatitis In The Dog

Bloom and Handelsman (1937) (14) reported one case of diabetes mellitus and pancreatitis in a dog. They indicated that acute inflammation and necrosis of the peripancreatic fatty tissue and subacute pancreatitis might have been a complicating factor in the development of diabetes mellitus in the dog.

Milks and Stephenson (1937) (15) presented several case histories of dogs with diabetes mellitus. One case had necrotic pancreatitis and two others had a history of digestive upsets. Because of this, the authors implicated pancreatitis as a probable cause of pancreatic atrophy and diabetes mellitus.

Coffin and Thordal-Christensen (1953) (2) stated that many cases of acute pancreatitis that persist for several days will develop increased blood glucose, glycosuria, and polyuria "... due to destruction of the islet-cell tissue." They also noted that some cases of acute necrotic pancreatitis are often followed by diabetes mellitus a few weeks later.

Meier (1960) (16) indicated that, in dogs, diabetes mellitus probably occurs more often as a sequel to recurrent attacks of pancreatitis than as a result of primary malfunction of islet tissue.

Dixon and Sanford (1961) (17) described fourteen cases of diabetes mellitus in dogs. Two of those dogs also had subacute suppurative pancreatitis and another had chronic pancreatitis.

Small et al. (1964) (4) stated that "Ninety percent of the diabetes cases in dogs are associated with or are the result of chronic pancreatitis."

Anderson and Low (1965) (6) in a study of pancreatic diseases in the dog, reported that 70% of the dogs having diabetes mellitus previously had inflammation of the pancreatic acinar tissue. They concluded that "...diabetes mellitus in the dog is often a complication of acute or chronic pancreatitis and less frequently is a primary pathologic change of the islet tissue."

Perman and Stevens (1969) (18) felt that diabetes mellitus associated with beta cell destruction was frequently a result of repeated attacks of pancreatitis.

Anderson and Strafuss (1969) (9) in reviewing cases of pancreatic disease in dogs, found that 7 of 14 dogs with chronic pancreatitis were also diabetic.

de Lahunta et al. (1971) (19) discussed a 7-year-old male Beagle that had a history of anorexia, polydipsia, urinary incontinence, and emesis for 7 days. In the 24 hours preceding the examination, the dog had vomited continually. The animal was depressed, moderately dehydrated and had a fruity odor to his breath. There was no pain on palpation of the abdomen. The white blood cell count was 19,650 cells/mm³, and the blood glucose was 750 mg%. The dog died shortly after treatment was initiated. On necropsy examination, the pancreas was hard, nodular, and was about 0.16 normal size. Histologically, there was fibrosis and necrosis. Recurrent attacks of acute pancreatitis was suggested as the cause of the lesion.

Cotten and Cornelius (1971) (20) presented the necropsy findings of ten diabetic dogs that had concurrent disease. Seven dogs had pancreatitis, two

had hepatitis, and one had nephritis occurring with the diabetes.

Anderson (1972) (11) stated that blood and urine glucose should probably be determined in animals suspected of having acute pancreatitis because "...some dogs become transiently or permanently diabetic in conjunction with acute pancreatitis."

Greve et al. (1972) (21) successfully produced experimental acute pancreatitis with coexistent diabetes mellitus in 8 dogs.

Methods Of Producing Experimental

Pancreatitis In Dogs

Pfeffer et al. (1957) (22) used a closed duodenal loop obstruction with the bile duct ligated to produce acute hemorrhagic pancreatitis in dogs. They felt that congestion and occlusion of small blood vessels was the major contributing factor in the production of the pancreatitis.

Williams and Bryne (1968) (23) used the Pfeffer preparation to show that duodenal reflux with bile excluded could produce severe hemorrhagic pancreatitis in 67% of the experimental dogs studied.

Schapiro et al. (1973) (24) effectively induced acute hemorrhagic pancreatitis in dogs using the closed duodenal loop technique. They found that bile was not necessary to produce the disease, but its presence altered the appearance of the pancreatitis. The addition of bile to the loop contents caused an earlier disruption of the acinar tissue.

Papp et al. (1969) (25) and Herva (1970) (26) injected bile into the pancreatic duct system by cannulating the main pancreatic duct, and produced

acute hemorrhagic pancreatitis.

Sum et al. (1979) (27) cannulated the main pancreatic duct as it entered the duodenum and injected bile, bile salts, anionic detergent, trypsin, cationic detergent, a mixture of anionic and cationic detergents, and saline. The morphological appearance of the trypsin induced pancreatitis, (irregular areas of necrosis and hemorrhage), was different from the punched out areas of coagulation necrosis produced by the other substances. The injection of saline produced no abnormal changes.

Gjone et al. (1967) (28) produced experimental acute pancreatitis in dogs by injecting, under mild pressure, a mixture of sodium taurocholate and trypsin into the main pancreatic duct after the minor duct was ligated.

Geokas (1968) (29) was able to induce acute hemorrhagic pancreatitis by injecting pancreatic elastase into the pancreatic ductal system. He felt that pancreatic elastase played a major role in the production of vascular injury that occurred during acute pancreatitis.

Brobst et al. (1970) (30) produced experimental pancreatitis in three dogs by injecting 0.5 ml of carbon tetrachloride six times into the pancreatic parenchyma at six different sites. In one dog, the duodenum was opened and 4 ml of duodenal chyme was injected into the cannulated main pancreatic duct. In two other dogs varying amounts of duodenal chyme and trypsin were injected into the main duct.

Bliss and Sibley (1969) (31) injected a small amount of E. coli bacterial filtrate into the main pancreatic duct and then ligated it. 24 hours later E. coli filtrate was injected intravenously and the Shwartzman phenomenon

occurred in the pancreas producing acute hemorrhagic pancreatitis.

Thal and Brackney (1954) (32) used a 1:40 dilution of staphylococcal toxin to produce acute hemorrhagic pancreatitis in dogs by injecting it intra-ductally.

Greve et al. (1973) (21) studied experimental pancreatitis with coexistent diabetes mellitus in dogs. They induced the prediabetic state with a regimen of 50% partial pancreatectomy followed by treatment with bovine growth hormone and dexamethasone. Acute pancreatitis was then induced by injecting staphylococcal alpha-toxin into the ventral pancreatic duct. A cannula was introduced into the duct through a small incision. After the injection of toxin, the duct was ligated.

Partial Pancreatectomy In The Dog

Leveen et al (1969) (33) produced diabetes mellitus in dogs by removing the duodenal portion of the pancreas leaving only 10-15% of the splenic end.

Denny and Lucke (1962) (34) performed a partial pancreatectomy in a dog that had pancreatitis. The left lobe was affected while the rest of the pancreas appeared to be normal. The pancreas was ligated with chromic catgut ligatures at the junction of the necrotic and normal parts.

Dingwall and McDonell (1972) (35) presented indications for partial pancreatectomy in the dog. They also reviewed the anatomy of the pancreas and its various duct systems and described the procedure for removing a portion of the right pancreatic lobe. The serosa of the pancreas was gently torn with forceps along the line of division. The parenchyma was separated by inserting closed forceps between lobules and allowing the forceps to spring open. When

the main duct of the lobe was isolated, it was ligated with 00 silk suture and then transected. The resected portion of the pancreas was then removed from the mesentery. The mesenteric tear was sutured with interrupted absorbable sutures.

Greve et al. (1973) (21) used partial pancreatectomy and hormonal treatment to make dogs more susceptible to diabetes mellitus. They performed a 50% partial pancreatectomy in which half of each lobe was removed and the duodenal segment and all ducts were left intact.

Sum et al. (1974) (36) used partial pancreatectomies in dogs to find out what percentage of the pancreas must be removed to produce an altered glucose tolerance. The glucose tolerance test administered was the 1 gm./kg.^{0.7} IVGTT. In their study, equal sized portions were removed from each lobe. Changes in glucose tolerance were not observed until the dogs had less than 50% of the pancreas remaining.

The Oral Glucose Tolerance Test In Humans

Meyers and McKean (1935) (37) reviewed the literature concerning the 50-100 gm. glucose tolerance test. A blood glucose above 120 mg./dl. at two hours post-ingestion of the glucose load was considered to be diagnostic of diabetes mellitus. An abnormally high peak in blood glucose or a delayed fall was indicative of a borderline diabetic curve. After evaluating the literature they concluded that the oral glucose tolerance test (OGTT) was an unreliable aid in the diagnosis of diabetes mellitus and was of questionable value in the diagnosis of other conditions.

Mosenthal and Barry (1950) (38) studied the 100 gm. oral glucose

tolerance test and considered it to be the best method at that time for determining the existence of diabetes mellitus in patients. In an attempt to standardize the OGTT, they set the upper limit of the blood glucose at 150 mg./dl. for the first hour and at 100 mg./dl. for the second hour after the start of the test.

Duncan (1951) (39) described the preparation and method for performing the OGTT using 100 gm. glucose as the loading dose. He also discussed the interpretation and evaluation of results using the fasting and two-hour blood glucose values. A person was considered diabetic if the fasting blood glucose was greater than 120 mg./dl. and the two-hour blood glucose was greater than 130 mg./dl. The test could be simplified by using only one blood sample drawn at the second hour. Duncan considered the OGTT a diagnostic aid in determining whether or not a person was diabetic.

Unger (1957) (40) tested 152 normal individuals with the 100 gm. OGTT. 54.6% had two hour blood glucose values greater than 100 mg./dl. which was the standard proposed by Mosenthal and Barry. Both the one and two-hour criterias were exceeded in 26.3% of the cases. In repeated glucose tolerance tests of some of the subjects, only 75.5% of the results were reproducible. He concluded that variations in the two-hour OGTT were not unusual and that a small elevation of the second hour glucose sample was not diagnostic of diabetes mellitus.

The Committee on Statistics of the American Diabetes Association (1969) (41) published a report on the standardization of the OGTT. The report provided recommendations for preparation of the patient, dosage of glucose and proper administration of the test, for processing of the blood samples, and for interpretation of the test results. The recommended glucose load was 40 gm.

per square meter of body surface. Blood samples should be drawn at times 0, 60, 120, and 180 minutes. Several methods for evaluation and interpretation were discussed. One was the Fajans-Conn method in which plasma glucose values of 185 mg./dl. at 1 hour, 165 mg./dl. at $1\frac{1}{2}$ hours, and 140 mg./dl. at 2 hours was considered diagnostic for diabetes mellitus.

Olefsky and Reaven (1974) (42) compared the results of two identical oral glucose tolerance tests administered 48 hours apart to 31 adult subjects. The plasma glucose response to repeated glucose tolerance tests was significantly variable within an individual. Because of that, it was stressed that the diagnosis of diabetes mellitus based on one abnormal OGTT might be questionable.

The Cortisone Glucose Tolerance Test In Humans

Fajans and Conn (1954) (43) first described the procedure for performing and evaluating the cortisone glucose tolerance test (CGTT). $8\frac{1}{2}$ and 2 hours prior to performing the standard oral glucose tolerance test using 1.75 gm. glucose/kg., the subjects were given two doses of cortisone acetate orally. Each dose was 50 mg. unless the patient weighed more than 160 lbs., in which case each dose was 62.5 mg. A diagnosis of diabetes was made when the 1 hr. blood glucose value was greater than 160 mg./dl. and the 2 hr. value was between 110 and 120 mg./dl. The CGTT was administered to 75 nondiabetic relatives of diabetics and to 37 individuals with no diabetic relatives (controls). 24% of the nondiabetic relatives of diabetics had a positive (diabetic) response to the test, while only 3% of the controls had a positive response. The results of previous standard oral glucose tolerance tests on the same individuals showed that 19% of the nondiabetic relatives of diabetics had diabetic glucose tolerance curves. Only one out of 50 controls exhibited a

diabetic glucose tolerance curve. The authors felt that the cortisone glucose tolerance test could possibly be a useful tool in determining which persons may be predisposed to diabetes.

Lambert et al. (1961) (14) compared the standard OGTT and the CGTT in 150 individuals. A positive response was considered to be as follows: a 1 hr. blood glucose greater than 225 mg./dl., a 1.5 hr. blood glucose greater than 195 mg./dl. and a 2 hr. blood glucose greater than 170 mg./dl. They summarized their results stating that the cortisone glucose tolerance test might not always be specific in detecting susceptibility to diabetes in those persons with diabetic relatives.

Fajans (1963) (45) defined a positive response to the CGTT as one in which the 1 hr. glucose value was greater than or equal to 160 mg./dl., and the 1.5 hr. glucose value was greater than or equal to 150 mg./dl., and the 2 hr. glucose value was greater than or equal to 140 mg./dl. These criteria applied to otherwise healthy individuals under 45 years of age. He said the test was still a research procedure that was more sensitive than the standard OGTT in detecting the prediabetic state and diminished functional beta cell reserve, and that it might be helpful in patients with borderline results of the standard OGTT. He also stated that a positive response to the test could be indicative of subclinical diabetes in persons closely related to diabetics.

Taton et al. (1964) (46) evaluated the sensitivity of the OGTT, the CGTT, and the intravenous glucose tolerance test (IVGTT) in normal individuals with no diabetic relatives. They concluded that the CGTT had no advantage over the OGTT in the detection of the prediabetic state. They also felt that the OGTT was more sensitive than the IVGTT.

Pozefsky et al. (1965) (47) studied the effect of age on the results of the CGTT. No significant differences in glucose values were noted during the first hour in subjects who had no familial history of diabetes, but during the second hour, glucose tolerance decreased progressively as the age of the subjects increased. Because of the influence of age on the glucose tolerance, it was proposed that normal standards for older age groups be made.

Kahn et al. (1969) (48) evaluated the sensitivity of the OGTT, CGTT, IVGTT, and the intravenous tolbutamide test in diagnosing diabetes or prediabetes in offspring of diabetic parents. They found the OGTT to be as sensitive as any other test in detecting abnormal glucose tolerance and that the CGTT was no more sensitive than the OGTT.

Rull et al. (1970) (49) determined plasma insulin values during the standard OGTT and the CGTT performed on nondiabetic patients who were closely related to diabetics. These patients had normal results on the OGTT. The results of the CGTT did distinguish the group with positive tests (subclinical diabetes) from those with negative CGTT's. In the group with positive CGTT's, the release of insulin was delayed and also lower than that of the patients with negative cortisone glucose tolerance tests. The authors concluded "...that during the cortisone glucose tolerance test, 'nondiabetic' relatives of diabetic patients who have positive tests (subclinical diabetes) exhibit a defect in the secretion of insulin which distinguishes them from subjects with negative tests."

The Intravenous Glucose Tolerance Test In Humans

Amatuzio et al. (1953) (50) performed the intravenous glucose tolerance test, (IVGTT), in normal humans and in some individuals with mild diabetes

mellitus. They described analytical and graphic methods for the calculation of the k-value, (the disappearance rate of glucose from the blood measured in percent decrease of glucose per minute). By determining the k-value, they could ascertain a difference in the glucose tolerance of normal individuals and of those with mild diabetes. They found that the rate of removal of glucose from the blood was constant in repeated tests, and also that the same results could be obtained using doses of 25 and 35 gms. of glucose. The significance of the k-values was as follows: normal--3.0-4.84, mild diabetes--0.93-2.46, severe diabetes--0.23-1.64.

Ikkos and Luft (1957) (51) used the IVGTT to study the glucose tolerance in humans and found the disappearance rate of glucose from the blood to be delayed in diabetics as compared to that of normal individuals. They agreed that the calculation of the k-value was an appropriate method for the evaluation of the IVGTT.

Lundbaek (1962) (52) advocated the use of the intravenous glucose tolerance test to diagnose diabetes mellitus on the basis of the k-value. He described in detail the method of calculating the k-value. A k-value less than 0.95 was diagnostic of diabetes mellitus while a k-value greater than 1.05 was considered normal. Lundbaek called the region between 0.95 and 1.05 an overlapping region. Individuals with k-values in this area would be observed and followed with repeated tests. The author felt that there was a rough correlation between the k-value and the degree of the severity of the diabetes.

Moorhouse et al. (1963) (53) studied the effect of varying glucose dosages on the k-value in normal and diabetic people. Variations in the dosage were from 0.25-3.0 gm./kg.^{0.7} given in a 25% solution over a four minute period.

The k-value increased progressively as the dose of glucose was increased in normal subjects, but in severely diabetic individuals, the k-value was low at all dosages. In mildly diabetic subjects, there was only a slight increase in the k-value with increased dosages of glucose. When the glucose dose was 20-30 gm., (the standard dose usually administered in the IVGTT), there was a significant overlap in the k-values of the normal and the mildly diabetic subjects. The higher doses of glucose distinctly separated the two groups. It was concluded that the IVGTT was a good indicator of abnormal carbohydrate metabolism when an adequate amount of glucose was used. They stated that the amount of insulin released in response to the glucose given was reflected in the k-value.

Moorhouse et al. (1964) (54) using a dosage of 1.0 gm./kg.^{0.7} of glucose in performing intravenous glucose tolerance tests confirmed that the logarithm of the venous blood glucose declined linearly with time. The k-value and the fasting blood glucose concentrations were inversely related in the moderately and severely diabetic individuals. This was believed to be due to insufficient amounts of insulin released in response to the glucose infusion. The normal subjects had higher k-values than the diabetics. In men, the k-values ranged as follows: normal males, 1.0-1.94, diabetics with fasting blood glucose less than 130 mg./dl., 0.43-0.83, diabetics with fasting blood glucose between 130-200 mg./dl., 0.28-0.50, and diabetics with fasting blood glucose greater than 200 mg./dl., 0.12-0.24.

Crockford et al. (1966) (55) studied the influence of age on the glucose tolerance using the IVGTT and found that glucose tolerance decreased with increasing age.

Butterfield et al. (1971) (56) criticized the 25-gm. intravenous glucose tolerance test because of significant overlap in the k-values of normal subjects and mildly diabetic subjects. They believed that the k-value was not a good indicator of overall peripheral glucose utilization.

Dyck and Moorhouse (1966) (57) introduced the high-dose intravenous glucose tolerance test (H-IVGTT). Their results suggested that the H-IVGTT was a more sensitive indicator of abnormal carbohydrate metabolism than the oral glucose tolerance test, but less sensitive than the cortisone glucose tolerance test. In the H-IVGTT, a 25% solution of glucose at a dosage of 50 gm./1.73 m² was administered intravenously over 4-6 minutes. The authors recognized that the conventional 25-gm. IVGTT produced considerable overlap in the k-values of normal and mildly diabetic patients. This insensitivity was stated to be due to a too-low dose of glucose. The H-IVGTT yielded k-values of normals and prediabetics that were separable into two distinct groups with little overlap.

Glucose Tolerance Tests In Canine,

Feline, And Porcine

Bloom and Handelsman (1937) (14) performed an oral glucose tolerance test on two diabetic dogs using 50 gm. glucose administered by stomach tube. They considered the results to definitely establish the diagnosis of diabetes mellitus.

Kaneko (1970) (58) described the oral and the intravenous glucose tolerance test for use in dogs. It was suggested that animals be placed on a high carbohydrate diet 3-5 days before the glucose tolerance test to avoid any decrease in glucose tolerance that may occur in animals on a low carbohydrate diet. For the oral glucose tolerance test, a dosage of 4 gms. glucose/kg. body

weight was recommended. The maximum glucose value, (120-140 mg./dl.), should be reached at the end of 1 hour. In normal dogs, the glucose should return to the fasting value by 2-3 hours. The oral glucose tolerance test may be affected by gastric emptying time, increased intestinal motility, or any other condition affecting small intestinal absorption. These disadvantages can be by-passed with the intravenous glucose tolerance test. Kaneko outlined the procedure for the IVGTT using 0.5 gm. glucose/kg. of a 50% solution injected over a 3-5 minute period. Blood samples should be drawn before the injection of glucose and at 30 minute intervals for 3 hours from the start of the injection. He considered the most important finding to be a normal glucose value by 60-90 minutes. An elevation in blood glucose at that time was indicative of diabetes. He also mentioned that the half-time of the disappearance rate of the injected glucose during the 1st hour could be calculated if the blood samples were drawn at 15 minute intervals. This could be used as a quantitative measure of the glucose utilization rate.

Hill and Kidder (1972) (59) using the oral glucose tolerance test found that dogs with pancreatic insufficiency had decreased glucose tolerance when compared with the glucose tolerance of normal dogs. The dosage of glucose used was 2 gm./kg. body weight of a 12.5% glucose solution. It was mentioned that with increased glucose concentration, the rate of glucose entering the small intestine was decreased.

Greve and Anderson (1973) (60) studied the high-dose intravenous glucose tolerance test, (H-IVGTT), in normal, prediabetic, and overt diabetic dogs and in dogs with juvenile pancreatic atrophy. They described, in detail, the procedure for the H-IVGTT using 1 gm. glucose/kg. body weight. They also discussed the calculation and the significance of the k-value, (the glucose

disappearance coefficient). The guidelines set for interpretation of the k-value were as follows: k greater than 2% = normal glucose tolerance, k between 1.9 and 1.1% = prediabetes, and k less than 1.0% = overt diabetes. The dogs with juvenile pancreatic atrophy were included in the prediabetic group. The authors found little overlap between the k-value of normals and pre-diabetics and no overlap between those two groups and the overt diabetic group.

Sun et al. (1974) (36) used the intravenous glucose tolerance test with a glucose dosage of 1 gm./kg.^{0.7} to study the effects of partial pancreatectomy on glucose tolerance. They found the glucose tolerance to be relatively normal until less than 50% of the pancreas remained.

Very little has been published concerning glucose tolerance in cats. Finn, Martin, and Manns (1970) (61) performed the intravenous glucose tolerance test using 0.5 gm. glucose/lb. body weight on five conscious normal cats and on one conscious diabetic cat with islet cell hyalinosi. They also performed the IVGTT on three normal cats anesthetized with sodium pentobarbital. The average value for the 0 minute sample in normal cats was 53 mg./dl. At the end of 60 minutes, the average value was 294 mg./dl., and 170 mg./dl. at 90 minutes. At 180 minutes, the average glucose value for the normal cats was 86 mg./dl. In contrast, the diabetic cat had a fasting glucose value of 239 mg./dl., a 60 minute value of 369 mg./dl., and a 90 minute value of 333 mg./dl.

There have been several glucose tolerance studies performed on swine. Hanawalt et al. (1947) (62) described the procedure for the 1 gm./kg. intravenous glucose tolerance test in weanling pigs. They concluded that the glucose tolerance of pigs was very similar to that of normal humans. In some cases, the blood glucose fell below fasting value at 2 hours and then

subsequently increased.

Curtis et al. (1962) (63) used the 1 gm. glucose/kg. intravenous glucose tolerance test to study glucose tolerance in newborn pigs. Blood samples were drawn at 0.5, 1.0, 1.5, 2.0, and 3.0 hours. Their results suggested that newborn pigs have a decreased ability to regulate carbohydrate metabolism as compared with older swine.

Meyer et al. (1962) (64) performed the intravenous glucose tolerance test in adult swine using 0.75 gm. glucose/kg. in a 50% solution. Blood samples were drawn at 0, 15, 30, 60, and 120 minutes. Based on the results, the authors divided the pigs into two groups. The first group had an average blood glucose of 250 mg./dl. at 15 minutes and a blood glucose value below the original value at 60 minutes. The second group had an average blood glucose of 300-350 mg./dl. at 15 minutes. It took at least 120 minutes for the glucose value to return to the original value.

Anderson and Elsley (1970) (65) described the method for performing the 50 gm. intravenous glucose tolerance test in adult sows. After the injection of glucose, the blood glucose concentration declined to the fasting concentration within 18-45 minutes. In all of the animals, the blood glucose fell below the fasting value by as much as 5 mg./dl. This was followed by a rise in blood glucose concentration above the fasting value by 10 mg./dl. When the logarithm of the blood glucose concentration was plotted against time, a straight line resulted but no attempt was made to calculate the k-values. Repeat tests were made in four animals 48 hours later. The time needed for the blood glucose concentration to return to the fasting value was the most repeatable characteristic of the test.

Reed and Kidder (1971) (66) performed the oral glucose tolerance test in young pigs using a dosage of 1.5 gm. glucose/kg. of a 20% glucose solution. They found the tolerance curves to be similar to those of man and dogs. A 50% glucose solution produced variable results showing that the higher concentration of glucose was undesirable for use in the oral glucose tolerance test. The 50% solution appeared to decrease gastric emptying time and also irritated the upper duodenum.

MATERIALS AND METHODS

I. Experimental Animals

Thirty adult mongrel dogs weighing 7.7-20.0 kg. were divided into three groups as follows:

- (a) Group 1 - nonsurgical controls
- (b) Group 2 - surgical controls in which 0.1 ml./kg. of saline was infused into the ventral pancreatic duct
- (c) Group 3 - dogs in which 0.1 ml./kg. of a 1:3 dilution of staphylococcal alpha-toxin¹ was infused into the ventral pancreatic duct system.

II. Diet

The dogs were fed a commercial ration² once daily and were given water ad libidum. They were fasted 12-24 hours before surgery and before the high-dose intravenous glucose tolerance tests were performed. Both food and water were withheld after surgery until the animals were able to drink and eat without vomiting.

III. Necropsy

All dogs were studied from day 1 through day 9. They were euthanatized and necropsied at the end of that time. During the necropsies, the abdomens were evaluated for the presence of fluid, peritonitis, and adhesions. The liver, gall bladder, kidneys, gastrointestinal tract and pancreas of each

¹Alpha-toxin, Courtesy R. K. Lindorfer Ph.D., Professor, Veterinary Microbiology, College of Veterinary Medicine, University of Minnesota, St. Paul, Minn.

²Kennel Ration^R, Quaker Oats Co., Chicago, Ill.

animal were examined. Each pancreas was described according to its firmness, color, size, and presence of abscesses and hematomas. The pancreatic tissue specimens from all dogs were fixed in 10% buffered neutral formalin, sectioned at 6 microns and stained with hematoxylin and eosin for histologic examination.

IV. Physical Status

The physical status of each dog was evaluated daily, in terms of alertness and activity, heart rate, respiration rate, rectal temperature, appetite, urination, and character of feces. When the abdomen was palpated to ascertain tenderness, an attempt was also made to palpate the pancreas.

V. High-dose Intravenous Glucose Tolerance Test (H-IVGTT)

The H-IVGTT used was modified after that used by Dyck and Moorhouse (57). It was performed on days 1, 6, (the day following surgery), and on day 9. The dosage of glucose was 1 gm. glucose/kg., (2 ml./kg. 50% dextrose).¹ The dose of glucose was injected over a 30 second period into a cephalic vein. That vein was not used again the same day. All blood samples were drawn from the jugular vein using EDTA as an anticoagulant. Samples were drawn at times 0, 5, 10, 15, 30, 45, and 60 minutes.

VI. Blood Chemistries

Clotted blood samples were drawn for blood chemistries on the same days that the glucose tolerance tests were performed. The following blood chemistries were determined:

- (a) Amylase after Cunningham and Moore (67)
- (b) Lipase after Cherry and Crandall (68)

¹Glucose Solution (Dextrose 50%), Haver-Lockhart Laboratories, Shawnee, Ks.

- (c) SGPT¹ modified after Reitman and Frankel (69)
- (d) Alkaline Phosphatase² modified after Kind and King (70)
- (e) Gamma Glutamyl Transpeptidase after Sigma Bulletin 415 (71)
- (f) Creatinine modified after Henry (72)
- (g) Glucose after Hyvarinen and Nikkila (73)

VII. Surgical Procedure

The surgical procedure was performed on day 5. A 50% partial pancreatectomy was done followed by the intraductal infusion of either 0.1 ml./kg. saline (group 2) or of 0.1 ml./kg. of a 1:3 dilution of staphylococcal alpha-toxin (group 3) into the ventral pancreatic duct.

Anesthesia was induced with thiethylal sodium³ to effect and the animal was intubated as soon as the swallowing reflex was abolished. Anesthesia was maintained with methoxyflurane⁴ in a semiclosed system. A slow intravenous drip of lactated Ringer's solution⁵ was administered throughout the surgical procedure. With the animal in dorsal recumbency, the abdomen was clipped and scrubbed with a surgical soap and then disinfected with an alcohol solution. A shroud was placed over the animal before the midline skin incision was made. It extended from the xiphoid to 3-4 cm. caudal to the umbilicus. Towels were clamped to the skin margins, and the abdomen was opened by a midline incision through the linea alba. After the falciform ligament was removed, the spleen

¹DADER, American Hospital Supply Corporation, Miami, Fla.

²Phosphazyme^R Set, Harleco 64654, Harleco, Philadelphia, Pa.

³Surital^R, Parke-Davis, Detroit, Michigan.

⁴Metofane^R, Pitman-Moore, Fort Washington, Pa.

⁵Travenol Laboratories, Inc., Morton Grove, Ill.

and stomach were brought outside the abdomen and held with moistened sponges. The greater omentum was exteriorized until the left lobe of the pancreas could be seen. Beginning at the distal end, the left lobe was separated from the omentum by tearing the omentum away from the pancreas with mosquito forceps. The vessels were ligated with 000 medium chromic gut¹ leaving the splenic vessels intact. Rarely, it was necessary to leave a small amount of pancreas connected to the splenic vein. The pancreas was clamped and ligated with 000 medium chromic gut at the pancreatic angle. The stomach and duodenum were then returned to their normal positions in the abdomen.

The descending duodenum was exteriorized along with the right lobe of the pancreas attached to the mesoduodenum. In most dogs, $1/3$ to $1/8$ of the distal portion of the right lobe passed directly over the caudal pancreaticoduodenal vessels. The pancreatic branches were carefully ligated and transected so that the pancreatic tissue could be bluntly dissected away from the main vessels with hemostats. Care was taken not to ligate the major vessels in order to avoid ischemia and necrosis of the duodenum. If necessary, small amounts of pancreatic tissue were left attached to the vessels. The rest of the right lobe, in many instances, could be carefully wiped free of the mesentery with a damp sponge leaving the mesoduodenum intact. In a few instances where the pancreatic tissue did not contact the duodenal branches of the caudal pancreaticoduodenal vessels, the pancreatic branches were simply ligated and transected making it easier to wipe the pancreas free from the mesoduodenum. The pancreas was then clamped and ligated with 000 medium chromic gut near its junction with the duodenum. Any tears in the mesoduodenum were closed with sutures.

¹000 chromic Ethicon^R, Ethicon Inc., Sommerville, New Jersey.

The next procedure was to cannulate the pancreatic duct. The ventral pancreatic duct was palpated where it entered the duodenum. A transverse incision was made in the duodenum directly opposite the ventral papilla. Gauze pledgets were inserted into the lumen of the duodenum on either side of the papilla to prevent intestinal juices from flowing over the papilla. The duct of the remnant of the left lobe was then catheterized with polyethylene tubing¹. The catheter was inserted as far as possible in each case. At that point, an appropriate volume of either diluted alpha-toxin or physiologic saline was infused into the duct system at a slow rate while the catheter was slowly withdrawn. The infusion was completed before the tip of the catheter was removed from the duct. No attempt was made to close the duct and, in a few cases, a small amount of toxin refluxed into the duodenum. The gauze pledgets were removed and the duodenotomy incision was closed with a continuous Cushing suture pattern using 000 chromic gut. The duodenum was then replaced in the abdomen. The linea alba and the peritoneum were closed together with 00 chromic gut² in a continuous suture pattern. The skin was closed with nonabsorbable suture.³

VIII. Treatment

Following surgery, the animals were administered sodium bicarbonate⁴ intravenously added to lactated Ringer's solution. The dogs were treated with lactated Ringer's solution subcutaneously or intravenously until they were able

¹Intramedic^R polyethylene tubing PE 10/S36, Clay-Adams, Inc., New York, N. Y.

²00 chromic Ethicon^R, Ethicon Inc., Sommerville, New Jersey.

³Vetafil^R, S. Jackson, Inc., Washington, D. C.

⁴Mogul Corp., Chagrin Falls, Ohio.

to maintain adequate hydration by drinking water.

IX. Statistical Analysis of the Data

Regression analysis was performed using within-group-day data collected from the glucose tolerance tests. The model used was $\log Y = \alpha + \beta T$ where Y = glucose, α = a constant, β = slope, and T = time. The $\hat{\alpha}$'s, $\hat{\beta}$'s, their standard deviations and the R^2 's are listed in Table 3 on page 36. The k-value is defined as $\beta \times 100$. Regression equations of subsets of the data were used to determine if fewer samples could be used to calculate k-values (simplified k-values) that would consistently approximate the standard k-values. Differences between the standard k-value and the simplified k-values were calculated. The means and standard deviations of those differences were also calculated and are listed in Table 7 on page 47.

The data collected from each of the measured variables, (fasting glucose, amylase, lipase, SGPT, alkaline phosphatase, GGT, and creatinine), and the individual k-values were used in a repeat measure, (split plot), analysis of variance, (ANOVA) (74). The means of the measured variables and the individual k-values of each group were also calculated for each test day. When a significant F-test was noted in the analysis of variance, the means were subjected to a Fisher's least significant difference test, (LSD test). The level of significance was 0.05. The analysis of variance for each of the variables is listed in the Appendix on page 101. The mean k-values are listed in Table 1, page 33, and the result of the LSD test on those means is listed in Table 2, page 35.

RESULTS

Clinical Observations

Group 1 - The rectal temperatures, respiration rates, and heart rates of all dogs in group 1 were within normal limits throughout the entire study. All dogs were alert and active, had good appetites and normal defecation and urination during that period.

Group 2 - The rectal temperatures, respiration rates, heart rates, defecation, and urination of all dogs in group 2 were within normal limits throughout the study. All animals were mildly to moderately depressed the day after surgery (day 6) and three of the ten remained so during the rest of the study. Six of the dogs vomited after recovering from anesthesia on the day of the surgery (day 5). All were eating normally on days 7 and 8. All had painful abdomens on day 6, but by day 9, only one still had abdominal pain. No masses were felt by abdominal palpation.

Group 3 - The rectal temperatures and respiration rates of all dogs in group 3 stayed within normal limits during the study. The average heart rate increased from 114 beats/min. on day 1 to 146 beats/min. on day 6, but then decreased to 89 beats/min. by day 9. All dogs had repeated episodes of emesis on the day of surgery (day 5) after recovering from anesthesia, and on day 6. All animals were moderately depressed on day 6, and three were still depressed on day 9. All had extremely painful abdomens on days 6 and 9. In two of those, a mass was palpated in the right anterior quadrant. Three dogs developed diarrhea, and five had poor appetites after the induction of pancreatitis on day 5.

Neuropsy Findings

Group 1 - No abnormal findings were noted in the abdominal organs of group 1.

Group 2 - Omentum and adjacent loops of intestine were adhered to the pancreas to some extent in all dogs. In one dog, there were adhesions between the pancreas and the right kidney, and in another dog there were adhesions between the liver and pancreas. A small volume of abdominal fluid was present in five of ten dogs. In five dogs, there was a small abscess around the ventral pancreatic duct. Hemorrhage was present at the ligated ends of the pancreas of all animals, and small abscesses were also present in two dogs. The pancreas of all animals were normal in color, slightly increased in size, and slightly firmer than normal.

Group 3 - Between 60-200 ml. of serosanguinous abdominal fluid was present in eight of the ten dogs. In all dogs, the entire remnant of pancreas was firm, friable, enlarged up to three times normal size, and was 50-90% necrotic. The necrotic portions were blackish-red color and the remaining tissue appeared hyperemic. Multiple abscesses varying in diameter from 0.3-1.5 cm. were present in the pancreas of seven dogs. In all dogs, there were extensive adhesions between the intestine, omentum, and the pancreas. Also, there were adhesions between the liver and pancreas in another dog.

Microscopic Observations

Group 1 - There were no lesions in the pancreas of the dogs in group 1.

Group 2 - The pancreatic remnants of group 2 animals generally showed a mild to moderate degree of purulent inflammation.

Group 3 - The pancreatic remnants of group 3 dogs generally exhibited severe inflammatory changes and varying degrees of necrosis.

Laboratory Findings

High-dose Intravenous Glucose Tolerance Test (H-IVGTT)

- (1) Characteristic features of a normal glucose tolerance included a large increase in the blood glucose concentration at 5 minutes after glucose injection, and then a gradual decline to a value somewhat higher than the fasting glucose value at 60 minutes. The blood glucose value of those dogs with impaired glucose tolerance decreased more slowly than that of normal dogs. Therefore, the 60 minute blood glucose values were higher in the abnormal dogs.
- (2) In group 1, the mean 5 minute glucose values ranged from 414 mg./dl., (day 9) to 509 mg./dl. (day 1). The mean 60 minute values ranged from 90 mg./dl. (day 9) to 105 mg./dl. (day 6).
- (3) In group 2, the mean 5 minute blood glucose values ranged from 475 mg./dl. (day 9) to 509 mg./dl. (day 6). The mean 60 minute values ranged from 94 mg./dl. (day 1) to 124 mg./dl. (day 9). The mean 60 minute values increased on each succeeding test day as follows: day 1 - 94 mg./dl., day 6 - 107 mg./dl., and day 9 - 124 mg./dl.
- (4) In group 3, the mean 5 minute blood glucose values ranged from 492 mg./dl. (day 1) to 528 mg./dl. (day 6). The mean 60 minute values increased on each succeeding test day as follows: day 1 - 83 mg./dl., day 6 - 110 mg./dl., and day 9 - 227 mg./dl.

Standard K-Values

- (1) The k-value was used as an indicator of glucose tolerance. The higher the k-value, the more rapidly glucose was removed from the plasma.
- (2) In group 1, there was no significant change in the mean k-value from one day to the next.
- (3) In group 2, there was no significant change from day 1 (3.13) to day 6 (2.91), but there was a significant decrease in the mean k-value on day 9 (2.23) as compared to day 6. The value on day 9 was also significantly lower than that of day 1.
- (4) In group 3, there was a significant decrease in the mean k-value from one day to the next. The mean k-values on the individual days were as follows: day 1, 3.12, day 6, 2.90, and day 9, 1.68.
- (5) On days 1 and 6, there were no significant differences in the mean k-values of the three groups.
- (6) On day 9, there were significant differences among the mean k-values of the three groups. The value of group 2 (2.23) was significantly lower than that of group 1 (2.76), and the value of group 3 (1.68) was significantly lower than that of both groups 1 and 2.

The k-values of each group on all three test days are listed in Table 3, on page 36 along with the corresponding R^2 s. Graphs illustrating the curves obtained when glucose mg./dl. is plotted against time (min.) are shown on pages 37-39, and graphs showing the log glucose (mg./dl.) plotted against time (min.) are presented on pages 40-42. Individual k-values are listed in the appendix on pages 102-105.

Table 1. Mean k-values for the H-IVGTT in dogs. (1: nonsurgical controls;
2: surgical controls; and 3: staphylococcal alpha-toxin).

Group	Day	N	Mean k-value
1	1	10	2.84
1	6	10	2.88
1	9	10	2.76
2	1	10	3.13
2	6	10	2.91
2	9	10	2.23
3	1	10	3.42
3	6	10	2.90
3	9	10	1.68

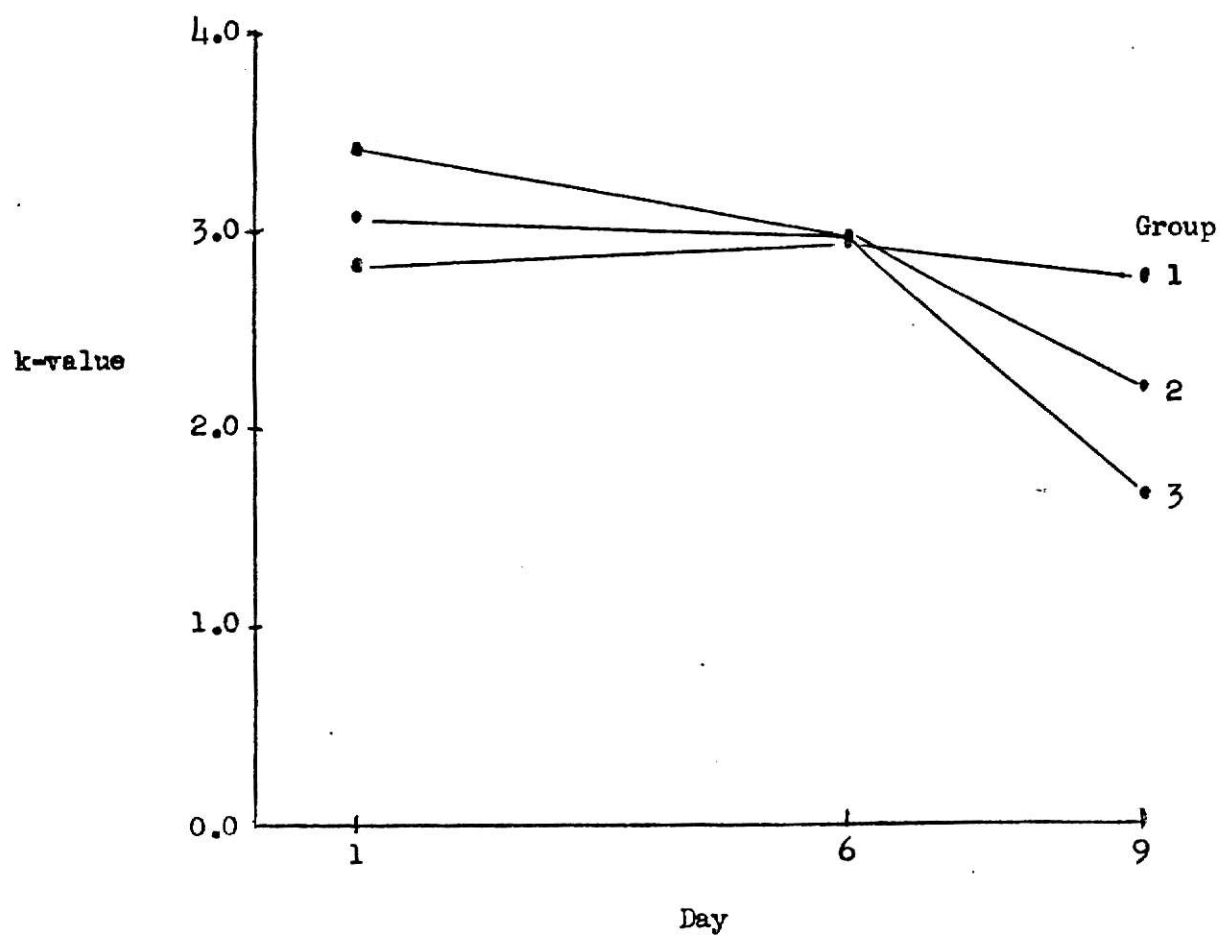


Figure 1. Mean k-values for the H-IVGTT in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Table 2. LSD test of mean k-values* of the H-IVGTT in Dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

		GROUP		
		1	2	3
DAY	1	2.84 a x	3.13 a x	3.42 a x
	6	2.88 a x	2.91 a x	2.90 a y
	9	2.76 a x	2.23 b y	1.68 c z

*Nonsignificant groupings have same letter.

A, b, and c represent differences within days, (across).

X, y, and z represent differences within groups, (down).

Table 3. Regression analysis of the H-IVGTT in dogs. (1: nonsurgical controls; 2: surgical controls; 3: staphylococcal alpha-toxin).

$\log Y = \alpha + \beta T$						
Day	N	$\alpha \pm SD$	$\beta \pm SD$	k (%)	R ²	SS _{log Y}
Group 1						
1	10	6.32 $\pm$.023	-0.0284 $\pm$.0011	2.84	0.92	20.46
6	10	6.23 $\pm$.022	-0.0288 $\pm$.0011	2.88	0.92	21.03
9	10	6.06 $\pm$.029	-0.0277 $\pm$.0014	2.77	0.87	19.69
Group 2						
1	10	6.26 $\pm$.026	-0.0313 $\pm$.0012	3.13	0.91	24.99
6	10	6.30 $\pm$.023	-0.0291 $\pm$.0011	2.91	0.92	21.57
9	10	6.20 $\pm$.029	-0.0223 $\pm$.0014	2.23	0.81	14.41
Group 3						
1	10	6.31 $\pm$.029	-0.0342 $\pm$.0014	3.42	0.91	30.19
6	10	6.30 $\pm$.034	-0.0287 $\pm$.0017	2.87	0.83	22.09
9	10	6.24 $\pm$.020	-0.0144 $\pm$.0010	1.44	0.80	6.10

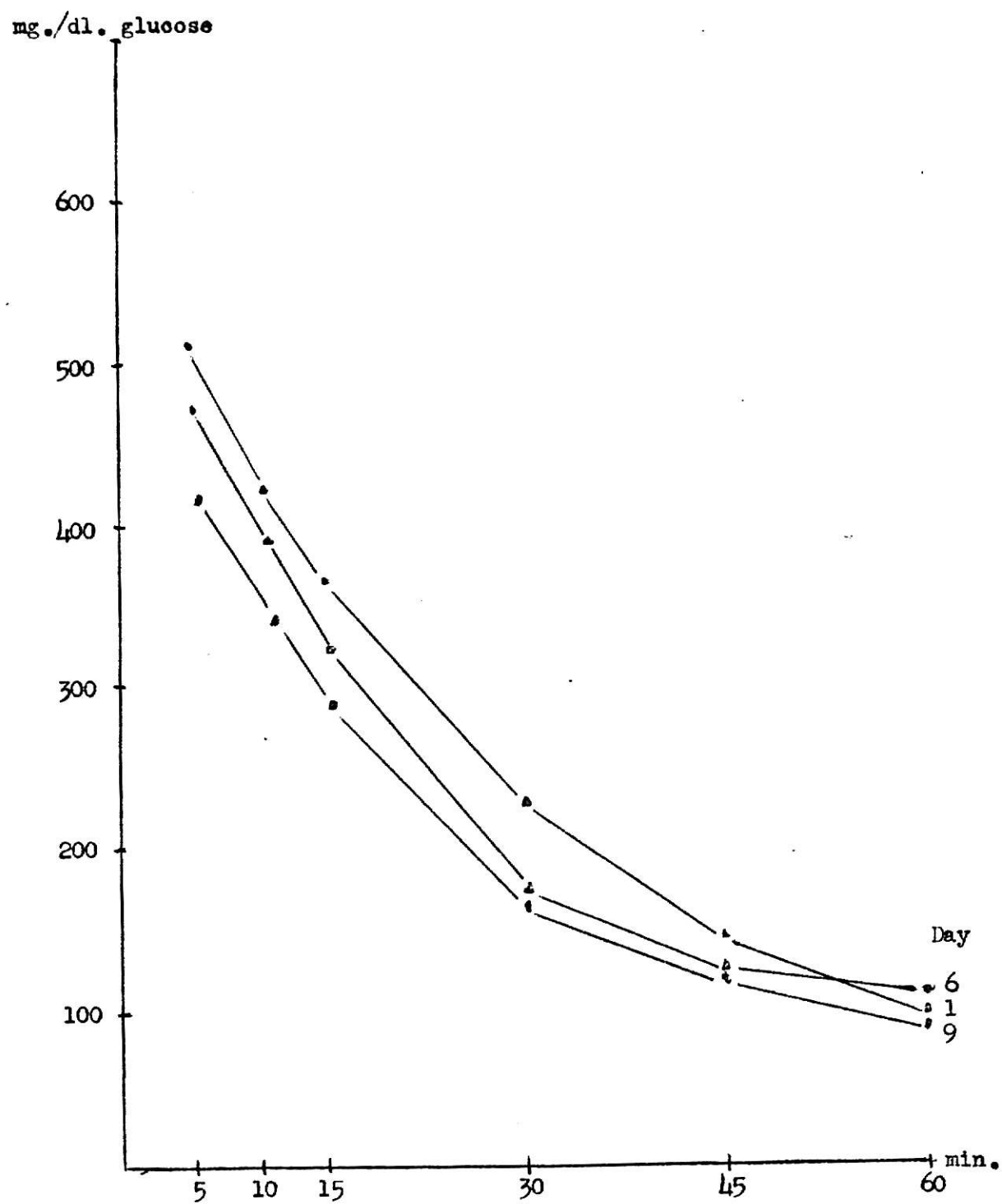


Figure 2. Mean glucose tolerance curves of group 1 dogs (nonsurgical controls).

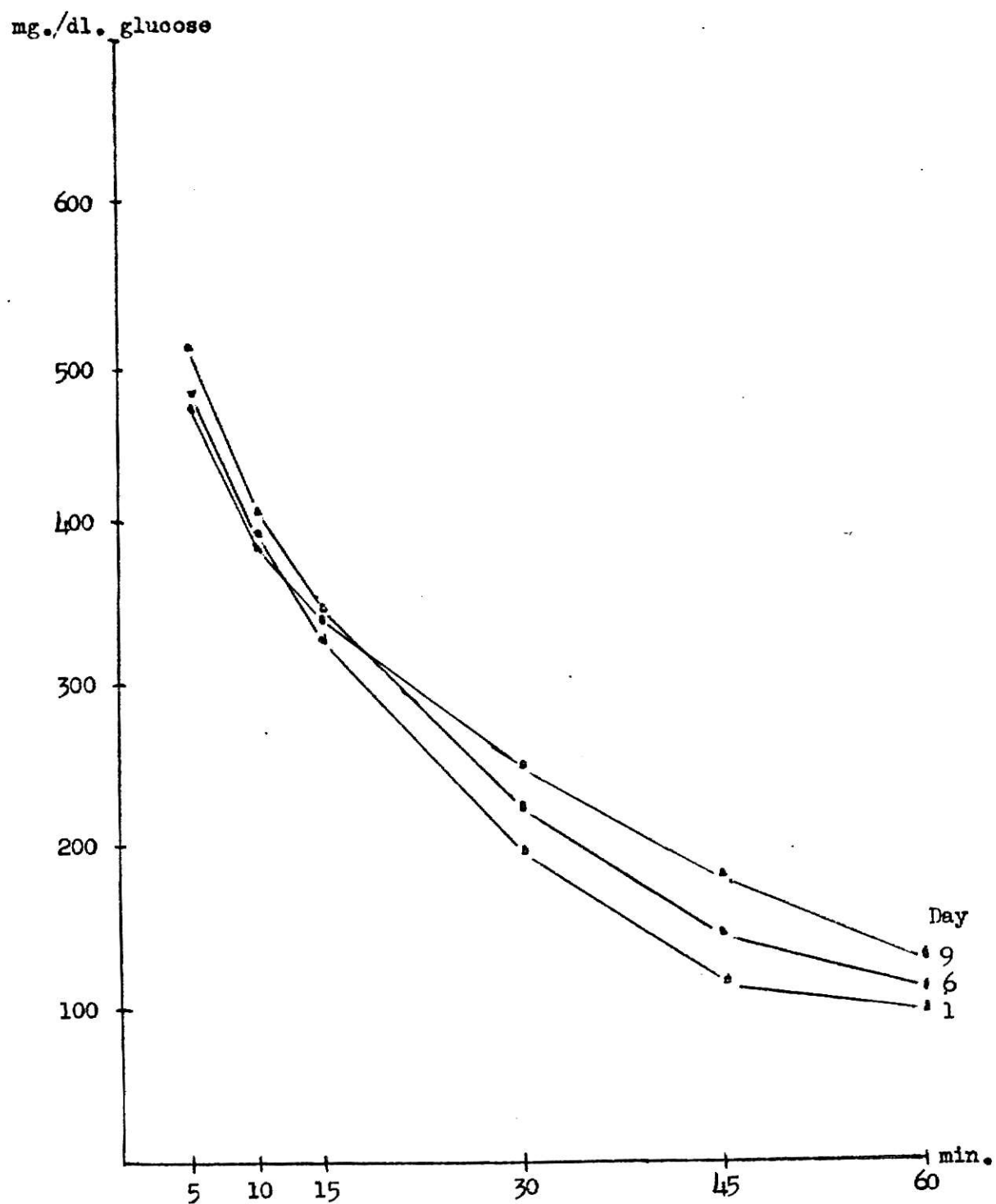


Figure 3. Mean glucose tolerance curves of group 2 dogs (surgical controls).

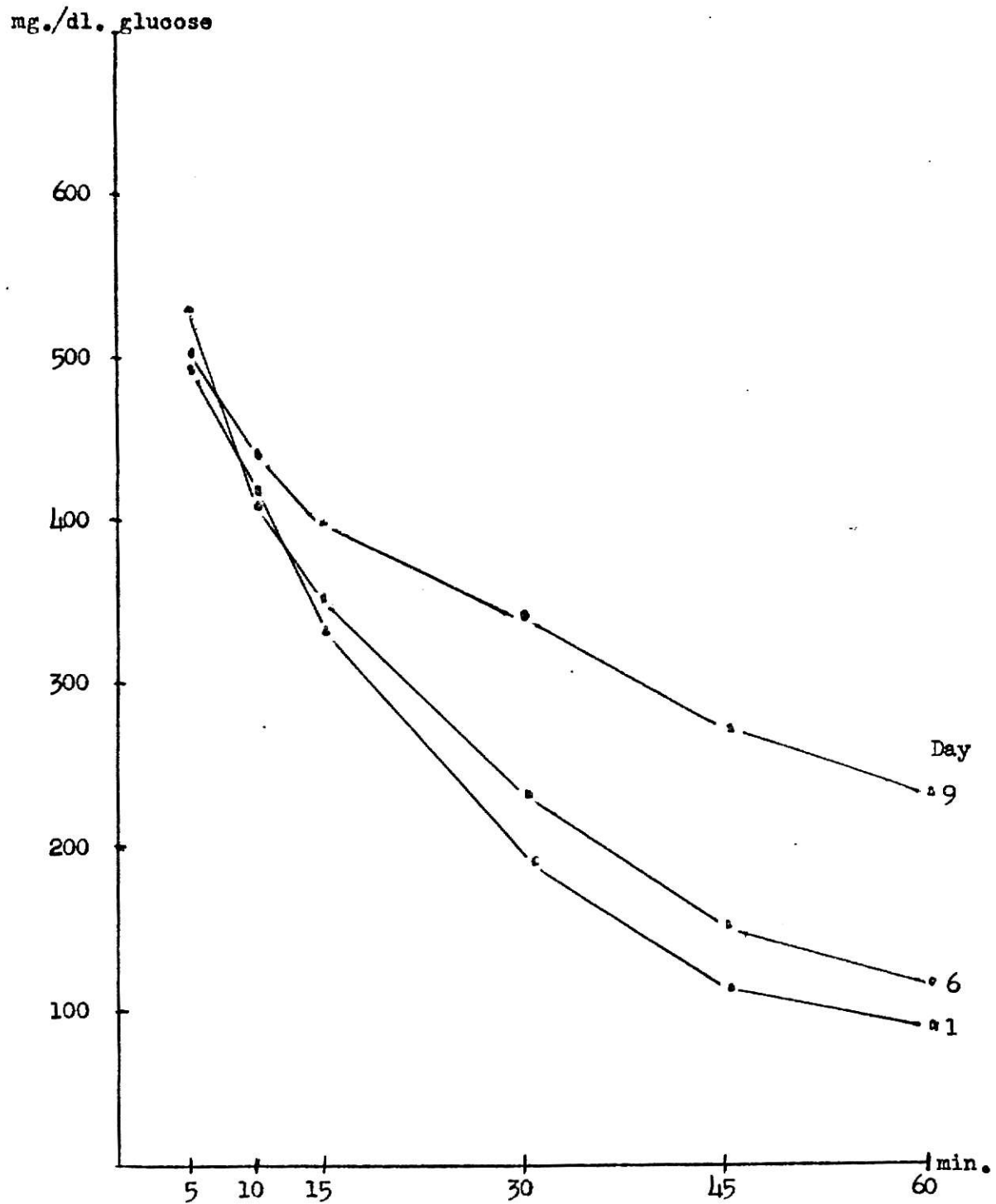


Figure 4. Mean glucose tolerance curves of group 3 dogs (staphylococcal alpha-toxin).

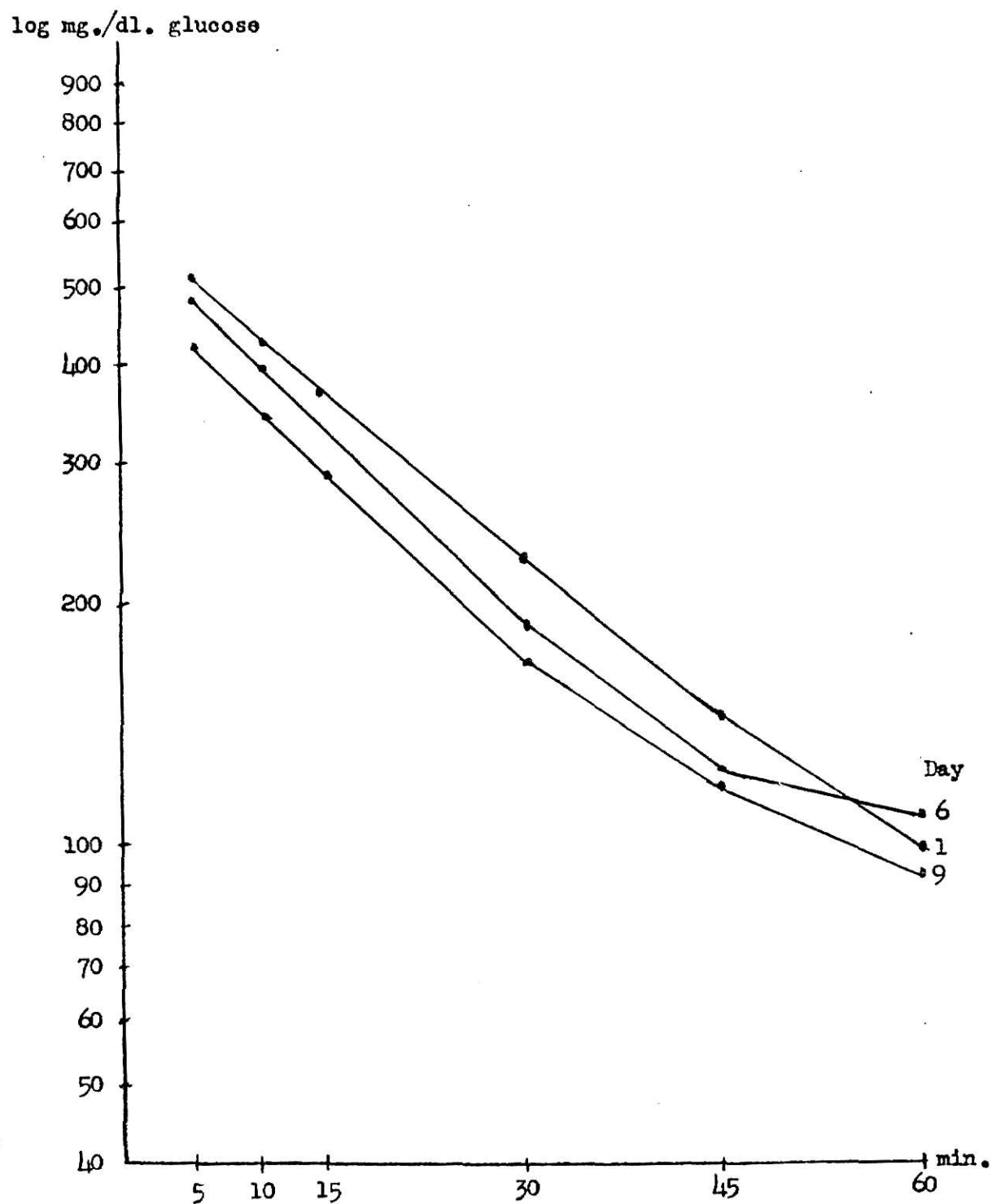


Figure 5. Semi-logarithmic plots of mean glucose tolerance curves of group 1 (nonsurgical controls).

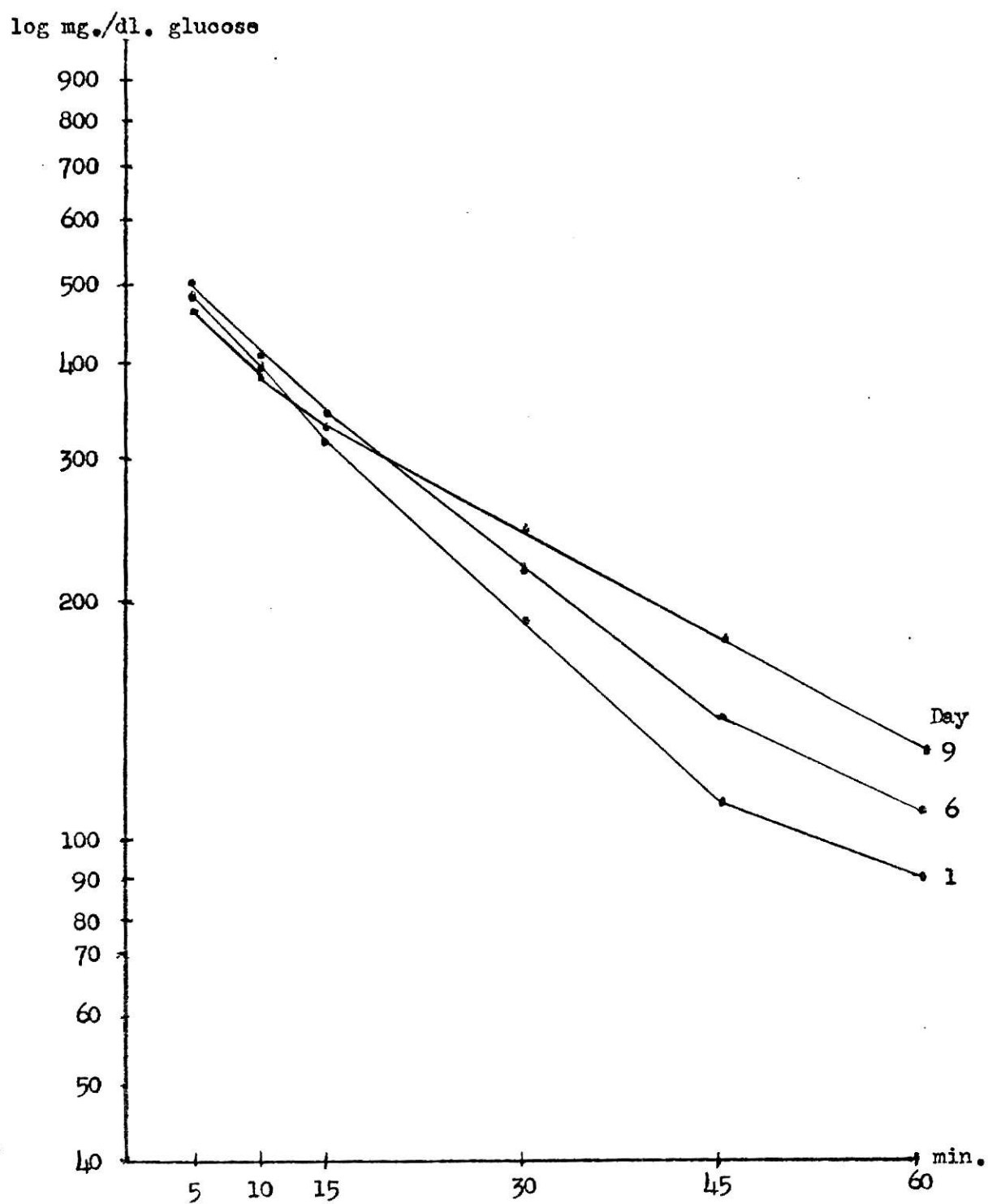


Figure 6. Semi-logarithmic plots of mean glucose tolerance curves of group 2 (surgical controls).

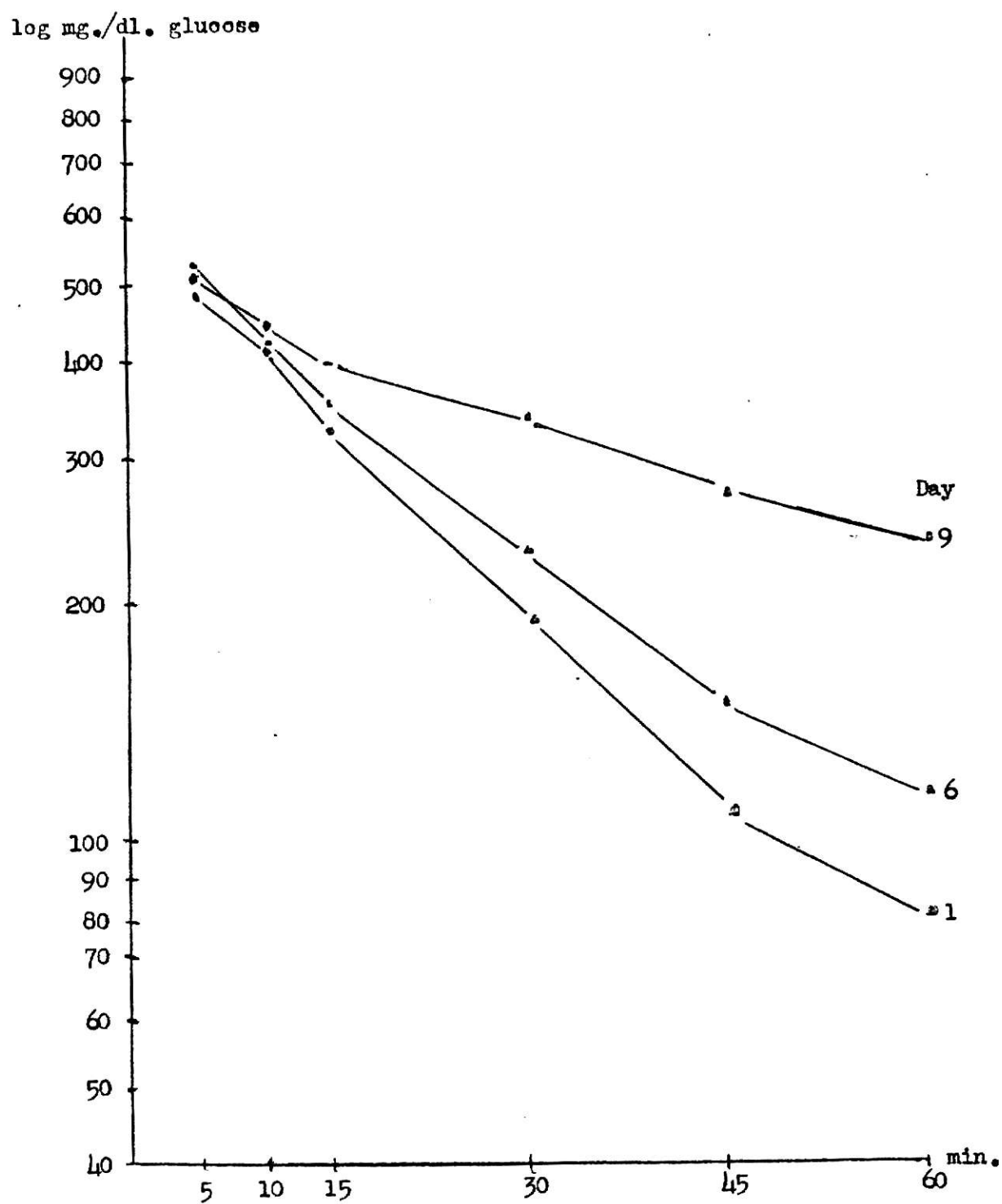


Figure 7. Semi-logarithmic plots of mean glucose tolerance curves of group 3 (staphylococcal alpha-toxin).

Simplified K-Values

- (1) K-values were also calculated using only two or three timed glucose samples to determine whether or not fewer samples could be used to calculate a simplified k-value close to the k-value calculated using all six timed samples (standard k-value). The different combinations were as follows: 5 and 60 min., 10 and 60 min., 5 and 45 min., 10 and 45 min., 5, 30, and 60 min., and 10, 30, and 60 min.
- (2) 6 of 9 times, the k-values calculated using 5 and 60 min. samples were closest to k-values calculated using all six samples, (standard k-values). 2 of 9 times, the k-values calculated using the 5, 30, and 60 min. samples were closest to the standard k-values, and 1 time the k-value using the 10 and 45 min. samples was closest to the standard k-value.
- (3) The mean difference between the simplified k-values and the standard k-value was smallest when the simplified k-value was calculated using 5 and 60 min. samples. The mean difference was greatest when the simplified k-value was calculated using 5 and 45 min. samples.

The simplified k-values along with their corresponding R^2 s are listed in Tables 4, 5, and 6. The mean differences between the standard k-values and the simplified k-values are presented in Table 7, page 47.

Table 4. Simplified k-values for the H-IVGTT in group 1 dogs (nonsurgical controls) as compared to the corresponding standard k-values.

Day	Sample Times	α	k	R ²	Standard k-Simplified k
1	Standard	6.32	2.84	0.92	
1	5, 60	6.37	2.75	0.97	-0.09
1	10, 60	6.31	2.66	0.96	-0.18
1	5, 45	6.39	3.20	0.93	+0.36
1	10, 45	6.36	3.13	0.92	+0.29
1	5, 30, 60	6.31	2.73	0.93	-0.11
1	10, 30, 60	6.27	2.63	0.92	-0.21
6	Standard	6.23	2.88	0.92	
6	5, 60	6.29	2.76	0.97	-0.12
6	10, 60	6.23	2.65	0.96	-0.23
6	5, 45	6.33	3.11	0.96	+0.53
6	10, 45	6.30	3.35	0.95	+0.47
6	5, 30, 60	6.21	2.74	0.92	-0.14
6	10, 30, 60	6.14	2.60	0.91	-0.28
9	Standard	6.06	2.77	0.87	
9	5, 60	6.16	2.68	0.96	-0.09
9	10, 60	6.07	2.54	0.95	-0.23
9	5, 45	6.18	3.21	0.93	+0.44
9	10, 45	6.12	3.09	0.90	+0.32
9	5, 30, 60	6.05	2.66	0.86	-0.11
9	10, 30, 60	5.97	2.49	0.83	-0.28

Table 5. Simplified k-values for the H-IVGTT in group 2 dogs (surgical controls) as compared to the corresponding standard k-values.

Day	Sample Times	α	k	R ²	Standard k- Simplified k
1	Standard	6.26	3.13	0.91	
1	5, 60	6.31	2.98	0.98	-0.15
1	10, 60	6.25	2.87	0.98	-0.26
1	5, 45	6.35	3.70	0.95	+0.57
1	10, 45	6.33	3.65	0.93	+0.52
1	5, 30, 60	6.25	2.95	0.92	-0.18
1	10, 30, 60	6.19	2.83	0.91	-0.30
6	Standard	6.30	2.91	0.92	
6	5, 60	6.37	2.89	0.96	-0.02
6	10, 60	6.28	2.73	0.95	-0.18
6	5, 45	6.39	3.29	0.92	+0.38
6	10, 45	6.31	3.13	0.90	+0.22
6	5, 30, 60	6.32	2.87	0.93	-0.04
6	10, 30, 60	6.24	2.71	0.92	-0.20
9	Standard	6.20	2.23	0.81	
9	5, 60	6.26	2.25	0.89	+0.02
9	10, 60	6.17	2.08	0.86	-0.15
9	5, 45	6.28	2.57	0.82	+0.34
9	10, 45	6.19	2.38	0.76	+0.15
9	5, 30, 60	6.24	2.24	0.84	+0.01
9	10, 30, 60	6.15	2.07	0.80	-0.16

Table 6. Simplified k-values for the H-IVGTT in group 3 dogs (staphylococcal alpha-toxin) as compared to the corresponding standard k-values.

Day	Sample Times	α	k	R ²	Standard k-Simplified k
1	Standard	6.31	3.42	0.91	
1	5, 60	6.35	3.26	0.98	-0.16
1	10, 60	6.34	3.24	0.97	-0.18
1	5, 45	6.39	3.92	0.92	+0.50
1	10, 45	6.43	4.00	0.90	+0.58
1	5, 30, 60	6.29	3.24	0.93	-0.18
1	10, 30, 60	6.28	3.20	0.91	-0.22
6	Standard	6.30	2.87	0.83	
6	5, 60	6.39	2.88	0.90	-0.01
6	10, 60	6.26	2.66	0.86	-0.21
6	5, 45	6.41	3.25	0.87	+0.38
6	10, 45	6.29	2.99	0.81	+0.12
6	5, 30, 60	6.33	2.87	0.87	0.00
6	10, 30, 60	6.22	2.64	0.82	-0.23
9	Standard	6.24	1.14	0.80	
9	5, 60	6.30	1.51	0.86	+0.07
9	10, 60	6.21	1.36	0.81	-0.08
9	5, 45	6.31	1.63	0.85	+0.19
9	10, 45	6.22	1.43	0.77	-0.01
9	5, 30, 60	6.29	1.51	0.83	+0.07
9	10, 30, 60	6.22	1.36	0.77	-0.08

Table 7. Means of the differences between the standard and simplified k-values of groups 1, 2, and 3.

Sample Times	Mean Difference	S.D.
5, 60	-0.06	± 0.08
10, 60	-0.19	± 0.05
5, 45	0.41	± 0.12
10, 45	0.30	± 0.20
5, 30, 60	-0.08	± 0.09
10, 30, 60	-0.22	± 0.07

Mean Fasting Blood Glucose Concentration (mg./dl.)

- (1) The mean fasting blood glucose of group 1 was significantly higher on day 6 (106.9 mg./dl.) than on days 1 (99.0 mg./dl.) and 9 (96.9 mg./dl.). The values of days 1 and 9 were not significantly different from each other.
- (2) In group 2, there was no significant change in the mean fasting blood glucose from day 1 to day 6 or from day 6 to day 9, but the glucose value on day 9 was significantly higher than that on day 1.
- (3) In group 3, all three mean fasting blood glucose values were significantly different from each other. There was a significant decrease in fasting blood glucose from day 1 to day 6 and, then, a significant rise from day 6 to day 9. The value on day 9 was also significantly higher than that on day 1.
- (4) On day 1, there were no significant differences among the mean fasting blood glucose values of the three groups.
- (5) On day 6, the mean fasting blood glucose value of group 3 (84.0 mg./dl.) was significantly lower than that of groups 1 (106.9 mg./dl.) and 2 (99.4 mg./dl.). The values of groups 1 and 2 were not significantly different from each other.
- (6) On day 9, the mean fasting blood glucose value of group 2 (104.6 mg./dl.) was not significantly different from that of groups 1 (96.6 mg./dl.) and 3 (111.8 mg./dl.), but the value of group 3 was significantly higher than that of group 1.

Table 8. Mean fasting blood glucose concentrations (mg./dl.) in dogs.
 (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal
 alpha-toxin.)

Group	Day	N	Mean
1	1	10	99.0
1	6	10	106.9
1	9	10	96.6
2	1	10	94.7
2	6	10	99.4
2	9	10	104.6
3	1	10	102.7
3	6	10	84.0
3	9	10	111.8

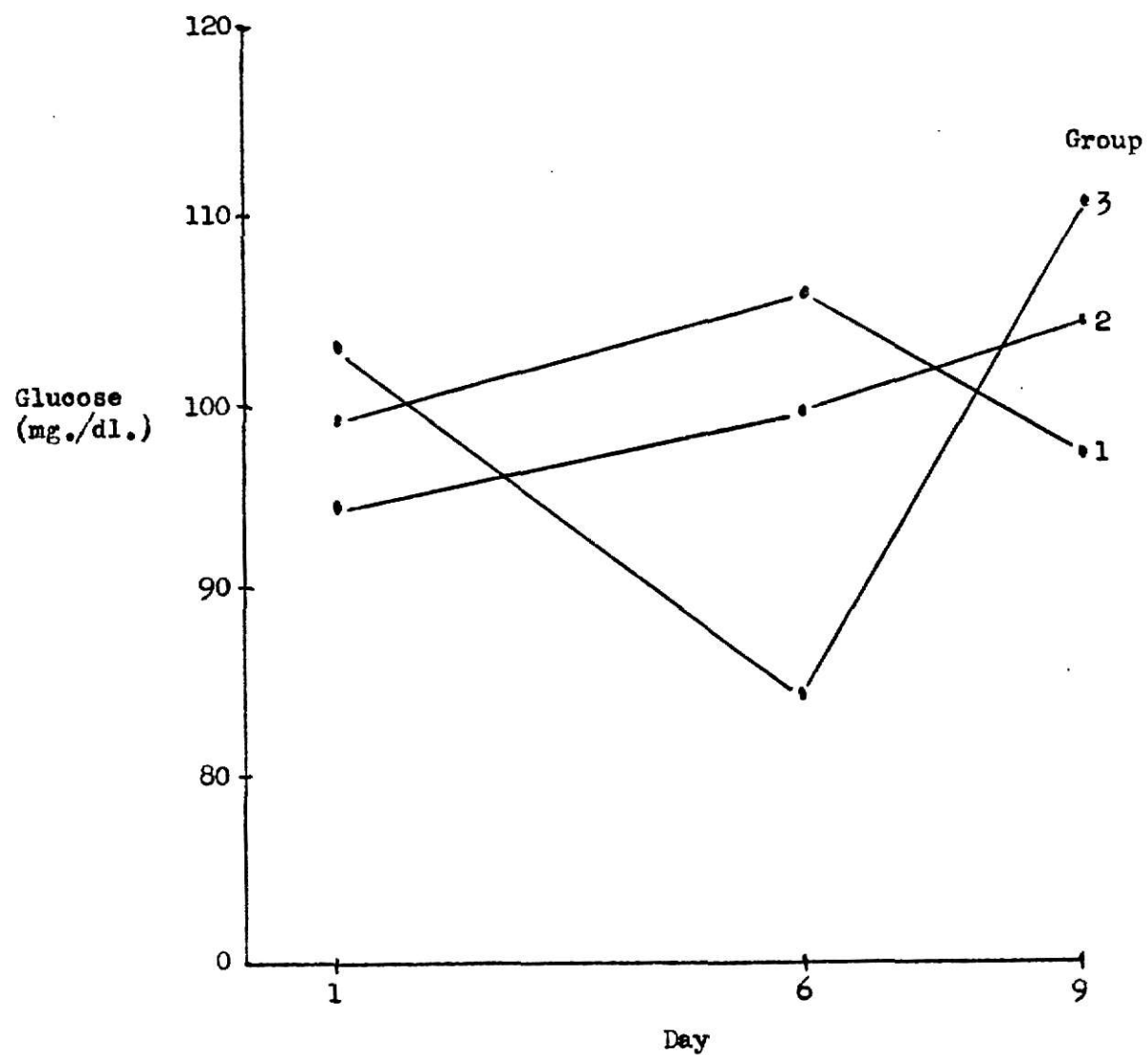


Figure 8. Mean fasting blood glucose values of dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Table 9. LSD test of mean fasting blood glucose concentrations (mg./dl.)* in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

		GROUP		
		1	2	3
DAY	1	99.0 xy a	94.7 x a	102.7 x a
	6	106.9 x a	99.4 xy a	84.0 y b
	9	96.6 y a	104.6 y ab	111.8 z b

*Nonsignificant groupings have same letter.

A, b, and c represent differences within days, (across).

X, y, and z represent differences within groups, (down).

Mean Amylase Values (U. = Δ O.D./min./ml.)

- (1) Although the mean amylase value of group 3 increased on day 6 (0.419 U.) from day 1 (0.146 U.) and then decreased on day 9 (0.280 U.), there were no significant changes in the mean amylase values of the three groups from one test day to the next.
- (2) There were no significant differences among the mean amylase values of the three groups on day 1 or on day 9.
- (3) On day 6, the mean amylase value of group 2 (0.280 U.) was not significantly different from those of groups 1 (0.135 U.) or 3 (0.419 U.), but the value of group 3 was significantly higher than that of group 1.

Table 10. Mean amylase values (U.) in dogs. (1: nonsurgical controls;
2: surgical controls; and 3: staphylococcal alpha-toxin).

Group	Day	N	Mean
1	1	10	0.208
1	6	10	0.135
1	9	10	0.114
2	1	10	0.105
2	6	10	0.280
2	9	10	0.146
3	1	10	0.146
3	6	10	0.149
3	9	10	0.280

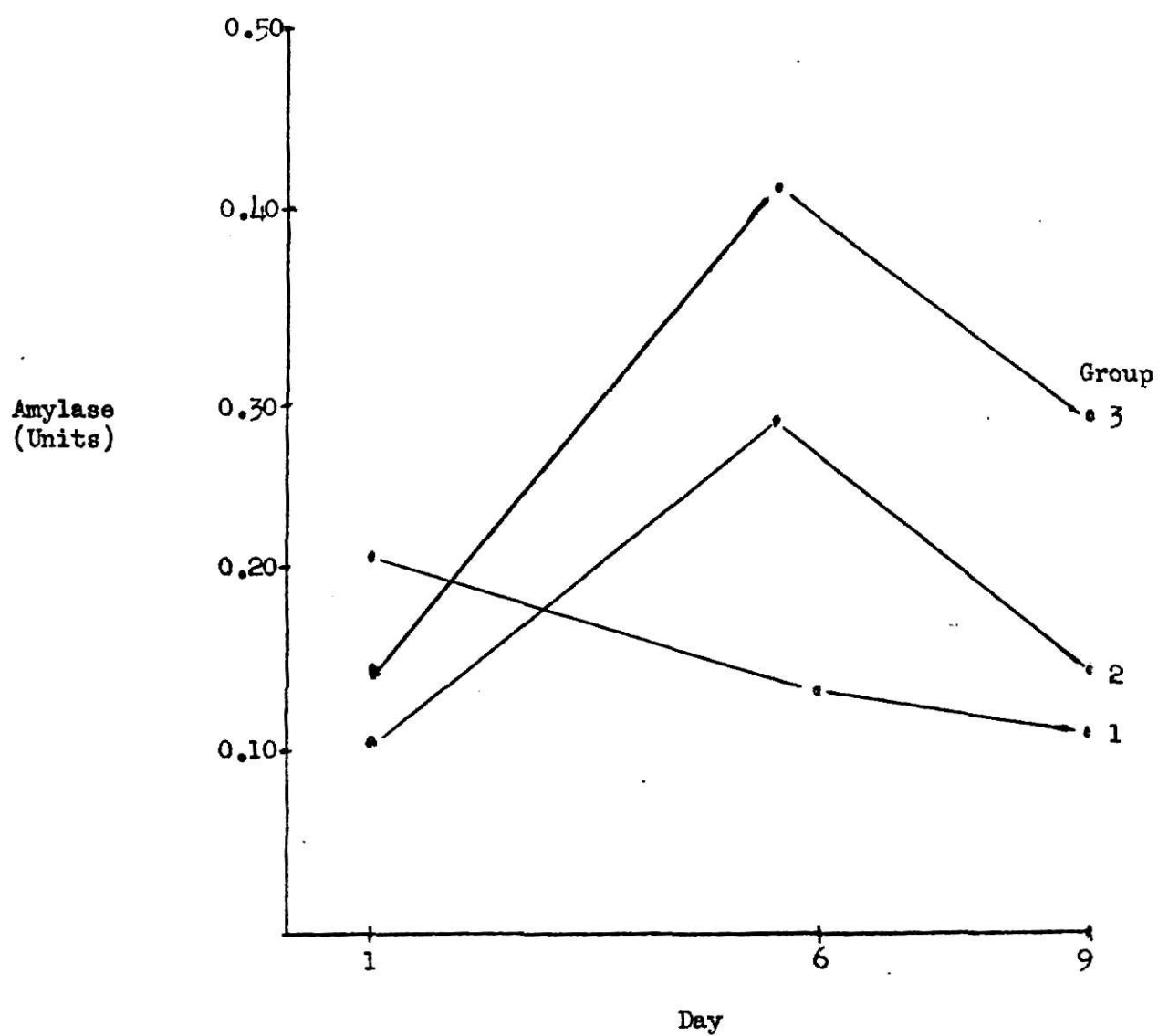


Figure 9. Mean amylase values of dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Table 11. LSD test of mean amylase values (U.)* in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

		GROUP		
		1	2	3
1		a	a	a
		0.208	0.105	0.146
	x	x	x	x
6		a	ab	b
		0.135	0.280	0.419
	x	x	x	x
9		a	a	a
		0.114	0.146	0.280
	x	x	x	x

*Nonsignificant groupings have same letter.

A, b, and c represent differences within days, (across).

X, y, and z represent differences within groups, (down).

Mean Lipase Values (Lipase Units/ml.)

- (1) In groups 1 and 2, there were no significant changes in the mean lipase values although the value of group 2 gradually increased on each succeeding day.
- (2) In group 3, all three mean lipase values were significantly different from each other. The value increased from day 1 (0.23 U.) to day 6 (1.91 U.), and then decreased on day 9 (1.04 U.)
- (3) On day 1, there were no significant differences among the mean lipase values of the three groups.
- (4) On day 6, there were no significant differences between the values of groups 1 (0.259 U.) and 2 (0.387 U.), but the value of group 3 (1.91 U.) was significantly higher than those of the other two groups.
- (5) The results for day 9 paralleled those of day 6. The value of group 1 was 0.289 U., group 2, 0.481 U., and group 3, 1.042 U.

Table 12. Mean lipase values (Lipase Units/ml.) in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Group	Day	N	Mean
1	1	10	0.191
1	6	10	0.259
1	9	10	0.288
2	1	10	0.152
2	6	10	0.387
2	9	10	0.481
3	1	10	0.230
3	6	10	1.907
3	9	10	1.042

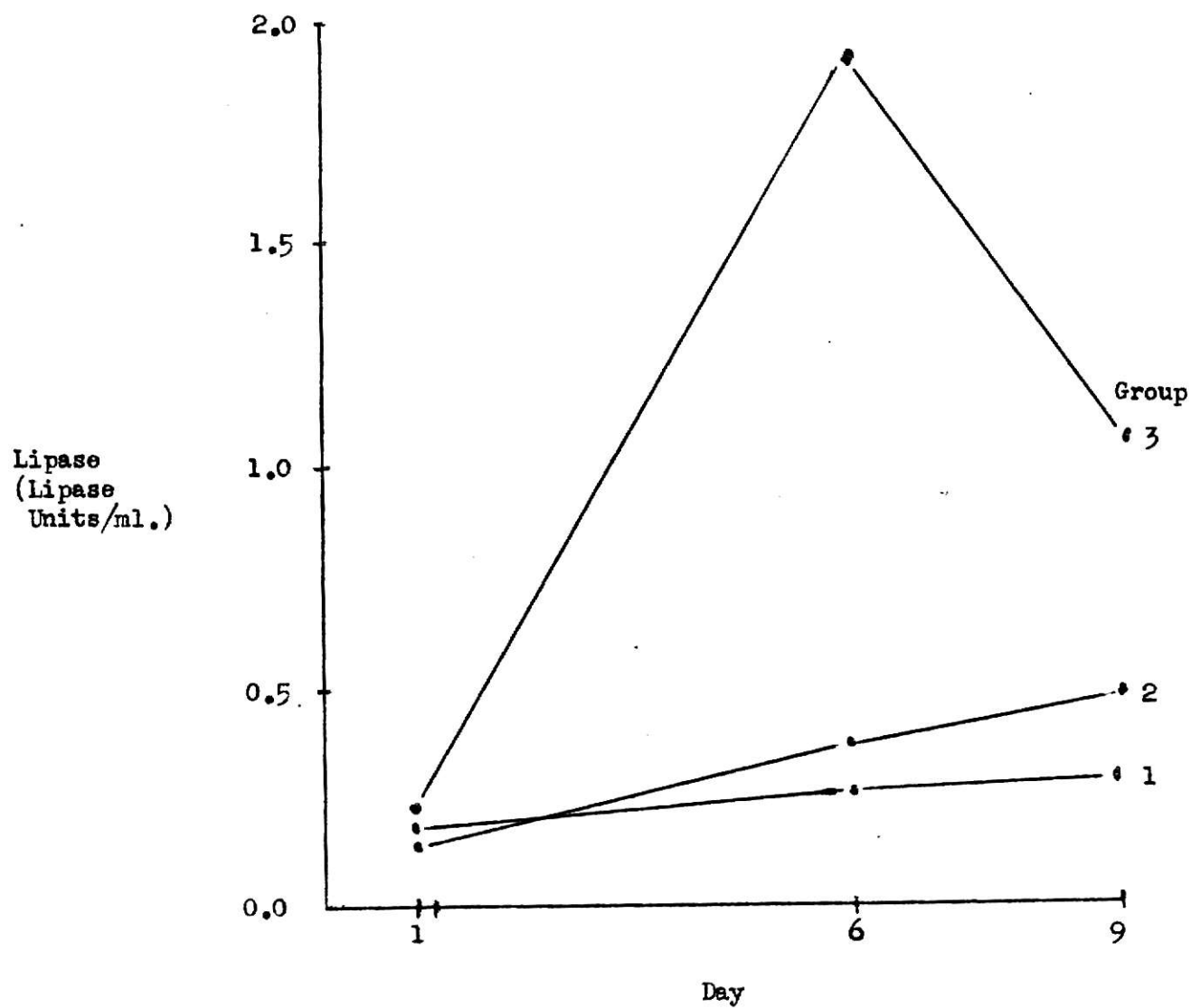


Figure 10. Mean lipase values in dogs. (1: nonsurgical controls; surgical controls; and 3: staphylococcal alpha-toxin).

Table 13. LSD test of mean lipase values (Lipase Units/ml.)* in dogs.
 (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal
 alpha-toxin).

		GROUP		
		1	2	3
1		a	a	a
		0.191	0.151	0.230
	x	x	x	x
6		a	a	b
		0.259	0.387	1.907
	x	x	y	y
9		a	a	b
		0.289	0.481	1.042
	x	x	z	z

*Nonsignificant groupings have same letter.

A, b, and c represent differences within days, (across).

X, y, and z represent differences within groups, (down).

Mean SGPT (Frankel Units)

- (1) In groups 1 and 2, there were no significant changes in mean SGPT values from one test day to the next.
- (2) In group 3, there was a significant rise in the mean SGPT value from day 1 (13.3 F.U.) to day 6 (45.7 F.U.). There was a decrease in the value from day 6 to day 9 (34.8 F.U.), but that was not a significant change. The mean SGPT value of day 9 was also significantly higher than that of day 1.
- (3) On day 1, there were no significant differences among the mean SGPT values of the three groups.
- (4) On day 6, there was no significant difference between the mean SGPT values of groups 1 (13.3 F.U.) and 2 (24.3 F.U.). The value of groups 3 (45.7 F.U.) was significantly higher than that of the other two groups.
- (5) On day 9, the differences between the mean SGPT values of the three groups were not significant.

Table 14. Mean SGPT values (F.U.) in dogs. (1: nonsurgical controls;
2: surgical controls; and 3: staphylococcal alpha-toxin).

Group	Day	N	Mean
1	1	10	18.9
1	6	10	13.3
1	9	10	24.0
2	1	10	19.1
2	6	10	24.3
2	9	10	18.7
3	1	10	13.3
3	6	10	45.7
3	9	10	34.8

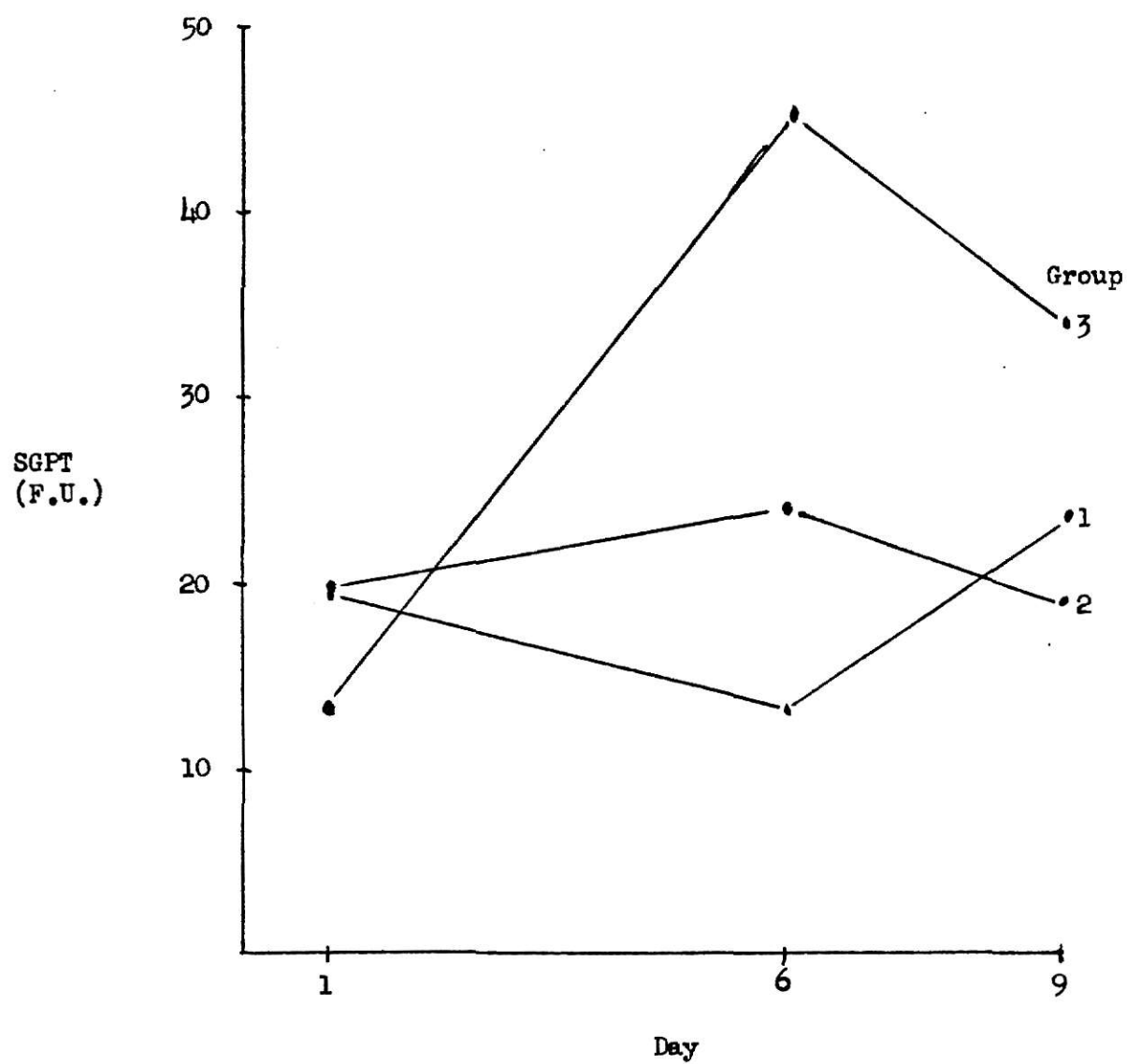


Figure 11. Mean SGPT values of dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Table 15. LSD test of mean SGPT values (F.U.)* in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

		GROUP		
		1	2	3
1		18.9	19.1	13.3
		a	a	a
	x	x	x	x
6		13.3	24.3	45.7
		a	a	b
	x	x	y	y
9		24.0	18.7	34.8
		a	a	a
	x	x	y	y

*Nonsignificant groupings have same letter.

A, b, and c represent differences within days, (across).

X, y, and z represent differences within groups, (down).

Mean Alkaline Phosphatase Values (Kind-King Units)

- (1) There were no significant changes in the mean alkaline phosphatase values of group 1.
- (2) In group 2, there was a significant rise in the mean alkaline phosphatase value from day 1 (11.1 K.K.U.) to day 6 (26.2 K.K.U.). The value on day 9 (21.4 K.K.U.) was also significantly higher than that on day 1, but not significantly lower than the value on day 6.
- (3) In group 3, the mean alkaline phosphatase value increased significantly from day 1 (6.7 K.K.U.) to day 6 (46.6 K.K.U.), and then decreased to a significantly lower value on day 9 (36.5 K.K.U.). All three values were significantly different from each other.
- (4) On day 1, there were no significant differences between the mean alkaline phosphatase values of the three groups.
- (5) On day 6, the mean values of all groups were significantly different from each other, i.e., the value of group 2 (26.2 K.K.U.) was higher than that of group 1 (10.0 K.K.U.) and the value of group 3 (46.6 K.K.U.) was higher than that of group 2.
- (6) The situation on day 9 was the same as that on day 6, except that the values were all somewhat lower.

Table 16. Mean alkaline phosphatase (K.K.U.) in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Group	Day	N	Mean
1	1	10	6.8
1	6	10	10.0
1	9	10	5.1
2	1	10	11.1
2	6	10	26.2
2	9	10	21.4
3	1	10	6.7
3	6	10	46.6
3	9	10	36.4

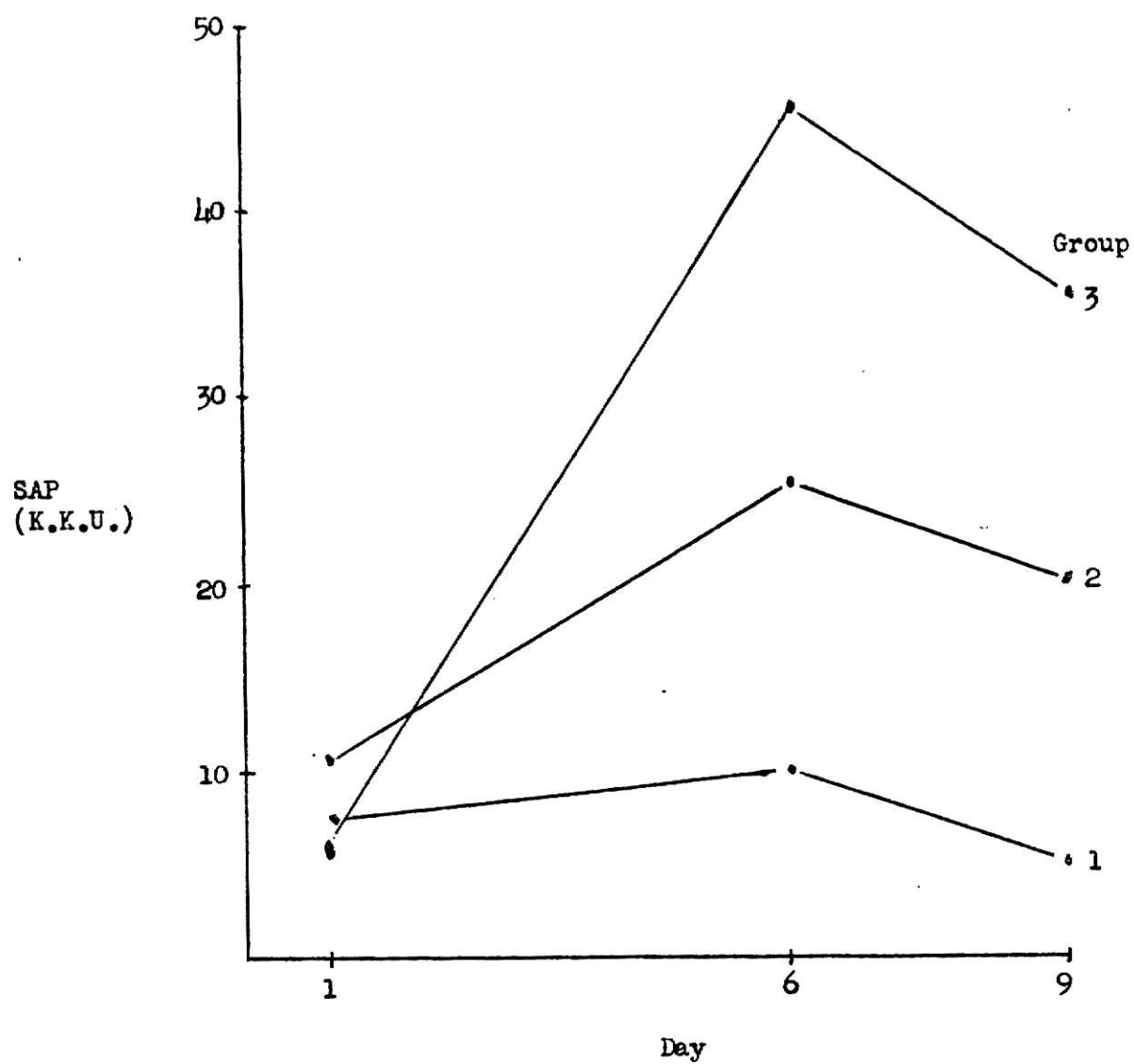


Figure 12. Mean SAP values of dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Table 17. LSD test of mean alkaline phosphatase values (K.K.U.)* in dogs.
 (1: surgical controls; 2: nonsurgical controls; and 3: staphylococcal
 alpha-toxin).

		GROUP		
		1	2	3
DAY	1	6.8 a x	11.1 a x	6.7 a x
	2	10.0 a x	26.2 b y	46.6 c y
	3	5.1 a x	21.4 b y	36.5 c z

*Nonsignificant groupings have same letter.

A, b, and c represent differences within days, (across).

X, y, and z represent differences within groups, (down).

Mean Gamma Glutamyl Transpeptidase (GGT) Values (Sigma Units)

The F-test done on the analysis of variance of the mean GGT values was not significant for treatment-day interaction. This means that (1) there were no significant differences between the mean GGT values of the three groups on any of the three test days, and (2) on days 1, 6, and 9, there were no significant differences between the mean values of the three groups.

Table 18. Mean gamma glutamyl transpeptidase values (Sigma Units) in dogs.
 (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Group	Day	N	Mean
1	1	10	0.746
1	6	10	1.506
1	9	10	1.186
2	1	10	1.071
2	6	10	1.595
2	9	10	0.696
3	1	10	1.736
3	6	10	1.836
3	9	10	2.831

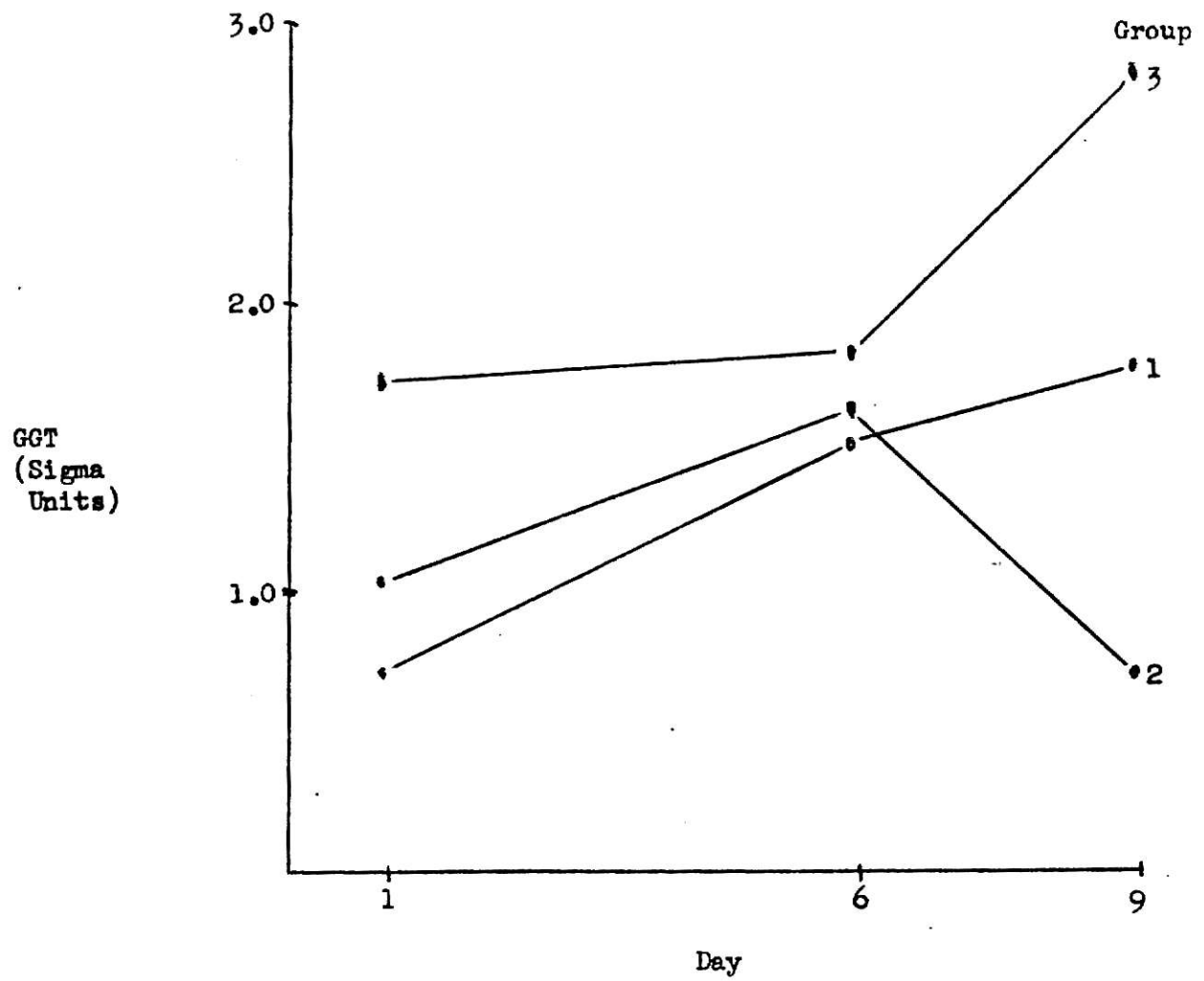


Figure 13. Mean GGT values of dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Mean Creatinine Values (mg./dl.)

The F-test done on the analysis of variance of the mean creatinine values was not significant for treatment-day interaction. This means that (1) there were no significant differences between the mean creatinine values of the three groups on any of the three test days, and (2) on days 1, 6, and 9, there were no significant differences between the mean values of the three groups.

Table 19. Mean creatinine values (mg./dl.) in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Group	Day	N	Mean
1	1	10	1.11
1	6	10	1.49
1	9	10	1.32
2	1	10	1.17
2	6	10	1.49
2	9	10	1.50
3	1	10	1.50
3	6	10	1.63
3	9	10	1.59

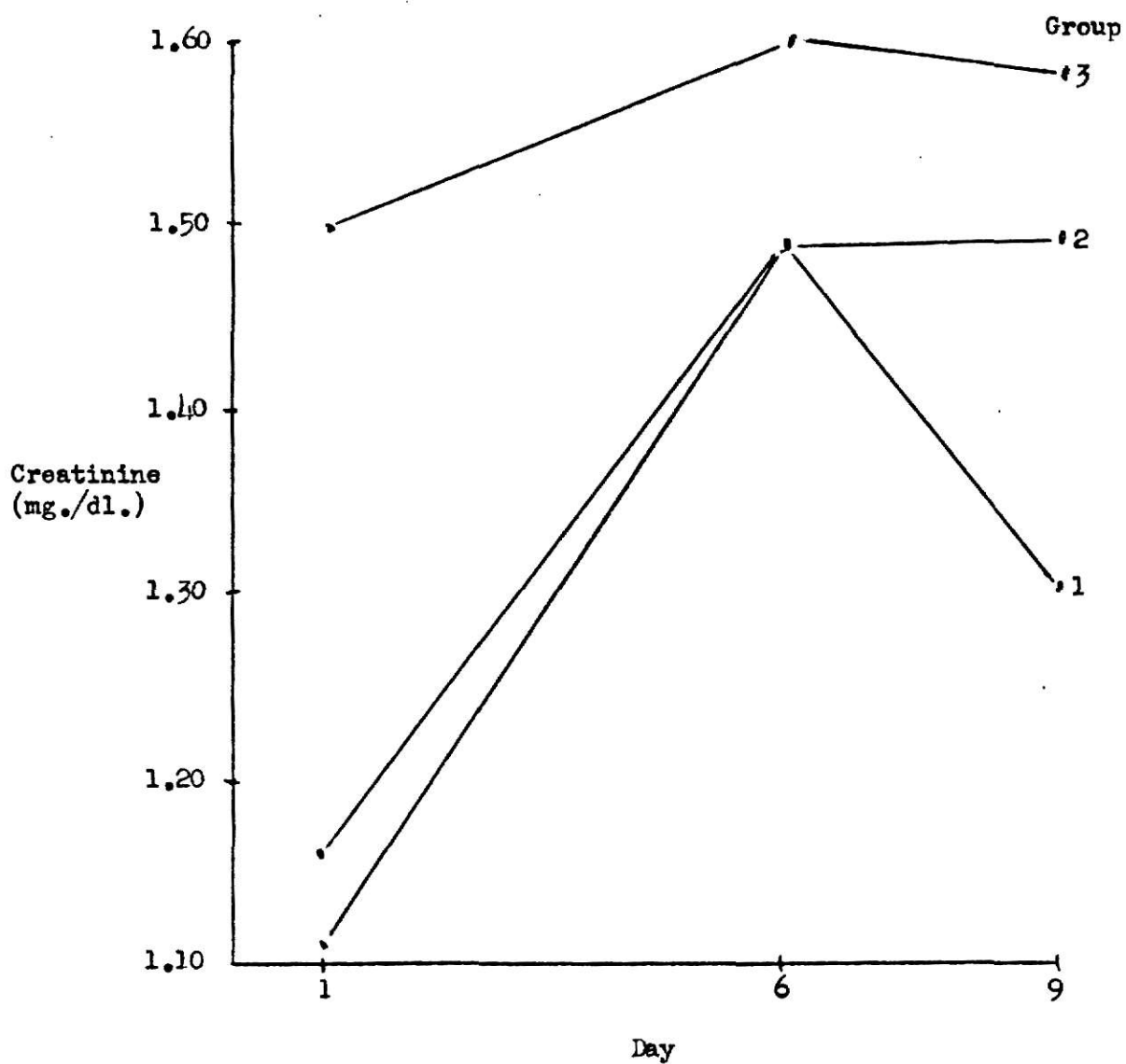


Figure 14. Mean creatinine values in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

DISCUSSION

Clinical Observations

All of the dogs subjected to staphylococcal alpha-toxin (group 3) had repeated episodes of emesis and severe abdominal pain. Both signs have frequently been reported as being characteristic of acute pancreatitis in dogs (1, 2, 3, 4, 5, 7, 10, 11, 12). Most of the dogs had generalized abdominal pain, but the pain was localized to the anterior abdomen in a few dogs. Peritonitis probably contributed greatly to the abdominal pain, especially in cases in which the pain was generalized.

The vomitus of these dogs was usually yellow-colored indicating that duodenal contents were present. In severe cases of naturally-occurring pancreatitis, hemorrhagic duodenitis and duodeno-gastric reflux may occur and cause blood to appear in the vomitus. None of the dogs in this study had blood-tinged vomitus. The vomiting could be caused by (1) irritation of the duodenum (duodenitis), (2) an enlarged pancreas impinging on the duodenum causing muscle spasm and partial obstruction, and (3) stimulation of the emetic center by toxic products absorbed from the inflamed pancreas.

Another sign of gastrointestinal disturbance was diarrhea. Three dogs in group 3 developed diarrhea after induction of pancreatitis while none of the dogs in group 2 did. The feces did not contain blood. Small et al. (4) included blood-tinged diarrhea as one of the symptoms of acute pancreatitis. The enteritis that commonly occurs with pancreatitis is probably responsible for the development of diarrhea.

The Glucose Disappearance Coefficient (k-Value)

The glucose disappearance coefficient (k-value) is the disappearance rate of glucose from the blood, measured in percent decrease of glucose per minute. It does not indicate how or whether the glucose is utilized; it simply expresses the rate at which the blood glucose enters other body compartments such as the brain, liver, kidney, muscle, adipose tissue, and urine (56, 75). Ikkos and Luft (51) found that only 4% of the injected glucose was excreted in the urine of normal humans. A large part of the glucose load is found in the urine of diabetics (56). During the first few minutes after glucose administration, much of the decrease in blood glucose is associated with urinary excretion and mixing of glucose in the vascular space (52). The glucose disappearance rate is significantly decreased in subclinical and overt diabetics (50).

Hamilton and Stein (76) found that after the intravenous injection of glucose, the blood glucose concentration declined in a simple exponential form. Plotting blood glucose values against time on semilogarithmic paper yields a close approximation to a straight line. The slope of that line is equal to the k-value divided by 100. The k-value has been calculated using the following formula:

$$C_2 = C_1 \cdot e^{-k(t_2 - t_1)}$$

$$k = \frac{\ln C_1 - \ln C_2}{t_2 - t_1}$$

C_2 = glucose concentration at time t_2

C_1 = glucose concentration at time t_1

k = glucose disappearance coefficient

e = base of the natural log

Assuming that C_2 is half of C_1 , the equation can be simplified to:

$$k = \frac{\ln C_1 - \ln (0.5 \times C_1)}{t_{\frac{1}{2}}}$$

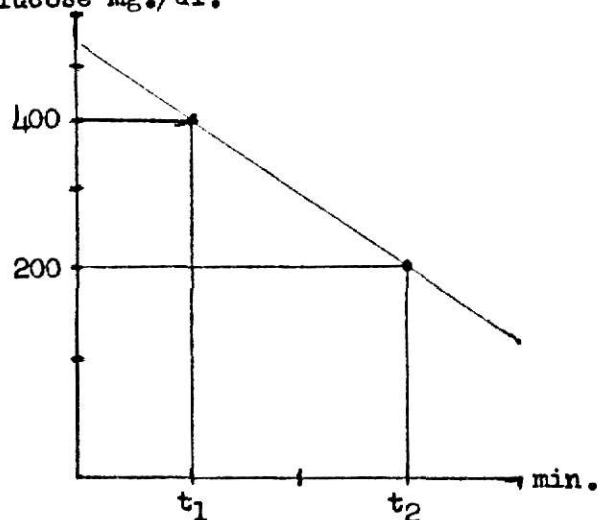
$$k = \frac{\ln \frac{C_1}{0.5 C_1}}{t_{\frac{1}{2}}}$$

$$k = \frac{\ln 2}{\frac{1}{2}} = \frac{0.693}{t_{\frac{1}{2}}}$$

To express k in percent decrease per minute: $k = \frac{69.3}{t_{\frac{1}{2}}}$. The k -value is

equal to $-\beta$, the slope of the line (Table 3, page 36) times 100. For example, the β for group 1, day 1 is $-0.0284 \pm .0011$. The k -value would then be $2.84 \pm .11$. In the figure below is an example of how the k -value can be calculated without the use of a computer.

Log glucose mg./dl.



$$C_2 = 200 \quad t_2 = 45$$

$$C_1 = 400 \quad t_1 = 15$$

$$k = \frac{0.693}{30} \times 100 = 2.31$$

Figure 15. An example of calculating the k -value using the straight line plotted on semilogarithmic paper.

Various methods have been used to calculate the k-value. Hamilton and Stein (76) plotted the blood glucose values from the 10th or 20th minute to the 60th minute against time on semilogarithmic paper. They used the resultant straight line to calculate the k-value. Amatuzio et al. (50) calculated a k-value called the increment index in which the logs of the excess blood glucose values above the fasting value were plotted semilogarithmically against time to produce a straight line. The k-value was then calculated from that line. Ikkos and Luft (51) calculated the k-values using both methods and concluded that the method of Hamilton and Stein was preferable. Dyck and Moorhouse (57) and Greve and Anderson (60) used a method similar to Hamilton and Stein's in that the actual blood glucose values were plotted against time. Blood glucose values obtained at 5 minute intervals between 15 and 50 minutes after the start of the test were used by Dyck and Moorhouse in the calculation of the k-value. Greve and Anderson used 5, 15, 30, 45, and 60 minute values. In the present study, six values (5, 10, 15, 30, 45, and 60 minutes after the beginning of glucose injection) were used to plot the straight line from which the k-value was calculated.

The glucose dose used in administering the IVGTT has also varied considerably. Amatuzio et al. (50) used doses of 25 and 35 gms. in man, while Ikkos and Luft (51) and Lundbaek (52) used 25 gms. Moorhouse et al. (53) used a dosage of $0.25-3.0 \text{ gm./kg.}^{0.7}$ which, according to their calculations, yielded a dose between 19 and 26 grams in men weighing between 66 and 107 kg. The k-values obtained using the lower doses of glucose quite frequently overlapped those of normal and mild diabetics. Dyck and Moorhouse (57) found a larger dose of glucose to yield k-values that could more distinctly separate normals and prediabetics into two distinct groups. The dosage used was 50 gm./1.73 m^2 yielding doses between 50-60 gm. This was called the high-dose, intravenous

glucose tolerance test (H-IVGTT).

In the study done by Greve and Anderson (60) on dogs, the dosage of glucose administered was 1 gm./kg., and five timed samples from 5-60 minutes were used to plot the line from which the k-value was calculated. The present study was performed in the same manner except that the 10 minute value was also plotted. Because the glucose dosage was higher and timed samples between 5-15 minutes were included in the line from which the k-value was calculated, the k-values from the present study and from Greve and Anderson's study cannot be closely compared to the k-values calculated by Dyck and Moorhouse. One must consider the difference in dose and the species size difference in comparing those k-values. Even though the k-values of Dyck and Moorhouse's and Greve and Anderson's studies are not closely comparable, it is important to note that, in both studies, the calculated k-values could discriminate between normals, prediabetics, and overt diabetics with little overlap among the three groups. The glucose dosage used in those studies was relatively high compared to previous studies in man in which 25-35 gms. glucose was used. In the study done by Greve and Anderson, the guidelines used to interpret the k-value were as follows: k greater than 2.0 = normal, k between 1.9-1.1 = prediabetic, k less than 1.0 = overt diabetic.

The overall k-value (Table 3, page 36) of group 3 dogs in the present study changed markedly from one test day to the next. There was a decrease from 3.42 ± 0.14 (day 1) to 2.87 ± 0.17 (day 6) to 1.44 ± 0.10 (day 9). The range of individual k-values was as follows: day 1, 2.87-4.30, day 6, 1.80-4.50, day 9, 1.11-2.04. It is apparent that the glucose tolerance decreased as time progressed. Surgical trauma; i.e., partial pancreatectomy, physical manipulation, ductal catheterization, and infusion of fluid into the ductal system most likely had some effect upon decreasing beta cell function and numbers,

but the pancreatitis caused by the addition of staph alpha-toxin probably was the major factor in decreasing the glucose tolerance. Soon after surgery on group 3 dogs, the beta cells were probably undergoing necrosis and releasing stored insulin at the same time. It is reasonable to assume that this process was still occurring the day after surgery when the second glucose tolerance test was being performed, and that a large number of islets had not yet been destroyed. This could explain the decreased, but normal overall k-value (> 2.0) that was obtained on day 6. By day 9, it is likely that a larger number of islets had been affected by the toxin-induced inflammation and that much of the readily available insulin had been exhausted. The mean fasting blood glucose of group 3 was highest on day 9, and the overall k-value was also lowest on that day.

The overall k-value of group 2 dogs also decreased gradually from one test day to the next, but the change was not as dramatic as that of group 3. The k-value decreased from 3.13 ± 0.12 (day 1) to 2.91 ± 0.11 (day 6) to 2.23 ± 0.14 (day 9). The range of the individual k-values was as follows: day 1, 2.40-3.56, day 6, 1.86-3.50, day 9, 1.38-3.04. The k-values of this group indicated that the surgical procedure caused only a mild decrease on the glucose tolerance in most cases.

When the two groups are compared, it can be seen that (1) group 3 dogs were generally more physically ill than group 2 dogs, (2) the lowest overall k-value of group 3 dogs would be classified in the prediabetic group by Greve and Anderson's criteria, and the lowest overall k-value of group 2 dogs would be classified as normal, (3) on day 6, only one dog in each group had k-values less than 2.0, but on day 9, nine of ten dogs in group 3 had k-values less than 2.0, while only three dogs in group 2 had k-values less than 2.0. From the above, it is evident that staph alpha-toxin pancreatitis definitely has a

deleterious effect upon glucose tolerance.

As expected, the overall k-value on the nonsurgical control group (group 1) was greater than 2.0 on all 3 test days. The individual k-values from all three test days ranged from 2.28-3.78.

Relationship Of The Present Study To That Of Greve, Dayton, And Anderson

Greve et al. (21), in their study, submitted two groups of dogs to 50% partial pancreatectomies. Following the surgery, both groups were treated with bovine growth hormone (BGH) and dexamethasone (Dx) to render the animals more susceptible to diabetes mellitus. Ten days after the first surgery was done, staph alpha-toxin was infused into the ventral pancreatic duct of one group (AP), and a sham operation was performed on the other group (NAP).

The overall k-value of all dogs before surgery or treatment was 2.67 ± 0.32 (NAP group) and 3.01 ± 0.38 (AP group). The control and presurgical overall k-values of the dogs in the present study are listed in Table 3, page 36, and are similar to the above k-values obtained by Greve et al.

24 hours after the partial pancreatectomies were done, the overall k-values of both the AP and NAP groups were not significantly decreased. A similar finding was obtained in the present study, where in the surgical control group (group 2), the decrease in the k-value from day 1 to day 6 was not significant. It should be pointed out, however, that the group 2 dogs were also subjected to saline infusion of the pancreatic ducts the same day the partial pancreatectomies were performed. The NAP dogs in the study of Greve et al. were subjected to ductal catheterization 10 days later.

The lowest overall k-value obtained in the study done by Greve et al. was 1.13 ± 0.44 in the AP dogs the day after staph alpha-toxin was infused into

the ventral pancreatic duct. The lowest overall k-value found in this study was 1.44 ± 0.10 in group 3 on day 9, 96 hours after surgery. Here, differences in the two studies must be noted. Greve et al. waited 10 days for the pancreas to recover from the partial pancreatectomy before inducing pancreatitis with staph alpha-toxin. During that time, bovine growth hormone and dexamethasone were administered to make the islet tissue more susceptible to the diabetogenic effect of pancreatitis. Another important difference in the two studies is that Greve et al. ligated the ventral pancreatic duct so that the staph alpha-toxin and pancreatic enzymes could not drain from the pancreas. The duct was not ligated in the present study, so that the pancreatitis produced would more closely resemble the naturally-occurring disease. Because Greve et al. pretreated the dogs with BGH and Dx and ligated the ventral pancreatic duct, the dogs were more ill and had lower k-values the day after surgery than the group 3 dogs in the present study. Of the 8 dogs in the AP group of the study done by Greve et al., 3 became mildly ill and had increased serum amylase and lipase values. 3 dogs become ketoacidotic, hyperglycemic, and had increased serum amylase and lipase values. One of those dogs died three days after the surgery. The remaining 2 dogs became comatose from the pancreatitis and ketoacidotic diabetes mellitus and died 24 hours after toxin was given. The islets of the dogs in their study were stressed by the diabetogenic effects of the BGH-Dx before pancreatitis was induced. This could be the reason that the lowest k-values were found the day after surgery. In the present study, the stress on the islets began shortly after surgery. 24 hours post-operatively, the stored insulin was not completely exhausted. It was not until 96 hours after surgery that the maximum effect of the disease process on the islets was noted. This more closely conforms to what is known about the sequence of events in naturally occurring pancreatitis where the dog is not diabetic before

the onset. Greve et al. studied dogs that were essentially diabetic before the onset of pancreatitis. Following treatment with BGH/Dx the dogs had elevated fasting blood glucose values and glycosuria.

Simplified k-Values

The H-IVGTT is a sensitive test that veterinarians can use to detect impaired glucose tolerance in dogs. Greve and Anderson (60) have set guidelines for the evaluation of the k-value. However, veterinarians might be reluctant to perform the test because it requires that multiple, precisely timed blood samples be drawn. For this reason, an attempt was made to find a combination of two or three timed samples that would yield a simplified k-value close to the standard k-value.

From the results on pages 44-47, it appears that k-values calculated using 5 and 60 minute samples produced k-values closest to the standard. 5 of 9 times, the simplified k-values calculated from the 5 and 60 minute combination were closest to the standard k-values. 6 of 9 times, the difference was less than 0.10. The largest difference was 0.16. In all instances, the R^2 was the highest when the 5 and 60 minute samples were used to plot the line from which the simplified k-value was calculated.

The next best combination was the 5, 30 and 60 minute combination. 6 of 9 times the difference was less than 0.15; the largest difference was 0.18. The R^2 calculated from this combination was, of course, less than that of the 5 and 60 minute combination.

The differences between the other simplified k-values and the standards were too great to be acceptable. The poorest combination was that using the 5 and 45 minute samples. 8 of 9 times, it yielded the largest differences between simplified and the standard k-values.

The variation among the timed glucose values for the dogs in a typical group is depicted in the Figure 16, below. It can be seen that the variation in timed samples tended to increase with time except for the 60 minute samples. Because the variation among the 5 and 60 minute samples was less and because the endpoints tended to contribute most to the slope of the line, it seems likely that the k-value calculated using the 5-60 minute combination would provide the closest approximation to the standard k-value.

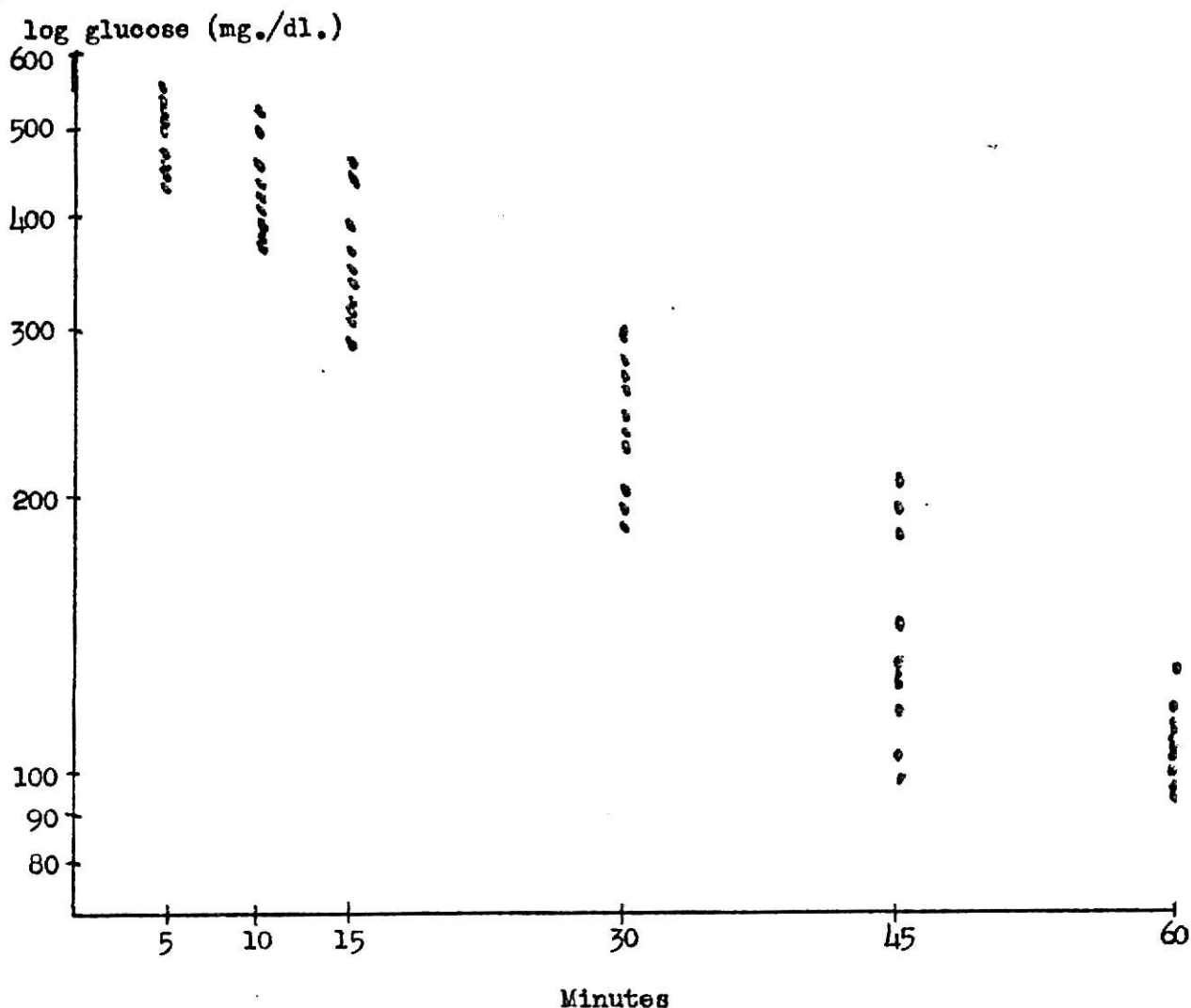


Figure 16. An example of the semi-logarithmic plot of glucose values from H-IVGTT's showing the variation among timed values for 10 dogs. (nonsurgical control group).

Blood Chemistries

Fasting Blood Glucose

The mean fasting blood glucose of group 1 increased from day 1 to day 6, and then decreased on day 9. Although these changes were statistically significant, the values were within the normal limits of 75-110 mg./dl. (77). The mean fasting blood glucose value of group 2 gradually increased from day 1 to day 9. The value on day 9 was significantly higher than that on day 1, but again the values were within normal limits. It is possible that the dogs could have been more excited and apprehensive about the venipuncture on the days that the fasting glucose was highest. Excited animals often release endogenous epinephrine, which stimulates glycogenolysis and gluconeogenesis in the liver (78). Therefore, the blood glucose values may be increased. It is most likely, however, that the differences in mean fasting blood glucose values of groups 1 and 2 were due to normal day-to-day variation.

The mean fasting blood glucose value of group 3 decreased significantly from day 1 to day 6, and then increased significantly on day 9. Staphylococcal alpha-toxin in the pancreas may have injured the beta cells causing the release of stored insulin after surgery. This could then explain the decreased blood glucose obtained on day 6, but it also should be noted that these dogs were fasted on days 5 and 6. By day 9, much of the stored insulin would have been exhausted and the islets' capacity to produce new insulin would be diminished. This would result in an elevated fasting blood glucose as on day 9, (111.8 mg./dl.).

The liver is also important in the regulation of blood glucose. Fasting blood glucose is largely maintained by gluconeogenesis in the liver. If the functional hepatic mass were diminished, the liver would be less able to

maintain an adequate output of glucose to meet the body's needs in a fasting state (78), and fasting blood glucose would decline. While staph alpha-toxin could reach the liver via the portal system and cause diffuse hepatic necrosis, it is doubtful that there was enough toxin delivered to the liver to cause massive necrosis. The SGPT value rose to its highest value of 45.7 F.U./ml. on day 9. It is unlikely that the liver necrosis represented by that value was severe enough to be the major factor causing the lower fasting glucose on day 6. It could, however, have been a contributing factor.

Serum Amylase and Lipase

Elevations in serum amylase and lipase values have been widely accepted as supportive evidence for a diagnosis of pancreatitis in dogs with an "acute abdomen". Continued secretion of amylase in the presence of ductal obstruction and disrupted acini contributes greatly to the serum amylase rise that occurs in pancreatitis (79). As the disease progresses, gradual accumulation of inflammatory exudate prolongs ductal obstruction, thus diverting amylase and lipase into the circulation (8). Experimental evidence suggests that serum amylase and lipase activities increase to a greater extent when pressure is applied to ducts than when the duct is simply ligated (80). Brobst (8) considered serum amylase values to be "...an index of the degree of ductal obstruction of the pancreas." Herva isolated several proteolytic enzymes from canine pancreatic tissue during bile-induced pancreatitis (26). Although he did not identify the enzymes, he felt that they were important in the development of ischemia and cellular necrosis. Enzymes may also directly damage the pancreatic microcirculation causing further ischemia, necrosis, and release of amylase and lipase (81).

Organs of the dog other than the pancreas also contain amylase and may

contribute to serum amylase activity. The liver is generally considered to be the primary source of serum amylase during normal conditions (8). The small intestine also contains amylase, and in intestinal obstruction, serum amylase activity may increase (82). Dehydration and lowered blood pressure, which often accompany pancreatitis, may decrease the glomerular filtration rate. As a result, the amount of amylase excreted by the kidney is decreased. Similarly, serum amylase values in uremic dogs may be expected to be increased (4, 83, 84).

In the present study, there was a small rise in serum amylase activity of group 2 dogs the day after surgery. Even though the increase was not statistically significant, it probably reflects the trauma done to the pancreas during surgery. Dingwall and McDonnell (35) found that slight elevations in serum amylase activity could occur for 24 hours post-operatively not only after partial pancreatectomy, but also when the pancreas was simply exposed and examined. The dogs in which staph alpha-toxin was infused into the ducts (group 3) had an increase in serum amylase which was significantly higher than that of the nonsurgical controls on day 6. The mean value (0.419) was above the normal upper limit (0.34) set by Moore (85), indicating that the group 3 dogs had a more severe pancreatitis.

Most clinicians prefer to measure both enzyme activities in diagnosing pancreatitis since the degree of elevation in serum amylase activity does not correlate well with the severity of pancreatitis (8). Gage and Anderson (7) reported that "Some cases of acute pancreatitis in dogs are not accompanied by an increased serum amylase value." Increases in serum lipase activity are primarily due to pancreatitis since the main source of lipase is the pancreas (8). In man, hyperlipasemia may also occur in intestinal obstruction, peritonitis, and renal insufficiency (86).

Greve et al. (21) found that the serum activity of amylase and lipase

tend to increase and decrease simultaneously, and the results of group 3 in the present study agree with their findings. The mean lipase value of group 2 gradually increased from day 1 to day 9, but the mean amylase value increased from day 1 to day 6, and then decreased on day 9. The lipase values for group 2 were within the normal range of 0-0.68 lipase units/ml. (85) throughout the experiment, and the pancreatic tissue in most of these animals was essentially normal on necropsy examination.

Serum Glutamic Pyruvic Transaminase (SGPT)

The liver of the dog contains high concentrations of SGPT. Significant elevations in SGPT are considered to be specific for hepatic necrosis. Normal values are 10-50 F.U./ml. according to Cornelius (87). SGPT activities of 50-400 F.U./ml. indicate moderate hepatic necrosis, and values greater than 400 F.U./ml. are an indication of severe liver necrosis. Focal necrosis of the liver may occur in a dog with acute pancreatitis if the inflamed pancreas adheres to it. Generalized peritonitis occurring with pancreatitis may affect the serosa of the liver causing a mild hepatic necrosis. In group 3, staph alpha-toxin may have leaked from the pancreas adding to the severity of the peritonitis and hepatic necrosis. Also, some amount of staph alpha-toxin must have been picked up by the portal system and carried to the liver. Adhesions between the pancreas and the liver were found in one dog of group 3.

There was a significant increase in the mean SGPT value of group 3 dogs from 13.3 F.U./ml. (day 1) to 45.7 F.U./ml. (day 6), and then a decrease to 38.4 F.U./ml. on day 9. The rise on day 6 may have been an indication of mild hepatic necrosis in a small portion of the liver, but all values were within normal limits. In group 2, there was a slight elevation in the SGPT value (24.3 F.U./ml.), but the rise was not significant and was well within normal

limits. This elevation may have been a result of the mild peritonitis that occurred in some of the dogs in that group. In group 1, there were no significant changes in the mean SGPT values from one test day to the next.

Serum Alkaline Phosphatase (SAP)

Serum alkaline phosphatase from the liver is produced by biliary ductal cells. The upper limit of normal serum values is 12.5 K.K.U. (85). Elevations can occur with intrahepatic cholestestasis due to hepatic necrosis and with extrahepatic bile duct obstruction. Alkaline phosphatase is also found in bone, intestine, and kidney (88). In using SAP to evaluate liver function, one must be reasonable assured that abnormalities in these other tissues do not exist. In acute pancreatitis, increases in SAP may be due to (1) focal areas of liver swelling and necrosis caused by peritonitis, (2) duodenitis, and (3) partial occlusion of the bile duct due to swelling associated with inflammation of the pancreas.

There was a significant rise in the mean SAP values of groups 2 and 3 the day after surgery. The mean value of group 2 rose from 11.1 K.K.U. (day 1) to 26.2 K.K.U. on day 6 and then decreased slightly, but not significantly on day 9. The mean SAP value of group 3 rose from 6.7 K.K.U. on day 1 to 46.6 K.K.U. on day 6, and then decreased significantly to 36.5 K.K.U. on day 9. The difference in the elevation of the SAP of the two groups may reflect the difference in the severity of the disease process occurring in the pancreas. Manipulation of the pancreas of the dogs in group 2 during partial pancreatectomies and also the catheterization of the ventral pancreatic duct with infusion of saline into the pancreatic ductal system was probably sufficient to cause a mild to moderate pancreatitis. The infusion of the staph alpha-toxin into the ductal system produced a severe pancreatitis and accompanying

peritonitis (group 3); therefore, a greater degree of liver swelling and necrosis probably occurred resulting in a greater increase in the mean SAP values.

Serum Gamma Glutamyl Transpeptidase (GGT)

In humans, serum GGT values have been reported to correlate closely with serum alkaline phosphatase (SAP) values in liver disease. The greatest elevations of both occur when the biliary tract is affected. Whitfield et al. (89) found that the serum GGT value increased to a greater extent than the SAP value, and concluded that serum GGT was a more sensitive indicator of biliary tract disease.

So far, there have been no published reports on normal GGT values in dogs. GGT values were determined in this study to test the hypothesis that GGT increased in staph alpha-toxin pancreatitis in dogs. In the non-surgical control group (group 1), there were no significant changes in the mean GGT and the mean SAP values. In the surgical control group (group 2) there was a significant rise in SAP from day 1 to day 6 and then a slight nonsignificant decrease on day 9. There were no significant changes in the mean GGT values of group 2 even though there was an increase on day 6 from day 1, and then a decrease on day 9. The values of groups 1 and 2 were similar. In the staph alpha-toxin group (group 3) there was a significant increase in the mean SAP value from day 1 to day 6, and then a significant decrease on day 9. The mean GGT value increased from day 1 to day 6 to day 9, but none of the values were significantly different from each other.

These results provide no evidence that GGT and SAP values increase similarly in the dog during moderately severe staph alpha-toxin pancreatitis. Firm conclusions cannot be made until further studies on serum GGT values in the dog are performed.

Plasma Creatinine

Plasma creatinine is a good indicator of glomerular filtration rate. Creatinine is excreted primarily by glomerular filtration with minimal tubular secretion. Because plasma concentration is not affected by diet, exercise, or age, creatinine can be used as an indicator of glomerular filtration rate (90). Therefore, elevation of plasma creatinine indicates impairment of renal function. The normal range of plasma creatinine values is 1-2 mg./dl. (90).

The changes in mean creatinine values of all three groups were not statistically or clinically significant. All mean values of the three groups were within normal limits. The highest value obtained was that of group 3 on day 6 (1.63 mg./dl.). Dehydration, after surgery, could account for the higher values of groups 2 and 3 on days 6 and 9, but group 1 on day 6, and group 3 on day 1 had mean values nearly as high. These changes are probably due to day-to-day variation.

CONCLUSIONS

- (1) The glucose tolerance of group 3 dogs receiving staphylococcal alpha-toxin was significantly decreased by the effects of the ensuing acute pancreatitis as compared to group 2 (surgical/saline controls) and group 1 (non-operated controls).
- (2) The high-dose intravenous glucose tolerance test (H-IVGTT) is a reliable tool in the assessment of glucose tolerance in dogs. It was possible to distinguish between normal and prediabetic dogs using the k-value.
- (3) Simplified k-values based on 5 and 60 minute blood glucose values gave the closest approximations to the standard k-values. Although the standard k-value is a more accurate estimation of glucose tolerance, the simplified k-value calculated using 5 and 60 minute samples may be substituted for the standard k-value in clinical use if the loss of accuracy can be accepted. The standard k-value is recommended for investigative work.
- (4) 50% partial pancreatectomy with ductal catheterization and saline infusion was followed by clinical and clinico-pathologic signs of mild acute pancreatitis in group 2.

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APPENDIX

Table 20. Analysis of variance for blood chemical values in dogs.

Source	d.f.	<u>Glucose</u> M.S.	<u>Amylase</u> M.S.	<u>Lipase</u> M.S.	<u>SGPT</u> M.S.
Treatment (T)	2	16.993	0.1415	5.944	1363.0
Animal	27	171.84	0.0080	0.270	706.1
Day (D)	2	460.03	0.1298	3.335	968.9
T x D	4	1042.27	0.0823	2.005	1066.6
Error	54	88.41	0.0124	0.308	258.5

Table 21. Analysis of variance for blood chemical values in dogs.

Source	d.f.	<u>GGT</u> M.S.	<u>Creatinine</u> M.S.	<u>k-value</u> M.S.	<u>Alk P'tase</u> M.S.
Treatment (T)	2	10.03	0.5609	1.916×10^5	3849.5
Animal	27	2.78	0.1710	4.060×10^5	103.2
Day (D)	2	1.84	0.6365	6.674×10^4	2916.5
T x D	4	2.66	0.0665	1.818×10^4	1020.8
Error	54	1.35	0.0522	2.089×10^5	100.8

Table 22. Individual k-values for the H-IVGTT in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin).

Group	Dog	Day	α	$\beta \times 100$ (k-value)	R ²
1	1	1	6.26	2.90	0.95
1	1	6	6.22	3.78	0.98
1	1	9	6.22	3.54	0.96
1	2	1	6.18	2.63	0.98
1	2	6	6.19	2.76	0.96
1	2	9	5.92	2.48	0.75
1	3	1	6.37	2.28	0.98
1	3	6	6.27	2.91	0.97
1	3	9	6.08	2.31	0.97
1	4	1	6.50	3.34	0.99
1	4	6	6.29	2.85	0.98
1	4	9	6.07	2.87	0.99
1	5	1	6.24	2.58	0.97
1	5	6	6.10	2.42	0.96
1	5	9	5.81	2.40	0.95
1	6	1	6.32	3.20	0.98
1	6	6	6.23	3.16	0.94
1	6	9	6.00	2.97	0.97
1	7	1	6.26	3.13	0.91
1	7	6	6.14	2.72	0.93
1	7	9	5.91	2.88	0.82
1	8	1	6.38	2.57	0.99
1	8	6	6.17	2.61	0.96

Table 22. Individual k-values for the H-IVGTT in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin). (contd.)

Group	Dog	Day	α	$\beta \times 100$ (k-value)	R^2
1	8	9	6.15	2.28	0.98
1	9	1	6.46	2.75	1.00
1	9	6	6.20	2.57	0.99
1	9	9	6.21	2.95	1.00
1	10	1	6.25	2.96	0.98
1	10	6	6.37	3.05	0.96
1	10	9	6.22	2.96	1.00
2	11	1	6.37	2.93	1.00
2	11	6	6.41	3.22	0.99
2	11	9	6.35	1.69	0.99
2	12	1	6.29	3.31	0.98
2	12	6	6.40	3.51	0.97
2	12	9	6.20	2.38	1.00
2	13	1	6.12	3.56	0.87
2	13	6	6.42	3.94	0.97
2	13	9	6.11	1.38	0.99
2	14	1	6.28	3.34	0.98
2	14	6	6.35	2.84	1.00
2	14	9	6.15	2.21	0.96
2	15	1	6.39	3.38	0.99
2	15	6	6.31	3.04	1.00
2	15	9	6.21	3.11	0.97
2	16	1	6.16	3.18	0.90
2	16	6	6.17	2.77	0.96

Table 22. Individual k-values for the H-IVGTT in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin). (contd.)

Group	Dog	Day	α	$\beta \times 100$ (k-value)	R ²
2	16	9	6.11 ₄	2.81	0.97
2	17	1	6.31	2.81 ₄	0.99
2	17	6	6.35	3.09	0.98
2	17	9	6.21 ₄	2.35	1.00
2	18	1	6.30	3.11 ₄	0.98
2	18	6	6.21	2.26	0.99
2	18	9	6.20	1.53	0.95
2	19	1	6.12	2.10	0.98
2	19	6	6.18	2.61	0.99
2	19	9	6.15	2.63	0.93
2	20	1	6.23	2.89	0.96
2	20	6	6.21	1.86	0.99
2	20	9	6.22	2.19	0.90
3	21	1	6.11 ₄	4.32	0.93
3	21	6	6.90	4.50	0.98
3	21	9	6.23	1.36	0.97
3	22	1	6.11	3.11	0.97
3	22	6	6.11	2.51 ₄	0.94
3	22	9	6.21	1.11	0.97
3	23	1	6.33	3.25	0.95
3	23	6	5.99	2.10	0.97
3	23	9	6.08	1.18	0.93
3	24	1	6.08	2.87	0.89
3	24	6	6.07	2.58	0.99

Table 22. Individual k-values for the H-IVGTT in dogs. (1: nonsurgical controls; 2: surgical controls; and 3: staphylococcal alpha-toxin). (contd.)

Group	Dog	Day	α	$-\beta \times 100$ (k-value)	R ²
3	24	9	6.29	1.92	0.99
3	25	1	6.32	3.20	0.97
3	25	6	6.06	1.81	0.99
3	25	9	6.28	1.84	1.00
3	26	1	6.42	3.04	1.00
3	26	6	6.40	2.60	0.98
3	26	9	6.19	1.15	0.99
3	27	1	6.31	3.76	0.95
3	27	6	6.30	4.07	0.97
3	27	9	6.30	2.04	0.98
3	28	1	6.33	3.43	0.98
3	28	6	6.14	2.24	0.90
3	28	9	6.18	1.14	0.97
3	29	1	6.08	3.48	0.90
3	29	6	6.43	3.00	0.99
3	29	9	6.33	1.51	0.98
3	30	1	6.43	3.48	0.97
3	30	6	6.32	3.29	1.00
3	30	9	6.11	1.38	0.99

THE EFFECT OF ACUTE STAPHYLOCOCCAL ALPHA-TOXIN
PANCREATITIS ON THE GLUCOSE TOLERANCE
OF DOGS

by

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ABSTRACT

Pancreatitis is the major predisposing cause of diabetes mellitus in the dog. Diabetes may develop during the first episode or after several episodes of pancreatitis. The first objective of this study was to determine whether or not experimental acute pancreatitis impaired the glucose tolerance of dogs. The k-values calculated from the high-dose intravenous glucose tolerance test (H-IVGTT) were used to evaluate glucose tolerance. The second objective of the study was to determine if a simplified k-value calculated using 2-3 blood samples could closely approximate the standard k-value calculated using all 6 timed samples.

The study was performed using 3 groups of 10 dogs each. The groups were as follows: group 1--nonsurgical control dogs, group 2--surgical controls, group 3--pancreatitis dogs. On day 5, 50% partial pancreatectomies followed by ductal catheterizations were performed on the dogs in groups 2 and 3. Saline was infused into the ductal systems of group 2 dogs, and staphylococcal alpha-toxin was infused into the ducts of group 3 dogs. On days 1, 6, and 9, the following laboratory investigations were performed on all three groups: (1) H-IVGTT, (2) fasting blood glucose, (3) amylase, (4) lipase, (5) SGPT, (6) alkaline phosphatase, (7) gamma glutamyl transpeptidase, and (8) creatinine. Simplified k-values were calculated using six combinations of 2 and 3 timed blood glucose values.

The results showed that (1) 50% partial pancreatectomy produced clinical and clinico-pathologic signs of mild pancreatitis, (2) staph alpha-toxin produced signs of moderately severe pancreatitis, (3) the glucose tolerance of group 3 dogs was markedly decreased on day 9 as compared with group 1 and 2 dogs, and (4) the simplified k-values calculated using the 5 and 60 minute

blood sample values yielded the closest approximations of the standard k-values.

The conclusions from the study were (1) staph alpha-toxin pancreatitis causes decreased glucose tolerance in dogs, and (2) a simplified k-value calculated using 5 and 60 minute blood glucose values may be used in the clinical situation to approximate the standard k-value. The standard k-value is preferred for investigative work.