ACUTE PANCREATITIS AND DIABETES MELLITUS. A CLINICAL AND BIOCHEMICAL STUDY IN THE DOG.

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I N T R O D U C T I O N

Acute pancreatitis and diabetes mellitus are known to occur singly in the dog and, furthermore, recurrent episodes of pancreatitis often lead to diabetes mellitus after the pancreas is extensively destroyed; i.e., chronic pancreatitis. A recent study by Cotton et al (25) of spontaneous diabetes mellitus in the dog strongly suggests that simultaneous occurrence of diabetes mellitus and acute pancreatitis is more common than previously thought to be. Other studies done in the field of diabetes and acute pancreatitis in the dog and cat indicate a possible relationship between those two diseases (48, 49, 53).

This syndrome is well realized and described in man. It is a very feared disease because of the high mortality (96). The physiopathological events that occur in acute pancreatitis and diabetes involve almost every vital function within the body. The most extreme situation is diabetic coma (severe keto-acidoses). When present, it requires urgent and immediate treatment and even then, the death rate in man is high. The predominant symptoms of the syndrome are attributed to acute pancreatic inflammation, and diabetes is very often overlooked. It becomes more and more evident, however, that many individuals thought dying of acute pancreatitis eventually die because of (1) hypoinsulinemia and impaired energy-utilisation, (2) disturbed acid-base and mineral balance, and (3) toxic effect of ketones on nerve and livercells; i.e., the diabetic complications. Children with juvenile onset of diabetic acidosis can be reversed from the keto-acidosis state whereas dogs with diabetic coma are likely to die under present treatment practices. Coexisting acute pancreatitis exaggerates the problem.

The concept of simultaneous acute pancreatitis and diabetes mellitus has only to a limited extend gained access to the veterinary literature and practice. Very little experimental work is based on this idea.

The purpose of this experimental investigation in the dog is (1) to test the hypothesis whether acute pancreatitis can initiate the physiopathological events leading to permanent diabetes mellitus and (2) to study the clinical and laboratory features diagnostic of (a) experimental hormonal diabetes and (b) acute pancreatitis and diabetes mellitus.

REVIEW OF LITERATURE

SPONTANEOUS DIABETES MELLITUS IN THE DOG

Diabetes mellitus in the dog is a clinical syndrome characterized initially by polyuria, polydipsia, and polyphagia. Dermatosis, weight loss, cataract, and blindness will occur as the disease progresses. It occurs most frequently in obese, spayed females of 7 years or more of age. Glycosuria and ketonuria will strongly suggest that the animal is suffering from diabetes mellitus.

One of the first papers in the American literature was by Milks, 1932, (1). He described "some cases of diabetes mellitus" where glycosuria was a persistent feature even though not always accompanied with the usual diabetic signs. He encountered the primary complaints as being cough, irritation of the eyes, blindness, alopecia, and weight loss. Only one case was brought to the veterinarian with a history of polyuria and polydipsia. No blood analysis were made, but the glycosuria indicated that the blood glucose had exceeded the renal threshold (approximately 180 mg%). Milks expressed his strong feelings about some association between the presence of sugar in the urine and certain cases of alopecia and eye lesions. Even though his diagnoses were presented as tentative rather than final (because of the then-prevailing view that diabetes mellitus did not occur in animals), the cases closely resembled clinical diabetes mellitus as it is accepted today.

Cushing, 1934, (2) reported a case of diabetes mellitus in an eight-year-old obese, spayed bitch. The dog had lost weight and became gradually emaciated in spite of a ravenous appetite. Incontinence was observed for a period of 6-7 month. The vision was impaired and the physical examination showed bi-

lateral cataracts. Hyperglycemia (361.5 mg%) and glycosuria (4.7%) were present. The pancreas was abnormal at autopsy. There was a walnut-sized mass of fibrous tissue without any normal pancreatic tissue. The kidneys had undergone tubular degeneration and the liver was infiltrated with fat. Cushing concluded: "This is undoubtedly a case of diabetes in a dog. An interesting fact is the apparent absence of a pancreas".

A comprehensive and detailed description of diabetes mellitus in the dog was first given by Bloom and Handelsmand, 1937, (3). The striking point in their paper was the destinction between two types of diabetes mellitus. Type # 1 was the uncomplicated syndrome without keto-acidosis and coma, whereas type # 2 was presented with ketonemia and ketonuria. The paper is extremely valuable because it contains a detailed description of symptomatology, clinical pathology and an evaluation of the diagnostic procedures, such as blood sugar determination and oral glucose tolerance test. A survey of the etiology, pathology, and treatment for both the mild and the keto-acidotic form was given. It appeared that the incidence of spontaneous diabetes mellitus in the dog was 2 out of 2443.

Milks and Stephenson, 1937, (4) described ten cases of diabetes mellitus or "sugar diabetes". One owner complained about polyuria, polydipsia, weight loss, and emesis in his old, obese, spayed female dog. Two dogs developed a severe enteritis resulting in diarrhea and emaciation. Analysis for glucose in blood and urine were generally performed and hyperglycemia and glycosuria were always present as a strong indication of diabetes mellitus.

A single case report of diabetes in a dog has been given by Christensen, 1939, (5). A twelve-year-old English Setter bitch collapsed during exercise

and had initially signs of muscular weakness and incoordination. Urinalysis was performed and glycosuria was revealed. On the basis of the weakness and the glycosuria, a diagnosis of diabetes mellitus was made. The diet was adjusted but insulin administration was necessary to control the disease (6 units per day).

As an example of the difficulties in the differential diagnosis of diabetes mellitus, McBride, 1941, (6) reported a case of diabetes in an eleven-year-old Boston Terrier bitch, suspected to be suffering from nephritis. At the time of admission, the dog was emaciated and had bilateral opacity of the lenses. The urine was highly positive for sugar and hyperglycemia was present in a moderate degree (193 mg%). The author concluded that (1) "diabetes mellitus may be confused with clinical symptoms of a deficient heart with nephritis complications" and that (2) "cataracts in old dogs will suggest diabetes".

Pollock and Bauman, 1949, (7) cited evidence for an emotional period as a contributing factor in the release mechanism of spontaneous diabetes mellitus in the dog. A six-year-old Irish Setter bitch developed polyuria, polydipsia, glycosuria and hyperglycemia after spending five weeks in a kennel. The animal appeared emaciated, and it had pale visible mucous membranes. The urine revealed 4-plus (++++) sugar and 1 plus (+) acetone. Hematological examination revealed slight anemia and leucocytosis. Insulin was administered and the animal improved remarkably. Later on, however, the owner wanted euthanasia. Necropsy disclosed an enlarged pancreas with few islets. The remaining beta-cells were degenerated and free of granules. The authors felt that the emotional stress was an essential stimulus to give rise to diabetes, although it was not known if abnormal glucose tolerance was present prior to the "shock".

It occurred to Schlotthauer and Millar, 1951, (8) that the essential clinical manifestations of spontaneous diabetes mellitus were polyuria and polydipsia, whereas emesis, cataract, and alopecia appeared with less frequency. Hyperglycemia and glycosuria were present in all dogs. Ketonemia or ketonuria was not emphasized as being characteristic in their report. As stated earlier, the syndrome was observed in old, spayed females, originally obese, but gradually losing weight. One of seven dogs was a male; the eighth case was a male cat.

On the basis of polyuria, polydipsia, voracious appetite, and continuous weight loss, Millar, 1952, (9) diagnosed diabetes mellitus in a seven-year-old Alsation bitch. The urine contained glucose and hyperglycemia existed (384 mg%). The urine specific gravity was 1.002 and 1.020 on two tests, thus being lower than is usual in diabetes mellitus.

Ricketts et al, 1953, (10) reviewed spontaneous diabetes mellitus in the dog and cited polyuria and polydipsia as the cardinal clinical manifestations. The plasma glucose values ranged from 237-780 mg%. Seven cases were presented with ketonuria, three had acidosis, and hypercholesterolemia was generally present. The microscopic examination failed to reveal the presence of any normal beta-cells.

The coincidence of diabetes mellitus, obesity, and pyometra was investigated by Krook et al, (1969, (11). Their analysis of this complex indicated that "predisposition or resistance to any of the three diseases was associated with predisposition or resistance to all three of the diseases". Their diagnosis of diabetes mellitus was based on the presence of hyperglycemia and glycosuria.

In a review article, Meier, 1960, (12) described diabetes mellitus in a number of species, including horse, cow, sheep, pig, dog, cat, and chinese hamster. This survey is a very valuable key to the understanding of the syndrome in animals. The incidence in dogs appeared to be 1:200, and for cats 1:800 seemed to be a reliable figure. He assumed that acute or chronic relapsing pancreatitis were important factors in the subsequent occurrence of diabetes mellitus.

In order to establish a relationship between pregnancy, pseudopregnancy, and diabetes mellitus, Wilkinson, 1960, (13) investigated 56 cases of diabetes mellitus in dogs and cats. It appeared in this work that pregnancy and pseudopregnancy required an increased insulin output and hence these hormones contributed to development of diabetes mellitus. A detailed table of the major clinical manifestations was included. The author suggested that a significant relationship exists between breed (Dachshund and mongrel dogs encountered 33 out of 56), age (5-12 years), and sex (twice as many females as males) in diabetes mellitus. There were no apparent signs of pancreatic inflammation or dysfunction.

In a comprehensive study of diabetes, Meier, 1961, (14) established the incidence of diabetes mellitus in dogs to be 1:260 according to a literature review and to be 1:200 based on his own observations. The clinical observations and the clinical pathology did not differ from the general accepted pattern.

In fourteen dogs with diabetes mellitus, Dixon and Sanford, 1961, (15) cited polyuria, polydipsia, and weight loss as being the essential clinical features. Hyperphagia or aphagia and emesis occurred, as well as bilateral cataracts. The range of blood glucose was 152 to 350 mg%. Glycosuria appeared to be a

constant finding in the urinalysis. Ketonemia and ketonuria were observed in twelve out of fourteen cases. The outhors suggested treatment with low carbohydrate, and low fat diet, and with insulin. The pathological findings in eight out of fourteen cases have been reported by Dixon and Sanford, 1962, (16). They were mainly subacute or chronic pancreatitis, lipidosis of the liver, beta-cells agranulocytosis or vacuolization and glomerulosclerosis.

In reporting two cases of diabetes mellitus in dogs that were presented with polyuria, polydipsia, emesis, diarrhea, and progressive weight loss, Resnick, 1963, (17) attempted to control the disease with an oral hypoglycemic agent (Tolbutamide). The result was discouraging because it seemed impossible to obtain a normal blood glucose concentration using Tolbutamide. Stabilization of the plasma glucose was done using adequate subcutaneous administration of insulin (regular and/or N.P.H. insulin), thus implying that the diabetes was controllable.

Joshua, 1963, (18) reviewed the most prominent features of diabetes mellitus in dogs; i.e., incidence, symptomatology, etiology, diagnostic procedures, and treatment. Oral hypoglycemic agents were again used, but they were unable to control diabetes in the dog. In fact, they appeared to damage the pancreatic tissue and to endanger the animal's life.

Groen et al, 1964, (19) reported a case of diabetes mellitus in a dog, probably due to hyperproduction of anterior pituitary hormones and especially the growth hormone. Their paper contains a detailed study of the physical findings in diabetes, the behavior of the animal, and the laboratory findings. They found a close resemblance between the symptoms of spontaneous diabetes mellitus in dog and in man. It appeared to them that it was "if possible, even

more striking than in the case of experimental pancreatic diabetes".

A brief communication concerning spontaneous diabetes mellitus in the dog was given by Wilkinson, 1964, (20). The discussion centeres around incidence, etiology, and diagnostic procedures in spontaneous diabetes in dogs.

Berkow and Ricketts, 1965, (21) suggested that spontaneous diabetes mellitus should be considered whenever symptoms of polyuria, polydipsia, polyphagia, and weight loss occurred in a dog. They investigated seven cases and confirmed the diagnosis in each case by finding glycosuria and hyperglycemia. Usually they found the disease in older, obese dogs, but it also occurred in young individuals. Three of the dogs were treated with oral hypoglycemic agents, but they did not respond well to this type of drugs. They found insulin to be far more dependable as an aid in the control of the diabetic state.

The pathology of diabetes mellitus has been studied by Gepts and Toussaint, 1967, (22) and their paper contained a very valuable review of clinical data of spontaneous diabetes mellitus in the dog.

The clinical management of diabetes mellitus has been discussed in detail by Gordon, 1967, (23). He reported nine cases in the dog and one case in the cat. The successful treatment of the syndrome was dependant on insulin rather than or oral hypoglycemic agents.

Hall, 1970, (24) briefly reviewed the concepts of diabetes mellitus, especially the diagnosis and treatment. He concluded that "diabetes mellitus is a chronic disease syndrome generally manifested by polyuria, polydipsia, polyphagia, and weight loss. Glycosuria and hyperglycemia are characteristic laboratory findings".

In a recent article, Cotton et al, 1971, (25) reported a clinicopathological study of diabetes in the dog. The significant findings were: (1) Hyperglycemia, (2) hyperamylasemia, (3) increased BUN, (4) increased plasma creatinine, and (5) leucocytosis. Their findings strongly suggest acinar pancreas involvement in diabetes mellitus in the dog.

EXPERIMENTAL DIABETES MELLITUS IN THE DOG

Several attempts have been made to produce an experimental model for diabetes mellitus; a model that would enable the investigator to develop a better understanding of etiology, pathogenesis, diagnosis, and treatment of spontaneous diabetes mellitus in man and animals.

Total or subtotal (partial) pancreatectomy (27, 28, 29) can be employed to produce diabetes mellitus. Ligation of the pancreatic duct and simultaneous partial pancreatectomy has been described (29). Chemical diabetes mellitus has traditionally been produced by using alloxan (28, 29, 30, 31, 32). The effect of alloxan is selective on the beta-cells and the prevailing changes are hyalinization and degranulation of the beta-cells (29). Use of other alloxan derivatives has been suggested (29). The alloxan degranulating effect on the islets' beta-cells can be enhanced by partial pancreatectomy and/or anterior pituitary extract (30).

Drug diabetes can be produced by using antibiotics (streptozotocin) and antihypersensitive drugs (benzothiadiazine). The mechanism is not yet known (29). Streptozotocin will cause diabetes by either intravenous or intraperitoneal administration (29, 33). Degranulation of the beta-cells appears to be a

constant lesion (30). Benzothiadiazine has a diabetogenic effect when given orally (29, 34).

Pancreatectomy, chemical agents, and drugs render the animal diabetic by acting directly on the islet tissue (removal or destruction of the beta-cells). For this reason these methods give rise to a "pancreatic diabetes", assuming that no other tissues or organs are involved primarily (29).

Diabetes induced by methods causing a state of insulin deficiency or causing destruction of insulin are called "extra pancreatic" or "extra pancreatic beta-cellular diabetes", assuming that the action primarily has its origin in tissues outside the pancreatic beta-cells (29). To this category belongs the so-called pituitary diabetes, defined as diabetes induced by administration of anterior pituitary growth hormone (28, 29, 30, 31, 32). Because this method was of major importance in this work, it will be reviewed more in detail.

Altzuler et al. (35) registered an elevation of the body glucose pool after injection of bovine growth hormone (BGH) to mongrel dogs. They concluded that there was an increased glucose utilization and hence glucose production exerted by the effect of growth hormone. Campbell and Rastogy (36) recorded the following changes in blood plasma and serum of dogs given 2 mg BGH per kg body weight per day: (1) Increased serum insulin activity, (2) insulin increase preceded plasma glucose elevation, (3) decreased glucose/insulin ratio, (4) significantly increased insulin in dogs with hyperglycemia, and (5) increased plasma free fatty acids. These changes indicated a severe exhaustion of the insulin reserve in the pancreatic beta-cells resulting in transient or permanent diabetes mellitus.

Altzuler et al (37) observed glycosuria and hyperglycemia in mormal-fed mongrel dogs given 3 mg BGH per kg body weight per day intramuscularly for five to nine days. Rathgeb et al (38) investigated two methods of preparing dogs for BGH injection. Group # 1 consisted of fasting dogs and group # 2 of normal-fed dogs. Both groups received 1 mg BGH per kg body weight per day. Group # 1 did not develop hyperglycemia whereas group # 2 did. Both groups had increased serum insulin levels. The results suggested that the glucose concentration in blood can be increased by giving BGH and that the glycogen storage is of great importance in this metabolic interaction. Canine growth hormone (CGH) has also been used to induce extra-pancreatic diabetes as shown by Rathgeb et al (39). Daily administration of 1 mg CGH per kg body weight per day resulted in hyperglycemia, hyperinsulinemia, increased glucose uptake and production (C^{14} measurement). Effects also were traced to fat metabolism, where FFA output appeared to be increased. A recent study of the diabetogenic effect of bovine pituitary extract have been done by Louis et al (40). They found a significant increase of serum insulin and glucose by administration of pituitary extract for two to three consecutive days. The glucose tolerance also was impaired. A detailed description of BGH, its chemistry, release, action, diabetogenic effect, and whole metabolism was published in 1968 (41).

A combined effect of pancreatectomy, BGH and ACTH have been studied in rats by Bates and Garrison (42). They concluded that BGH and ACTH were equally effective in the production of diabetes when the animals were 80% partial pancreatectomized. Houssay and Anderson (43) argued that the action of ACTH was much less intense than that of BGH. Warren et al (46) have given a detailed outline of methods causing hyperglycemia.

SPONTANEOUS DIABETES MELLITUS IN MAN

Diabetes mellitus in man consists of two different forms: Juvenile-onset and maturity-onset diabetes (44, 45). The juvenile form is usually severe and the child becomes acutely ill, developing symptoms of polyuria, polydipsia, polyphagia, and rapid weight loss. Abdominal pain can occur and disturbances of vision have been reported. It not treated, the child rapidly develops keto-acidosis and, subsequently, diabetic coma resulting in death. It is accepted that this juvenile form occurs in children from 0 to 15 years of age. The diagnosis of juvenile-onset diabetes is based on a fasting blood glucose determination. Values above 120 mg% glucose indicate diabetes in the child. The treatment of juvenile-onset diabetes is, first, fluid therapy in order to maintain a good renal blood flow (RBF) so as to eliminate the toxic ketone bodies from the blood. Secondarily, insulin must be administered subcutaneously. Juvenile-onset diabetes usually requires insulin with a low carbohydrate and low fat diet thereafter.

The maturity-onset form of human diabetes mellitus occurs in the age group from 40 and peaks between 60 and 70 years of age. The individual develops a mild degree of glucose intolerance with subsequent polyuria and polydipsia due to hyperglycemia. Keto-acidosis and coma are very seldom reported. The glucose tolerance tests are needed to diagnose the maturity-onset with confidence. It is obvious that precautions must be taken in the interpretation of the values because the glucose tolerance decreases with the age, Kienholz (150). The available tolerance tests are (151): (1) Oral glucose tolerance test (OGTT). (2) intravenous glucose tolerance test (IVGTT), (3) high dose intravenous glucose tolerance test (H-IVGTT), (4) insulin tolerance test,

(5) high carbohydrate meal tolerance, (6) Tolbutamide^{R} test, and (7) corticoid augmented oral glucose tolerance test. The preferred test is still the OGTT because of the relative simple procedure and good reliability. In the maturity-onset type, dietary care and precautions are necessary, but oral hypoglycemic drugs can be utilized with good results. This is in contrast to diabetes in dogs, where oral hypoglycemic agents are contraindicated in any age group.

SPONTANEOUS ACUTE PANCREATITIS IN THE DOG

A valuable description of spontaneous acute pancreatitis in the dog was made by Pritchett, 1940, (47). A twelve-year-old male Fox Terrier was presented with a history of sudden and repeated attacks of emesis. Assuming the dog had been poisoned, a physical examination was carried out. The temperature was high (105°F), and tachycardia and congested mucous membranes were found at the physical examination. Abdominal palpation disclosed severe pain and the dog "continuously cried out with acute pain". After performing anesthesia to facilitate examination, a "large, firm, disc-shaped mass" was palpated in the anterior part of the abdomen (epigastric region). The author thought of this as being a tumor in abdominal organ (liver or pancreas). No attempt was made to keep the animal alive and euthanasia was selected by the owner. Autopsy revealed large quantities of dilute hemorrhagic fluid present in the abdominal cavity. The pancreas and adjacent intestines were reddish, discolored, and thickened. Fibrin covered the pancreas. Microscopic examination disclosed diffuse hemorrhagic inflammation in the pancreas together with scattered focal necrosis.

In a survey of 1800 dogs, Coffin and Thordal-Christensen, 1953, (48) selected 70 cases of pancreatitis and recorded the predominant symptoms in acute (necrotizing) pancreatitis to be: Collapse, severe abdominal pain, emesis, and bloody diarrhea. Simultaneous occurrence of hyperglycemia and glycosuria indicated disturbances in the carbohydrate metabolism. They strongly suggested that the physical examination be followed by a blood sugar analysis in order to confirm the diagnosis of acute pancreatitis. Their treatment of choice was supportive, consisting mainly of fluid.

Thordal-Christensen and Coffin, 1956, (49) described in detail the symptomatology of acute (hemorrhagic or necrotizing) pancreatitis. Once again, emphasis was put on peripheral circulatory collapse, severe abdominal pain, and emesis. Furthermore, they encountered disinclination to move, rapid pulse, and shallow respiration. The body temperature was above normal (103-105°F) at onset, but decreased simultaneously with the cardio-vascular deterioration, ultimately becoming subnormal. Hyperglycemia occurred in two cases. Hemoconcentration and leucocytosis were constant features in the laboratory examination.

A protracted case of acute pancreatitis disclosed information of a sudden vigorous onset, Singleton and Rhodes, 1957, (50). The dog survived for 12 days during which period of time the laboratory results were: (1) Hemoglobin of 16.1 g%, (2) WBC of 15,000 per mm^3, and (3) blood urea of 215 mg%. No evidence of hyperglycemia was reported and the authors concluded that the animal survived longer because diabetes mellitus did not develop in the acute phase. The high blood urea of 215 mg% initially misled the clinician, and a diagnosis of nephritis was made. The reason for the high blood urea presumably was renal "shutdown", which often occurs in acute pancreatitis.

Wolff, 1960, (51) described persistent emesis, acute onset of abdominal pain, shock, and cyanosis in a three-year-old spayed female Schnauzer. A diagnosis of acute hemorrhagic pancreatic necrosis was made on a biopsy specimen obtained via exploratory laparotomy. Due to surgical shock, no laboratory tests were performed, but the author suggested "that serum amylase determination and urinalysis might have been helpful in differentiating this condition from acute intestinal obstruction, infectious canine hepatitis, acute nephritis, and peritonitis".

A comprehensive report of pancreatitis in the dog and cat was investigated by Small et al, 1964, (52). The clinical features of acute pancreatitis were characterized by sudden onset of acute severe pain in epigastric region, circulatory collapse, emesis, occasionally blood-tinged diarrhea, and normal temperature elevated to 104-105°F or subnormal. The criteria for the laboratory diagnosis were (1) hyperamylasemia, 2130 units or higher 2-6 hours after the onset and declining by 2-6 days later, (2) hyperlipasemia remaining elevated for 5-15 days, (3) glycosuria, and (4) hemoconcentration (PCV 55-65). Their treatment of choice was (a) fluid, (b) corticosteroids, (c) calcium lactate, (d) antimicrobial agents in huge doses, and (e) kallikrein-trypsin-inactivator (TRASYLOL^{R}).

Anderson and Low, 1965, (53) reported a summary of clinical data from 103 cases of canine pancreatic diseases. Acute onset of abdominal pain, emesis, restlessness, and circulatory collapse predominated in the clinical picture. Hyperamylasemia and hyperlipasemia and occasionally, hyperlipemia, were reported as being of diagnostic importance. They stated that diabetes mellitus could occur simultaneously with acute pancreatic inflammation.

In case of duodenal obstruction, Sragner, 1965, (54) presented evidence for subsequent occurrence of acute hemorrhagic pancreatitis. The animal developed persistant severe emesis, abdominal pain, congested mucous membranes and wiry pulse. A large mass could be palpated in the epigastric region and radiological examination disclosed severe obstruction of duodenum. The laboratory results revealed: (1) WBC of 16,500 per mm^3, (2) BUN of 120 mg%, and (3) PCV of 58%. Surgery failed to improve the condition and amylase values at 15,000 Somogyi units were measured. The dog deteriorated and died after three days.

Anderson, 1968, (55) gave detailed information concerning acute pancreatitis in terms of symptomatology, diagnosis, treatment, and prevention.

Brobst, 1970, (56) gave a detailed outline of the clinical pathology of pancreatic disease.

On the basis of the reviewed literature (48, 49, 50, 52, 54) acute pancreatitis must be suspected whenever an animal is presented with peripheral circulatory collapse, persistent emesis, and severe, acute abdominal pain. The hypotension might not be fully developed at admission, but is to be expected following vast destruction of the pancreas and release of vasoactive substances. Diarrhea, shallow respiration, disinclination to move, and decreased or increased temperature are not consistent features. The laboratory diagnosis appears to be of great importance. Emphasis is put on hyperamylasemia and hyperlipasemia. Leucocytosis, hyperlipemia, increased PCV, hyperglycemia, and glycosuria are not constant findings and can be misleading in the diagnosis. Recently, it has been suggested (58) that radiography is an aid to diagnosis, but radiographic criteria for diagnosis are not well established in veterinary medicine.

The following treatment has been advocated (58): (1) Restoration of fluid and electrolyte loss, (2) atropine to decrease glandular secretion and help cardiac and peripheral circulation, (3) antiemetic agents to reduce further electrolyte loss (especially duodenal content), (4) broad-spectrum antibiotic in high doses, (5) analgesics to relieve severe pain, and (6) vitamins, minerals, glucose, and amino-acids to restore lost tissue metabolites. The prognosis is guarded because of severe tissue destruction, peritonitis, and reduced kidney function (renal "shutdown" due to hypovolemia, uremia), and hepatic and cerebral disorders.

PATHOGENESIS OF ACUTE PANCREATITIS IN THE DOG

Singleton and Rhodes (50) assumed that biliary obstruction at a point between the ampulla of Vater and the major duodenal papilla preceded acute hemorrhagic pancreatitis. In this case it was obvious that reflux into the pancreatic duct with activated enzymes and/or bacteria could take place. Small et al (52) indicates that "trauma, blockage of the duct due to tumor or enteric disease and, commonly, acute bacterial infections originating as ascending infections to the pancreatic duct presumably could mediate or induce pancreatic inflammation".

Sragner (54) found evidence for intestinal obstruction in the pathogenesis of acute hemorrhagic pancreatitis in the dog.

Pathogenesis is essentially unknown; obesity, middle age and fat engorgement are commonly associated with onset.

SPONTANEOUS ACUTE PANCREATITIS AND DIABETES MELLITUS IN THE DOG

Substantial loss of pancreatic (acinar) tissue due to inflammation or trauma (acute or chronic) theoretically will predispose the individual to develop subsequent diabetes mellitus, because the beta-cells in some extend must be involved in any process taking place in the acinar pancreatic tissue. It has been well established that chronic pancreatitis is a potential factor in the development of diabetes mellitus (2, 4, 8, 15, 16, 25, 48, 49). However, it could be of importance to evaluate and establish a possible relationship between the spontaneous acute pancreatitis and coincidental or subsequent development of diabetes mellitus. This relationship is well known in man, and some references appear in the veterinary literature concerning the concurrent existence of the two diseases.

Calzavara, 1924, (26) observed hyperglycemia and glycosuria in a case of necrotizing acute pancreatitis in a dog. Bloom and Handelsmand (3) implicated subacute pancreatitis and scattered necrosis in the pancreatic and peripancreatic tissue as direct or indirect etiologic and pathogenic factors in the development of diabetes mellitus. Milks and Stephenson (4) found multifocal pancreatic necrosis in a case of canine diabetes mellitus. Coffin and Thordal-Christensen, 1953, (48) emphasized the important diagnostic aids of glycosuria and hyperglycemia in acute pancreatitis thus indicating impaired glucose tolerance. They recorded hyperglycemia and glycosuria in two of fourteen cases. Thordal-Christensen and Coffin, 1956, (49) indicated again that hyperglycemia and glycosuria were common findings in acute necrotizing pancreatitis. Wolff, 1961, (51) assumed that hyperglycemia, glycosuria, and ketonuria would be present in the acute phase of acute pancreatitis. Dixon and Sanford, 1961 and 1962,

(15, 16) described two cases of diabetes in the dog accompanied with subacute, suppurative pancreatitis. Jubb and Kennedy, 1963, (72) found pancreatic necrosis to be the most common cause of diabetes mellitus in the dog. Small et al, 1964, (52) felt that glycosuria was "a constant" observation in the acute pancreatitis. This indicates that hyperglycemia is present. Anderson and Low, 1965 (53) concluded "that diabetes mellitus in the dog is often a complication of acute or chronic pancreatitis". Cotton et al, 1971, (25) reported necropsy findings in ten dogs with naturally occurring diabetes mellitus and their significant findings were: (1) Purulent pancreatitis (2 cases), (2) Necrosis of pancreas (4 cases), and (3) Autolysis of pancreas (2 cases). Nephritis, hepatitis, and chronic pancreatitis were also associated with diabetes mellitus.

The above cited referances imply that spontaneous acute pancreatitis in some cases, and maybe the majority, is followed by disturbances of the glucose-metabolism. The exact incidence is not well known, and it is still questionable whether transient or permanent diabetes will develop.

EXPERIMENTAL ACUTE PANCREATITIS IN THE DOG

Several attempts have been made to create this condition experimentally in the dog in order to elucidate the pathogenesis, symptomatology, and clinical pathology of acute pancreatitis.

I Pfeffer Technique

Pfeffer et al (57) deviced the "closed loop technique" or "Pfeffer technique" and this method has since been used in order to induce acute pancreatitis in

dogs (58, 59, 60). Even in germ-free dogs where bacterial reflux is not possible, acute hemorrhagic pancreatitis can be induced by using the closed loop technique, thus indicating that regurgitation of bile alone is sufficient to initiate the events that lead to acute pancreatitis. Williams and Byrne (61) concluded that regurgitation of duodenal content free of bile or bilesalts could produce severe acute hemorrhagic pancreatitis in the majority (67%) of their dogs with a Pfeffer preparation. In monkeys, Johnson and Doppman (62) used the closed duodenal loop technique to produce acute pancreatitis. White (58) assumed that this type of pancreatitis (regurgitation) is purely artificial, and that it will never occur in spontaneous acute pancreatitis in man. By ligation of the pancreatic duct, regurgitative pancreatitis can be prevented (60).

II Duct Ligation

Pancreatic duct ligation has recently been extensively used as a mean of inducing acute pancreatitis in the dog. Grözinger et al (63), Gjone et al (64), and Hagen et al (65a, 65b) initiated acute hemorrhagic pancreatitis in dogs by injecting a mixture of taurocholate and trypsin in the major duct (ductus Santorini) of pancreas after this had been ligated. Konok and Thompson (66) studied the pancreatic ductal mucosa as a barrier in the pathogenesis of pancreatitis and as an initiator of inflammation they used infusion of various bile and bile salt combinations with trypsin and or pancreatic juice. Bliss and Sibley (67), studying the Schwartzman phenomenon in dogs, produced acute hemorrhagic pancreatitis by a strain of E.coli. Anderson (68) infused undiluted and diluted staphyloccoccal alpha-toxin into the ventral pancreatic duct and created lethal and sublethal acute hemorrhagic pancreatitis. Sum et al (69) exposed the pancreas in dogs to bile, bile salts, trypsin, anionic

detergents, cationic detergents, mixtures of anionic and cationic detergents, and saline. They found a significantly different clinical picture between the six groups. In a comprehensive study, 1970, Paavo (70) subjected dogs to acute hemorrhagic pancreatitis using biliary components as a major source. The above studies strongly suggest that biliary salts and pancreatic activated enzymes are essential factors in the development of spontaneous acute pancreatitis.

III Alcohol

White (58) pointed out alcohol as a major problem in the experimental pancreatitis etiology. The role of this compound is still poorly understood, although many investigations have been carried out concerning the role of alcohol in both experimental and spontaneous acute pancreatitis in man (71).

SPONTANEOUS ACUTE PANCREATITIS IN MAN

"Acute pancreatitis is one of the most fulminating diseases with which we have to deal". This citation by Rodriquez (72) clearly define the severity of acute pancreatitis in man, and the subsequent intensive treatment necessary to maintain the patients' life. Pain is the first cardinal sign of acute pancreatitis (58, 73, 74, 75, 76, 77, 78). It can occur at any time of the day and will be sudden, violent, and persistent. It appears to be characteristic that the pain does not respond well to analgesics; e.g., morphine and its derivatives (58, 74, 75). The location of the pain is described to be in the upper left epigastric region and the supraumbilical area (58, 74). Referral of pain to the hypochondrial region is observed (73). Some cases manifest severe pain in the

lower abdominal region (79) and this localization could be misleading for the diagnosis (mimics appendicitis). The second classical sign in acute pancreatitis appears to be nausea and emesis (58, 73, 74, 75, 76, 79, 80). Presumably emesis normally relieves pain but in cases of acute pancreatitis the emesis enhances the boring pain (58). The vomited material may (75) or may not (58) contain blood. It always is reported to be bile-stained. Respiratory difficulties occur very often in acute pancreatitis (58, 75). The gastrointestinal response to acute pancreatitis usually is dominant, consisting of ileus and bloody diarrhea (58, 75, 79, 80). Flatus may occur in the initial period (74). Some authors emphasize dehydration as being present in the acute phase of the disease, but it is not accepted as being a characteristic physical finding (79). Fever appears in some cases (59, 79). The pulse is usually quick and very weak (58, 78). Shock and coma is reported as a fairly common complication to the disease in man (58, 81). Other complications are observed and listed as: (1) Hypocalcemic tetany, (2) uremia due to renal shutdown, (3) anemia due to the toxic effect of substances released from pancreas, (4) hypoproteinemia due to liver involvement, (5) hyperbilirubinemia and jaundice (liver or bile duct involvement), and (6) diabetes mellitus (hyperglycemia, glycosuria), Schallenberger (79). In addition to this, Gambill et al (75) observed hydrothorax and ascites in cases of prolonged acute pancreatitis. The ascites has been described in detail of Kavin (82). Laboratory diagnosis consists of the following analytic data: (1) Hyperamylasemia (58, 75, 79, 80), (2) hyperlipasemia (58, 79), (3) leucocytosis (a) 7,200/cum to 24,000/cumm (75) and (b) 15,000/cumm to 42,000/cumm (76), (4) increased PCV (75), (5) hyperglycemia (58, 74, 75, 79, 80), (6) hypocalcemia (75), (7) hyperlipemia (83), (8) changes in urine amylase clearance (58), and (9) glycosuria.

White (58) emphasized that "the diagnosis of acute pancreatitis rests principally on three blood tests: Hyperglycemia, hyperamylasemia, and hyperlipasemia". The diagnosis is based on the clinical signs and the laboratory data. Radiography together with abdominal exploration are valuable aids in the confirmation of the diagnosis (58).

Treatment principally is of two types: The medical and the surgical approach. The guidelines for the medical treatment appear to be (58): (1) Relieve the pain (a) morphine-pethidine or derivatives intravenously, (b) procaine intravenously, (c) epidural analgesia, (2) parasympatholytic action (atropinizing), (3) fluid and electrolyte restoration, (4) blood transfusion, (5) huge amount of antimicrobial agents, and (6) antienzyme treatment (Trasylol^{R} i.e.).

SPONTANEOUS ACUTE PANCREATITIS AND DIABETES MELLITUS IN MAN

Wells, 1922, (84) reported a case of traumatic injury to the pancreas resulting in development of subsequent diabetes mellitus. Rodriquez, 1924, (73) described semicomatose acute pancreatitis with glycosuria and ketonuria. A blood sugar value of 600 mg per 100 ml blood was recorded. Schott, 1926, (85) described a patient complaining primarily of acute pancreatitis. Glycosuria, ketonuria, and hyperglycemia were detected in the laboratory examination. Warfield, 1927, (86) studied four cases of acute pancreatitis. Two ended in death presumably due to the severe ketonemia and ketonuria that did not respond to treatment with insulin or fluid. Relapsing pancreatitis has been reported and can aggravate a latent diabetes considerably as described by Schwartz, 1931, (87). Jones, 1932, (88) found diabetes mellitus to be a com-

plicating factor to acute pancreatitis even with blood sugar values of 140 mg% (below the renal threshold). The most outstanding contribution to the theory of acute pancreatitis and diabetes mellitus as a subsequent factor was given by Schumacher (89) in 1940. He presented a case of diabetes mellitus following an attack of severe acute pancreatitis and he gave an outline and survey of the available literature until 1940. It was assumed that disturbances in carbohydrate metabolism very often occurred in acute pancreatitis, that glycosuria "is probably present in 10-12% of all cases", and that hyperglycemia occurred with "considerable regularity". Altered glucose tolerance "may be demonstrated in an even higher percentage of the cases". It was concluded that "definitive diabetes coming on abruptly or shortly after the acute illness is very impressive" and that "pancreatic sequestration increases the likelyhood of diabetes".

Smith, 1942, (90) argued that diabetic coma could occur following a surgical approach to the treatment of acute pancreatitis. The patient died and Smith felt strongly that the chances for survival were small when diabetes occurred as a complicating factor to acute pancreatitis. Kussmaul respiration developed in a case of acute pancreatitis and enabled Steiner and Tracy, 1943, (91) to make a tentative diagnosis of acute pancreatitis and diabetes mellitus. The laboratory results disclosed evidence for hyperglycemia, hyperlipemia, and hypercholesterolemia. They concluded that the vast necrosis of the pancreas was "responsible for the development of fatal diabetic coma". Paxton and Payne, 1948, (76) recorded 1500 mg percent glucose in blood in patients with acute pancreatitis, thus implying that the glucose metabolism was severely impaired. Warren et al, 1950, (77) indicated that acute pancreatitis often will be followed by diabetes mellitus. Diabetes following traumatic

injury (auto-accident) to the pancreas was reported by Gelin and Pirart, 1957, (92). Gjone, 1957, (93) examined post mortem two cases of acute pancreatitis that presumably suffered from simultaneous diabetes mellitus. Andrews, 1960, (94) found impaired glucose tolerance, glycosuria, and hyperglycemia in a patient showing overt symptoms of acute pancreatitis. Blumental et al, 1963, (95) suggested a very close relationship between pancreatitis and diabetes mellitus. Blood glucose values ranging from 840–1030 mg% were measured by Gordon, 1965, (96) in three cases of acute pancreatitis with hyperamylasemia. Saxtrup-Nielsen and Simonsen, 1969, (97) concluded upon a vast literature review that it was important not only to treat pancreatitis but that the diabetes also needed special attention. A recent study by Silva et al, 1970, (98) encountered 16 cases of diabetes mellitus out of 68 patient with acute pancreatitis, thus indicating a percentage of 23.5. The study did not reveal evidence for significantly higher mortality rate when acute pancreatitis and diabetes occurred simultaneously.

The reverse problem concerning diabetes complicated by acute pancreatitis has been discussed in detail by Root, 1937, (99) and Hughes, 1961, (100). It appears that this sequence will severely endanger the life of the patient.

M A T E R I A L A N D M E T H O D S

I Experimental Subjects

16 mongrel dogs with a body weight of 10-15 kg were divided into two treatment groups: Group number one containing the non acute pancreatitis dogs (NAP-dogs) and group number two, the acute pancreatitis dogs (AP-dogs). The dogs were studied in pairs, one ultimately being designated the NAP-dog and one the AP-dog. They were maintained in our research ward for 26 days or until they died of the disease. The 1st and 2nd days were defined as acclimatization period during which time a PCV, WBC, differential count, and fecal flotation for parasites were done.

II Food and Water

The daily food ration consisted on one lb. commercial canned dog food*1 and one vitamin tablet*2. Food intake was recorded every day, and on days following surgical procedures, the dogs were given a powdered food concentrate*3 twice daily and one vitamin tablet. Water was given ad libidum and the daily intake was estimated. Prior to blood tests and surgical procedures, the food was withheld, 12-16 hours.

III Symptomatology

Physical examination and observation of clinical signs were made every day throughout the whole period; i.e. from day 1 until day 26 or until the ani-

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*1 Kennel Ration^{R}, Quacker Oats Co., Chicago, Ill.

*2 Pet-a-Vit^{R}, North American Pharmaceutical, N.Y.

*3 Esbilac^{R}, Smith-Douglass division of Borden Chemical, Borden Inc., N.Y.

mal died of acute disease. The below listed features were evaluated and recorded:

(1) Rectal temperature in degrees Fahrenheit (°F).

(2) General condition, involving the general appearance of the dog (alert, apprehensive, weak, depressed, ataxia, coma), eating, drinking, urination, weight changes, and status of hydration as measured by the skin.

(3) Digestive system was especially examined since this investigation dealt with a gastro-intestinal problem. The degree of pain, if present, was recorded: Slight (+), moderate (++), or severe (+++). Emesis was observed with regard to frequency, intensity, and constituenta. Abdominal palpation yielded valuable information. Whenever possible, liver and pancreas were carefully palpated; size and crepitation were especially emphasized in the assessment. Other organs such as intestines and spleen did not reveal any abnormalities exept some gas-accumulation in the gut. Abdominal fluid content was recorded when present, as was diarrhea. Auscultation of the abdomen was also done.

(4) Circulatory system including:

(a) Femoral pulse, its rate per minute and its characteristics (normal, weak, irregular).

(b) Heart: Auscultation on both right and left side, observing for murmurs and split heart sounds. Estimation of the degree of murmur was done whenever feasible (from 1st to 5th degree). Emphasis was only put on anatomical murmurs. The forcefulness of the heart was also considered and recorded.

(c) Visible membranes were characterized as normal, pale, hyperemic, or muddy. Most emphasis was put in the conjunctive and the oral mucosa.

(d) The adequacy of perfusion was assessed by digital pressure on the gingiva, followed by quick withdrawal of the pressure.

(5) Respiratory system including:

(a) Respiration evaluated by inspection of rate per minute and character of the respiration (normal, labored (= dyspnea), or Kussmaul).

(b) Auscultation of the lungs: Ventrally, medially, and dorsally on the thorax. The sounds were characterized as normal, tubular (when slightly labored respiration occurred), or rales (moist or dry).

(6) Urogenital system including examination of the kidney, bladder, and uterus or prostate.

IV Blood Sampling

Blood sampling was carried out according to Bentinck-Smith (101) and the jugular approach was used most commonly. EDTA-stabilized blood for glucose determination was drawn on days 3, 5, 7, and 8 through 25 or until the animal died. Clotted blood samples for amylase, lipase, creatinine, and S-GPT were obtained on days 3, 5, 7, 19, 20, and 25, and for lipase and amylase also on day 21. When sampling for blood gas (P_{O_2} and P_{CO_2}), pH, and electrolytes, heparinized*[1] samples were collected anaerobically and the sealed syringe was immediately placed in an ice water bath. These determinations were done within 2 hours on days 3, 5, 7, 19, 20, and 25. CBC determination was done on EDTA stabilized blood on days 3, 5, 7, 19, 20, and 25.

V Urine Sampling

Urine sampling was done on days 1 through 25 or until the animal died. An

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*[1] Heparin (Ammonium Salt). Sherwood Medical Industries Inc., St. Louis, Mo.

attempt was made to collect urine in a metabolic cage, but in some instances catheterization of the bladder was necessary because (1) spontaneous urination did not occur or (2) the urine was mixed with fecal material and therefore unsuitable for analysis.

VI Function Tests

To ascertain the integrity of the liver and the kidneys and in order to evaluate the extend of possible damage to these vital organs, the following function tests were performed:

(1) Hepatic function was estimated using the sulfobromophthalein*[1] retention in blood. The procedure was performed according to Cornelius (102). The BSP test was performed on days 4, 10, 20, and 26.

(2) Assessment of kidney function was primarily an estimation of the endogenous creatinine clearance as a direct measurement of the glomerular filtration rate (GFR). Calculation of the clearance was done from the following formular, after Osbaldiston (103):

$$\text{GFR (ml/min/kg)} = \frac{U_{Cr} \times U_V}{P_{Cr}}$$

where U_{Cr} is the urinary creatinine concentration, U_V the urine volume, and P_{Cr} the plasma creatinine concentration.

The following procedure was used: The animals were fasted 12 hours prior to the investigation and given 0.02 mg atropine*[2] per pound of body

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*1 DADE^R, Sulfobromophthalein Sodium Injection, U.S.P., Division of American Hospital Supply Corporation, Miami, Fla.

*2 Wellcome^R, Atropine Sulfate Injection. Burroughs Wellcome and Co. (U.S.A.) Inc., Tuckahoe, N.Y.

weight subcutaneously. Anesthesia was initiated and maintained on Sodium Pentobarbital*[1]. The average length of anesthesia was three hours. The animals were retained in lateral recumbency and the urinary bladder was carefully flushed with 40 cc of 0.9% sterile saline and emptied again. Before beginning the collection period, it was ascertained that no urine or saline was present in the bladder. Three quantitative collection periods of thirty minutes each were selected according to Moore (104). Between the periods, the bladder was emptied and flushed with 15-20 cc 0.9% sterile saline and this amount added to the sample for the preceding period. Blood samples were obtained in the middle of period one and three, presumably representing the average plasma creatinine concentration. The above described procedure was repeated on days 4, 10, 20, and 26. The creatinine clearance was calculated for all three periods using the average blood creatinine value based on samples from periods one and three.

(3) The high-dose intravenous glucose tolerance test (H-IVGTT) was performed on days 3, 5, 7, 10, 18, 20, and 25 in order to evaluate the status of glucose metabolism in (1) health and (2) after procedures damaging the beta-cells had been carried out (50% partial pancreatectomy, hormonal insulin antagonism, and acute staphylococcal alpha-toxin pancreatitis). The concept used in our investigation was modified after Dyck and Moorhouse (105): An EDTA-stabilized blood sample was obtained at time zero and infusion of 2 ml (1 g) 50% glucose solution*[2] per kg body weight was then done immediately in a cephalic vein.

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*[1] Nembutal[R] Sodium. Abbott Laboratories, North Chicago, Ill.

*[2] Glucose Solution (Dextrose 50%). Haver-Lockhart Laboratories, Shawnee, Ks.

This vein was not used for further sampling that day. The infusion time ranged from 0.5 - 1.0 minute. Blood samples were obtained at 5, 15, 30, 45, 60, 90, and 120 minutes post injection to provide data for a glucose tolerance curve.

VII Laboratory Procedures

(1) Hematology (CBC) including:

(a) Hemoglobin determination after Schalm (106).

(b) Hematocrit using microhematocrit method after Schalm (106).

(c) WBC count using the Electronic Coulter Counter*1, as described by Schalm (106).

(d) Differential count using WRIGHT's stain after Schalm (106).

(2) Blood chemistry involved determination of:

(a) Amylase after Sax and Trimble (107).

(b) Lipase modified after Henry (108) using the macromethod.

(c) Creatinine after Henry (109).

(d) Glucose after Hyvarinen and Nikkila (110).

(e) S-GPT after Reitman and Frankel (111).

(f) BSP according to describtion of DADE.

(g) Electrolytes:

(I) Potassium (K^+) and sodium (Na^+) using Coleman model 21 Flame Photometer*2.

(II) Chloride*3 after Collore et al (112).

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*1 Model A... Serial 1056, Coulter Electronic, Kenmore, Chicago, Ill.

*2 Coleman Instruments, Incorporation, Maywood, Ill.

*3 Buchler Standard-Chloridometer, Model 4-200, Fort Lee, N. Jersey.

(3) Blood gas and pH:

(a) P_{O_2}*1 according to Clark et al (113).

(b) P_{CO_2}*1 according to Severinghaus et Bradley (114).

(c) pH*1.

(4) HCO_3^- and base excess (B.E.) derived from the Siggaard-Andersen nomogram (115).

(5) Urinalysis followed an outline given by Wilkinson (116). Clarity, color, estimated volume, and odor was determined by inspection of the samples. Blood, ketones, glucose, protein, and pH were measured every day using Labstix^R*2 and Clinitest^R*2. Specific Gravity (S.G.) was recorded using a TS-meter*3.

VIII Surgical Procedures

The surgical procedures consisted of two different methods:

(1) 50% partial pancreatectomy (50 $\bar{P}$) on day 6 for both groups of dogs (NAP and AP).

(2) Induction of acute pancreatitis in the dog with the best glucose tolerance; i.e., the more normal glucose tolerance curve.

The initial steps were identical for the two surgical procedures and will be described as one: 0.02 mg atropine per pound of body weight was given subcutaneously prior to anesthesia, which was attained with thiamylal sodium, N.F.*4 to effect, estimated as 8 - 10 mg per pound of body weight. Endo-

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*1 Model 16. P_{O_2}, P_{CO_2}, pH analyzer. Corning Scientific Instruments, N.Y.

*2 Ames Company. Division Miles Laboratories, Inc., Elkhart, Indiana.

*3 TS-meter. American Optical, Co.,

*4 Surital^R, Parke-Davis, Detroit, Michigan.

tracheal intubation followed when the swallowing reflex had disappeared. The anesthesia was maintained on methoxyflurane*[1] in a semi-closed system. Respiration rate, pulse rate, and eye-reflexes were observed closely throughout the surgical procedure. The animals were retained in dorsal recumbency, all the hair was clipped from the abdomen before it was scrubbed with surgical soap, and finally disinfected with surgical alcohol and iodine solution. A shroud was used as draping and a midline incision through the skin was done from the xiphoid cartilage to 1 cm caudal to the umbilicus. The skin edges were clamped with towels and the abdomen opened by incising the linea alba in the same extend as the skin incision. The falciform ligament was removed blundly immediately after access to the abdominal cavity was gained. From this point, the procedure was as described under (1) and (2) below:

(1) 50% partial pancreatectomy (117, 118, 119): Approximately 50% of the pancreatic tissue was exised from the left and right lobes with minimal damage to the remaining duodenal segment and the pancreatic ducts (ventral and dorsal). Anatomical details and definitions of terms have been presented by Anderson (120).

The left lobe was approached initially. In order to get adequate exposure of this lobe and adjacent organs, the stomach and spleen were exteriorized and helt outside the incision with moistened sponges. The left lobe then was separated from its bed in the greater omentum by blunt dissection, beginning at its distal extremity. The vessels were clamped and ligated*[2]. The splenic vein was left intact and, if neces-

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*1 Metofane^{R}, Pitman-Moore, Fort Washington, Pennsylvania.

*2 4-0-chromic Ethicon^{R}. Ethicon Inc., Sommerville, New Jersey.

sary, a bit of pancreatic tissue was left adjacent to it to assure preservation of that vessel. The left lobe was clamped transversely just distal to the duodenal lymph node and ligated. The ligated stump of pancreas was overlaid with omentum by a simple continuous suture. There was no attempt made to close the omentum. The stomach and spleen were returned to the abdomen.

The right lobe was delivered into the incision with the duodenum and maintained in that position. The caudal pancreatic duodenal vessels in the mesoduodenum were ligated and the right lobe was bluntly dissected free of the mesoduodenum to its junction with the duodenum just caudal (0.3 - 1.0 cm) to the ventral pancreatic duct. At this point, the pancreas was clamped off and ligated. The mesoduodenum was carefully sutured and the ligated stump of pancreas was covered with mesoduodenum. Throughout the procedure, it was attempted to minimize traumatic injury to the tissue, but mild pancreatitis usually occurred as seen by increased amylase and lipase activities on day 7. The weight of the tissue was measured and recorded. The duodenum and pancreatic remnant was returned to the abdominal cavity.

(2) Induction of acute pancreatitis: The dog with the better glucose tolerance was subjected to acute staphylococcal alpha-toxin pancreatitis. The procedure was carried out on day 19 and the control dog received a sham operation on the same day.

(a) Acute pancreatitis (AP-dogs): The ventral pancreatic duct was exposed by bluntly removing the adjacent pancreatic tissue. When visible, the duct was ligated close to the duodenal wall. Through

a small incision in the duct wall, a catheter*1 was inserted and staphylococcal alpha-toxin*2 was infused by a syringe under slight manual pressure. A ligature was loosely placed close to the pancreatic tissue and, on removel of the catheter from the duct, this ligature was tightened, thus avoiding any escape of alpha-toxin through the duct incision. The pancreas was then placed in its normal position.

(b) Sham operation (NAP-dogs): This consisted of exposing the ventral pancreatic duct as described above without ligating it or infusing toxin into it.

Procedures (1) and (2) were then completed in the following manner: The peritoneum was closed with a continuous horizontal mattress suture. The external fascia was closed with interrupted sutures. Subcutaneous tissue was sutured using 2-0 sterile surgical gut*3 in a simple continuous suture. The skin was closed with a nylon monofilament suture*4. Survival surgery was practiced and no postoperative medication was given except as indicated under X (1) below.

IX Hormonal Treatment

Following the reduction of islet-cell mass by partial pancreatectomy, the dogs were rendered more susceptible to diabetes mellitus by hormonal treatment. This was done on days 16, 17, and 18 for both dogs, and the NAP-dogs

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*1 Intramedic^{R} polyethylene tubing PE 90/S36.

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

*3 2-0 chromic Ethicon^{R}. Ethicon Inc., Sommerville, New Jersey.

*4 2-0 Ethilon^{R}. Ethicon Inc., Sommerville, New Jersey.

were also given hormones on day 19 and day 20. Two hormones were used:

(1) Bovine growth hormone*[1] (BGH) in a dose of 5 mg/kg given intramuscularly twice daily.

(2) Dexamethasone*[2] (DX) 0.02 mg/kg was given intramuscularly twice daily after Bates (121) at the same time as BGH.

The administration of the hormones was done subsequent to feeding the animals.

X Treatment

Treatment of the AP-dogs was confined to the following choice of drugs:

(1) Antibiotic*[3] given intramuscularly in a dose of 10,000 units procaine penicillin-G and 12.5 mg Dihydro-streptomycin base per kg body weight whenever the temperature rose above 103°F or dropped below 99°F.

(2) Atropine given subcutaneously in a dose of 0.02 mg per pound body weight in order to stimulate heart action and decrease pancreatic secretion.

(3) Fluid and electrolytes:

(a) 0.9% saline intravenously when no acidosis occurred.

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*[1] Bovine growth hormone.

(a) Raben type (1 growth hormone per mg). Nutritional Biochemicals, Cleveland, Ohio.

(b) Courtesy NIAMD. Specifications: Growth hormone, bovine, NIH-GH-B16, Mean Relative Potency: 0.93 USP units per mg. (weight gain test in 100 g hypophysectomized female rats)

*[2] Azium[R]. Schering Corporation, New York.

*[3] Combiotic[R]. Pfizer Agricultural Division, New York.

(b) Lactated Ringer's solution*[1] with 17.8 mEq of sodium bicarbonate*[2] added per liter given intravenously, whenever the animal showed evident clinical signs of acidosis (Kussmaul respiration).

(4) Prochlorperazine and isopropamide*[3] in a dose of 1 cc subcutaneously.

(5) Vi-B-complex*[4] intravenously, 2 cc per dog per day.

XI Statistical Methods (according to Fryer (122)).

The statistical analysis included calculations of means, variances, and standard deviations for the measured variables and, later on, performance of a one-way analysis of variance (ANOVA). The Bartlett's test for homogeniety of variances; i.e., Ho ($\sigma_1^2 = \sigma_2^2 = \ldots = \sigma^2$ | only normality) was employed. In case of a significant F-test (F*) in the ANOVA, a Fishers' least significant difference test (LSD test) was done and a special table made up, comparing the means in the NAP- and AP-groups, arranging these means in an ordered array. In this way, the survey over the means should be faciliated. Both the ANOVA and the LSD test were used to test for significance at an alpha level of .05.

The intravenous glucose tolerance test again was subjected for pooling of data within the NAP- and AP-groups. Hence, the data will appear from days 3, 5, 7, 10, 18, 20, and 25.

The BSP and creatinine clearance data were pooled within the NAP- and AP-groups

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*1 Cutter Laboratories, Berkeley, California

*2 Abbott Laboratories, North Chicago, Ill.

*3 Darbazine^R. Norden Laboratories, Lincoln, Nebraska.

*4 Haver-Lockhart Laboratories, Shawnee, Kansas.

THIS BOOK CONTAINS NUMEROUS PAGES WITH DIAGRAMS THAT ARE CROOKED COMPARED TO THE REST OF THE INFORMATION ON THE PAGE.

THIS IS AS RECEIVED FROM CUSTOMER.

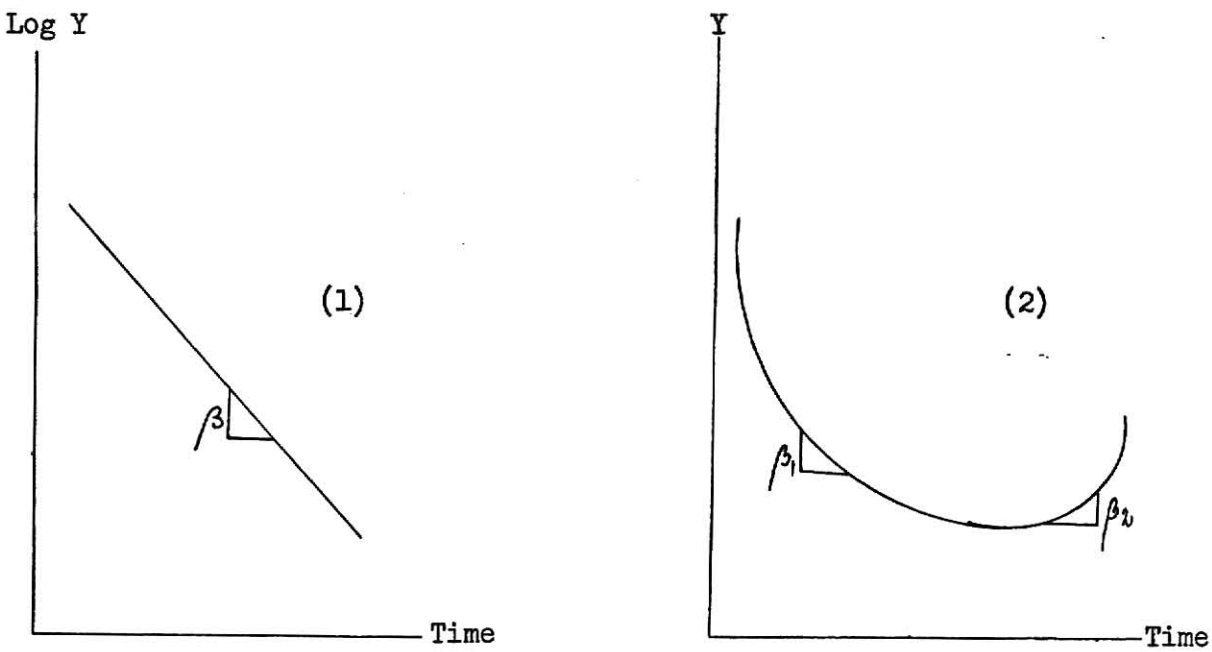
and the mean and S.E.M. were calculated. There was no test performed for significance of these variables.

Means and S.E.M. of glucose concentrations were calculated for every day for dogs in the NAP- and AP-groups. Tests for significance of LSD tests were not performed exept on days 3, 5, 7, 10, 18, 20, and 25, where the glucose-tolerance data were subjected to statistical regression analysis at an alpha level of .05. An attempt was made to create a model in which our data would fit best; i.e., high r^2 and hence minimized deviation from the trend line. The two models used were:

(1) $\text{Log } Y = \alpha + \beta T$ where α is a constant, β the slope, and T the time

(2) $Y = \alpha + \beta_1 \frac{1}{T} + \beta_2 T$ where α is a constant, β_1 the slope when the curve decreases and β_2 the slope when it increases, and T the time.

A schematical presentation of the two types of curves is done below:



R E S U L T S

CLINICAL OBSERVATIONS

The clinical information is listed in tables 1-16 (pages 43-58) comprising data obtained on days 15 through 22. This period of time was considered to reveal the most important data of the whole schedule, whereas days 1 to 14 and days 23 to 25 were of minor interest. The control dogs (NAP-dogs) had only one examination on day 19 whereas the acute pancreatic dogs (AP-dogs) received an examination (e) prior to surgery and (f) 12 hours after the incision was closed. This, of course, was arbitrary since the acute manifestations of pancreatitis could peak at any time after the pancreas was exposed to the staphylococcal alpha-toxin. However, this schedule appeared to yield a good survey of the clinical status of each animal at a certain time. Day 20 represents the 24 hour examination, and day 21 the 48 hour examination post surgery.

The clinical data provided for all dogs resembled each other on day 1 to day 14 and will be summarized below under item I. Observations done on days 23 to 25 were different for the NAP- and AP-groups of dogs and will be summarized under items IIa and IIb.

I All dogs (days 1 to 14)

Significant changes in the dogs' attitude and appearance first occurred on day 7, following the 50% partial pancreatectomy on day 6. The dogs appeared weak and depressed with poor appetite and were usually 4-5% dehydrated although the water intake was normal or even increased. Evidence of pain (arched back) was manifest when the abdomen was palpated. On days 7 to 10, this pain appeared to be diffuse. It radiated to all parts of the abdomen,

but later on it was more localized around the abdominal incision (day 10 to 12). The pain varied in intensity from slight to moderate. Emesis was not a constant finding following partial pancreatectomy, but occurred in 5 of 16 dogs (31%). The vomited material was usually yellow and foamy but in some instances it was brown, revealing evidence of blood loss distal to the stomach. The emesis appeared to be followed by pain. Pancreatomegaly occurred in one case, but hepatomegaly was not detected by abdominal palpation. Fluid was present in the abdominal cavity with very little frequency (10%). Pulse rate was increased occasionally but the character of the pulse remained normal. The visible membranes appeared normal or slightly congested (hyperemic) and the perfusion time did not alter in any case, indicating circulatory integrity. Respiration appeared to be somewhat impaired (labored) on the 7th day, but this feature disappeared on days 8 and 9.

IIa NAP-dogs (days 23 to 25)

The animals that only received hormone usually had slight abdominal pain localized around the incision. In some cases, the pain was more diffuse involving the whole abdominal cavity. The pain would persist or decline before euthanasia on day 26. Emesis was not recorded in any NAP-dog after day 23. No residual effect on the circulatory and respiratory systems was noted on days 23 to 25. The visible membranes in some cases appeared to be pale (15-20%); in other cases, hyperemic (10%). None of the NAP-dogs died spontaneously but NAP-dog # 5 was euthanatized on day 21 when its partner AP-dog # 5 died of the acute pancreatitis/diabetes mellitus syndrome. NAP-dog # 5 was entirely normal prior to euthanasia.

IIb AP-dogs (day 23 to 25)

Significant differences in the clinical manifestations were encountered in the post surgical period (1) between the NAP- and AP-group of dogs and (2) within the AP-group. While the NAP-dogs as described above had no mortality nor suffered from any severe deterioration, this occurred among the AP-dogs, although in different degrees:

(1) Mild manifestations were observed in dogs 2, 6, and 7,

(2) Severe disease appeared in dogs 1, 3, and 4,

(3) Coma occurred in dogs 5 and 8.

Characteristic clinical signs for dogs with mild disease were (a) depression, weakness, ataxia, and anorexia, (b) abdominal pain and distension, (c) emesis, usually after meals, (d) hyperemic or pale mucous membranes, and (e) weak pulse.

Characteristic clinical signs for dogs with severe disease were (a) depression, ataxia, dehydration, anorexia, weight loss, polyuria, and polydipsia, (b) abdominal pain of variable intensity, (c) occasionally diarrhea containing blood, (d) emesis, (e) hepato- and pancreatomegaly, (f) weak pulse, (g) pale or hyperemic mucous membranes, and (h) labored respiration.

The clinical signs for the two comatose dogs were (a) unconsciousness and recumbency, (b) dilated pupils, (c) severe and persistent emesis, (d) no abdominal pain, (e) hypogastric intraabdominal crepitation, (f) oliguria to anuria, (g) muddy mucous membranes, and (h) weak pulse.

TABLE 1

CLINICAL DATA

NAP-DOG # 1

DAY	°F TEMP.	GENERAL CONDITION										DIGESTIVE SYSTEM							CIRCULATORY SYSTEM											RESPIRATORY SYSTEM							
																			pulse			heart				visible membranes			respiration			lungs					
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	102.0	x							x				+					x			129	x			x				x	x				36	x			x			
16[b]	102.0	x							x				+					x			112	x			x				x	x				28	x			x			
17	102.0	x							x									x			121	x			x				x	x				26	x			x			
18	102.6	x							x	x	x		+					x		x[4]	129	x			x				x	x				37		x			x		
19[d]	102.1	x							x[1]	x	x		+					x		x[4]	121	x			x				x		x			39	x				x		
20[c]	102.6	x							x	x	x		+					x			123	x			x				x		x			41	x				x		
21	102.4	x							x	x	x	x	+					x			125	x			x				x		x			40	x				x		
22	103.0	x							x			x						x			137	x			x				x		x			39		x			x		

b) Hormonal regimen initiated c) Hormonal regimen discontinued d) Sham operation

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

4) Feces did not contain blood

TABLE 2

CLINICAL DATA

NAP-DOG # 2

DAY	°F TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM				CIRCULATORY SYSTEM										RESPIRATORY SYSTEM						
														pulse			heart				visible membranes			respiration			lungs			
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	101.2	x							x				+					x			91	x			x				x		x			21	x			x			
16[b]	101.4	x							x				+					x			76	x			x				x		x			26	x			x			
17	102.0	x							x				+					x			112	x			x				x		x			33	x			x			
18	102.0	x							x									x			94	x			x				x		x			29	x			x			
19[d]	101.2	x							x[1]									x		x[4]	91	x			x				x		x			29	x			x			
20[c]	102.4	x							x				+					x		x[4]	108	x			x				x			x		39		x			x		
21	101.8	x							x				+					x			131		x				x		x			x		30		x			x		
22	101.2	x							x				+					x			98	x			x				x		x			28		x		x			

b) Hormonal regimen initiated c) Hormonal regimen discontinued d) Sham operation

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

4) Feces did not contain blood

TABLE 3

CLINICAL DATA

NAP-DOG # 3

DAY	°F TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM						CIRCULATORY SYSTEM										RESPIRATORY SYSTEM						
																pulse			heart				visible membranes			respiration			lungs			
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	101.3	x							x									x			96	x			x				x	x			24	x			x			
16[b]	102.0	x							x												72	x			x				x	x			35	x			x			
17	101.3	x										x									88	x			x				x	x			38	x				x		
18	101.3	x							x												82	x			x				x	x			18	x			x			
19[d]	101.1	x							x[1]	x	x										68	x			x				x	x			26	x			x			
20[c]	102.0	x							x	x	x		++				x	x			82	x			x				x			x	25	x			x			
21	101.6	x							x	x	x		++					x			102	x			x				x		x		24	x			x			
22	101.5			x					x												160		x		x					x			36	x			x			

b) Hormonal regimen initiated c) Hormonal regimen discontinued d) Sham operation

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

TABLE 4

CLINICAL DATA

NAP-DOG # 4

DAY	°F TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM					CIRCULATORY SYSTEM									RESPIRATORY SYSTEM					
															pulse			heart			visible membranes			respiration			lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	101.6	x							x							x					72	x			x				x			x	20	x			x			
16[b]	101.2	x							x												92	x			x				x			x	32	x			x			
17	101.1	x							x												84	x			x				x			x	36	x			x			
18	102.4	x							x	x	x									x[4]	80	x			x				x			x	38	x				x		
19[d]	101.8	x							x[1]	x	x		++					x		x[4]	91	x			x				x			x	39	x				x		
20[c]	101.7			x					x	x	x		++							x[4]	89	x			x				x			x	38	x			x			
21	101.3	x							x	x	x		+								64	x			x				x	x			24	x			x			
22	101.3	x							x	x	x		+								90	x			x				x	x			30	x			x			

b) Hormonal regimen initiated c) Hormonal regimen discontinued d) Sham operation

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

4) Feces did not contain blood

TABLE 5

CLINICAL DATA

NAP-DOG # 5

DAY	°F TEMP.	GENERAL CONDITION									DIGESTIVE SYSTEM						CIRCULATORY SYSTEM										RESPIRATORY SYSTEM					
																		pulse			heart				visible membranes			respiration			lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	101.8	x							x												110	x			x				x			x	19	x			x			
16[b]	101.6	x							x												82	x			x				x	x			20	x			x			
17	102.0	x							x										x	x[4]	94	x			x				x	x			32	x			x			
18	101.4	x							x	x	x								x	x[4]	68			x	x				x	x			32	x			x			
19[d]	101.5				x				x[1]	x	x								x	x[4]	71	x			x				x	x			30	x			x			
20[c]	103.0			x					x	x	x		++						x		98	x			x					x			40		x			x		

b) Hormonal regimen initiated c) Hormonal regimen discontinued d) Sham operation

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

4) Feces did not contain blood

Comment: Euthanasia was selected on day 20.

TABLE 6

CLINICAL DATA

NAP-DOG # 6

DAY	°F TEMP.	GENERAL CONDITION										DIGESTIVE SYSTEM					CIRCULATORY SYSTEM										RESPIRATORY SYSTEM						
																	pulse			heart				visible membranes			respiration			lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	101.4	x							x									x			104	x			x				x	x			29	x			x			
16[b]	100.8	x							x				+								103	x			x				x	x			32	x			x			
17	101.2	x							x		x	x	+					x			112	x			x				x	x			70		x			x		
18	102.0	x							x		x	x	+					x			72	x				x			x	x			40	x				x		
19[d]	101.8	x							x[1]		x	x	+			x		x			80	x				x			x	x			40	x			x			
20[c]	102.2			x					x		x	x	x	++		x		x			63	x				x			x	x			43	x			x			
21	101.8	x							x		x	x				x		x			103	x				x			x	x			22	x			x			
22	102.8			x					x									x			124	x			x				x		x		32		x			x		

b) Hormonal regimen initiated c) Hormonal regimen discontinued d) Sham operation

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

TABLE 7

CLINICAL DATA

NAP-DOG # 7

DAY	°F. TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM						CIRCULATORY SYSTEM										RESPIRATORY SYSTEM					
																pulse			heart				visible membranes			respiration			lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	100.5	x							x									x			56	x			x				x	x			25	x			x			
16[b]	101.5	x							x												83	x			x				x	x			27	x			x			
17	101.3	x							x	x	x							x			89	x			x				x	x			23	x			x			
18	101.8	x							x	x	x							x			105	x					x		x	x			28	x			x			
19[d]	101.2	x							x[1]	x	x							x			102	x					x		x	x			52	x			x			
20[c]	101.8	x							x	x	x		+					x			88	x					x		x	x			36	x			x			
21	100.2	x							x									x			100	x					x		x	x			42	x			x			
22	101.2	x							x									x			113	x					x		x	x			36	x			x			

b) Hormonal regimen initiated c) Hormonal regimen discontinued d) Sham operation

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

TABLE 8

CLINICAL DATA

NAP-DOG # 8

DAY	°F TEMP.	GENERAL CONDITION							DIGESTIVE SYSTEM				CIRCULATORY SYSTEM								RESPIRATORY SYSTEM					
														pulse			heart			visible membranes			respiration		lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	100.3	x							x				+					x			112	x			x				x	x			24	x			x			
16[b]	101.2	x							x				+					x			113	x			x				x	x			29	x			x			
17	101.8	x							x				+					x			88	x			x				x	x			32	x			x			
18	101.9	x							x	x	x		++					x		x[4]	96	x			x				x	x			38	x				x		
19[d]	101.6	x							x[1]	x	x		+					x		x	108	x			x				x	x			24	x			x			
20[c]	102.5				x				x	x	x		++					x		x	98	x			x				x	x			35	x			x			

b) Hormonal regimen initiated c) Hormonal regimen discontinued d) Sham operation

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

4) Feces did not contain blood

Comment: Euthanasia was selected on day 20.

TABLE 9

CLINICAL DATA

AP-DOG # 1

DAY	°F TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM					CIRCULATORY SYSTEM										RESPIRATORY SYSTEM						
															pulse			heart				visible membranes			respiration			lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	101.8	x							x												111	x			x				x	x			24	x			x			
16[b]	102.4	x							x												103	x			x				x	x			25	x			x			
17	102.4	x							x	x	x										101	x			x				x	x			27	x			x			
18[c]	102.8	x							x	x	x										103	x			x				x	x			25		x			x		
19[e]	102.4	x							x[1]	x	x										107	x			x				x	x			31	x			x			
19[f]	102.8			x	x		x			x	x	x	+++	x[2]				x			208		x				x					x	53			x		x		
20	102.9			x	x		x			x	x	x	+++	x[2]				x			180		x				x				x		39		x			x		
21	102.8			x	x		x			x	x	x	+++	x[2]				x			161		x				x				x		27		x		x			
22	101.6			x			x			x	x	x	++					x	x		127	x			x				x		x		25		x			x		

b) Hormonal regimen initiated c) Hormonal regimen discontinued

e) Prior to surgical procedures f) 12 hours after surgical procedures

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

2) Emesis was severe and the vomited material yellow

Comment: The animal recovered from the acute attack but deteriorated towards day 25

TABLE 10

CLINICAL DATA

AP-DOG # 2

DAY	°F TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM							CIRCULATORY SYSTEM												RESPIRATORY SYSTEM							
																	pulse				heart					visible membranes				respiration				lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	100.8	x																x			104	x			x				x		x			24	x			x			
16[b]	100.8	x							x					x							108	x			x				x		x			21	x			x			
17	101.2	x							x				+								121	x			x				x	x				22	x			x			
18[c]	101.6	x							x	x	x		+								111	x			x				x	x				23	x			x			
19[e]	101.9	x							x[1]	x	x		+								108	x			x				x	x				25	x			x			
19[f]	102.6			x	x					x	x		+++	x[2]	x	x	x	x	x[3]		170		x	x		x		x	x			x		37		x			x		
20	101.3			x	x					x	x	x	++	x[2]		x		x			180		x					x	x			x		21		x			x		
21	101.4				x				x			x	++			x		x			164		x					x	x			x		18		x			x		
22	101.4				x							x	+++			x		x			128		x					x	x		x			19	x			x			

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

e) Prior to surgical procedures

f) 12 hours after surgical procedures

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

2) The vomited material was yellow

3) Semohemorrhagic fluid

Comment: The dog recovered from the acute attack and was almost clinically normal on day 25

TABLE 11

CLINICAL DATA

AP-DOG # 3

DAY	°F TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM						CIRCULATORY SYSTEM									RESPIRATORY SYSTEM					
																pulse			heart			visible membranes			respiration			lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	102.0	x							x				+					x			78	x			x			x			x		30	x				x		
16[b]	101.8	x							x												72	x			x			x	x				31	x			x			
17	101.9	x																x			64	x			x			x	x				43	x				x		
18[c]	101.7	x																			62	x			x			x	x				30	x				x		
19[e]	101.6	x							x[1]	x	x										64	x			x			x			x		21	x			x			
19[f]	102.6			x	x					x	x	x	++	x[2]		x		x	x	x[3]	190			x	x			x	x			x	30			x		x		
20	103.0			x	x		x			x	x	x	++	x[2]		x		x	x	x[3]	x[4]	203		x		x			x	x			x	36			x		x		
21	102.7			x	x					x	x	x	++			x		x	x	x[3]	x[4]	155		x		x			x	x			x	20		x			x		
22	102.6			x	x	x						x		x[2]		x	x			x[3]	x[4]	205		x	x				x	x			x	31			x		x		

b) Hormonal regimen initiated c) Hormonal regimen discontinued

e) Prior to surgical procedures f) 12 hours after surgical procedures

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

2) The vomited material was yellow 3) Serohemorrhagic fluid 4) Hemorrhagic diarrhea

Comment: The animal died on day 24 in spite of heavily treatment

TABLE 12

CLINICAL DATA

AP-DOG # 4

DAY	°F TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM						CIRCULATORY SYSTEM										RESPIRATORY SYSTEM							
																pulse			heart			visible membranes			respiration			lungs				
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	101.5	x							x												68	x				x		x	x			21	x			x			
16[b]	101.6	x							x												72	x				x		x	x			21	x			x			
17	101.5	x							x												72	x				x		x	x			36	x			x			
18[c]	101.4	x							x	x	x										84	x				x		x	x			52	x			x			
19[e]	101.5	x							x[1]	x	x							x		x	68	x				x		x	x			32	x			x			
19[f]	102.6			x	x	x						x	+++	x[2]	x	x	x	x		x[4]	250		x	x			x			x	x	43			x	x			
20	102:0		x	x			x			x	x	x	+++			x	x	x		x[4]	171		x			x		x	x			40			x				x
21	102.0		x	x			x			x	x	x	+++	x[2]		x		x		x[4]	155		x			x		x	x			25		x		x			
22	102.0		x				x					x	++	x[2]		x		x		x[4]	141	x				x		x	x			25		x		x			

b) Hormonal regimen initiated c) Hormonal regimen discontinued

e) Prior to surgical procedures f) 12 hours after surgical procedures

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

2) Emesis was severe and the vomited material brown

4) Hemorrhagic diarrhea

Comment: The animal recovered from the acute attack but deteriorated towards day 25

TABLE 13

CLINICAL DATA

AP-DOG # 5

DAY	°F TEMP.	GENERAL CONDITION										DIGESTIVE SYSTEM						CIRCULATORY SYSTEM												RESPIRATORY SYSTEM						
																		pulse				heart				visible membranes				respiration				lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	102.1	x							x									x			94	x			x				x	x			45	x			x			
16[b]	101.2	x							x				+					x			76	x			x				x	x			44	x			x			
17	101.8	x							x	x		x	+					x			111	x			x				x	x			50	x			x			
18[c]	101.5	x							x	x		x									96	x			x				x	x			47	x			x			
19[e]	101.5	x							x[1]	x		x						x		x	91	x			x				x	x			41	x			x			
19[f]	100.0							x						x[2]			x		x[3]	x[4]	19o		x	x			x				x		79			x		x		

b) Hormonal regimen initiated

e) Prior to surgical procedures f) 12 hours after surgical procedures

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

2) Emesis was severe and the vomited material brown

3) Serohemorrhagic fluid

4) Hemorrhagic diarrhea

Comment: The animal died in coma within 16 hours after surgery in spite of heavily treatment.

TABLE 14

CLINICAL DATA

AP-DOG # 6

DAY	°F TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM						CIRCULATORY SYSTEM										RESPIRATORY SYSTEM						
																pulse			heart				visible membranes			respiration				lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	101.7	x							x												81	x			x				x	x			21	x			x			
16[b]	101.5	x							x												62	x			x				x	x			36	x			x			
17	101.1	x							x				+					x			100	x			x				x	x			40	x			x			
18[c]	101.6	x							x	x	x		+					x			99	x			x				x	x			41	x			x			
19[e]	102.5	x							x[1]	x	x		+					x			64	x			x				x	x			39	x			x			
19[f]	106.0			x	x	x				x	x		+++	x[2]		x	x	x	x[3]	x[4]	168		x	x			x				x	x	39			x				x
20	103.8			x								x	+++	x[2]		x	x	x	x[3]		168		x				x	x			x		43			x		x		
21	104.0			x			x			x	x	x	+++				x	x	x[3]		139	x			x				x			x	24		x		x			
22	104.0	x					x			x	x	x	+++					x	x[3]		103	x			x				x	x			32		x		x			

b) Hormonal regimen initiated c) Hormonal regimen discontinued

e) Prior to surgical procedures f) 12 hours after surgical procedures

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

2) The vomited material was yellow 3) Serohemorrhagic fluid 4) Hemorrhagic diarrhea

Comment: The animal recovered from the acute attack and appeared clinically normal on day 25

TABLE 15

CLINICAL DATA

AP-DOGS # 7

DAY	°F TEMP.	GENERAL CONDITION								DIGESTIVE SYSTEM						CIRCULATORY SYSTEM											RESPIRATORY SYSTEM					
																pulse			heart				visible membranes			respiration			lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	100.7	x							x			x									71	x			x				x	x			16	x			x			
16[b]	100.9				x				x			x									73	x			x				x	x			13	x			x			
17	101.1				x				x			x									72	x			x				x	x			14	x			x			
18[c]	102.0				x				x			x									62	x				x			x		x		16	x			x			
19[e]	100.8	x							x[1]			x									62	x				x			x		x		20	x			x			
19[f]	103.2			x	x					x	x	x	++	x[2]				x	x	x[3]	200		x	x			x		x			x	x	23		x		x			
20	101.4			x	x							x	++		x						185		x	x			x		x			x		23		x		x			
21	101.8				x					x	x	x	++		x						90					x			x	x			20	x			x			
22	101.7	x										x	+		x						81		x			x			x	x			16	x			x			

b) Hormonal regimen initiated c) Hormonal regimen discontinued

e) Prior to surgical procedures f) 12 hours after surgical procedures

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

2) The vomited material was yellow 3) Serohemorrhagic fluid

Comment: The animal recovered from the acute attack and appeared clinically normal on day 25

TABLE 16

CLINICAL DATA

AP-DOG # 8

DAY	°F TEMP.	GENERAL CONDITION									DIGESTIVE SYSTEM						CIRCULATORY SYSTEM										RESPIRATORY SYSTEM					
																	pulse			heart				visible membranes			respiration			lungs		
		alert	apprehensive	weak	depressed	recumbent	ataxic	coma	appetite	polydipsia	polyuria	dehydration	pain	emesis	hepatomegaly	pancreatomegaly	crepitation	distension	fluid content	diarrhea	rate/min.	normal	weak	irregular	normal	murmurs	split sounds	force	perfusion	normal	pale	hyperemic	muddy	rate/min.	normal	labored	Kussmaul	clear	tubular	moist rales	dry rales
15	101.3	x							x												98	x							x	x			24	x			x			
16[b]	101.5	x							x												85	x			x				x	x			23	x			x			
17	101.8	x							x												96	x			x				x	x			24	x			x			
18[c]	102.0	x							x	x	x										88	x			x				x	x			28	x			x			
19[e]	101.8	x							x[1]	x	x		+					x			81	x			x				x	x			20	x			x			
19[f]	101.6			x	x			x		x	x	x	+++	x[2]		x	x	x	x[3]	x[4]	136		x	x		x		x			x	x	104			x		x		
20	102.4								x					x[2]		x	x		x[3]	x[4]	200		x	x		x		x				x	112			x		x		

b) Hormonal regimen initiated c) Hormonal regimen discontinued

e) Prior to surgical procedures f) 12 hours after surgical procedures

1) The animal showed good appetite but was not allowed to eat due to surgical procedures

2) Emesis was severe and the vomited material brown

3) Serohemorrhagic fluid 4) Hemorrhagic diarrhea

Comment: The animal died in coma within 36 hours after surgery in spite of heavily treatment

LABORATORY INVESTIGATIONS

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

A dose of 1 g/kg was given by intravenous injection to all dogs for all tests. The blood glucose concentration was measured over the 5 - 60 minute interval (5'-60').

(1) The normal dogs (all dogs on day 3) revealed (a) the return of the glucose tolerance curve to normal within 60 minutes (fig. 1: 111, p.63, fig. 2: 112, p. 64), (b) The data from these dogs fit the $Y = \alpha + \beta_1 \frac{1}{T} + \beta_2 T$ model better than the exponential function $\log Y = \alpha + \beta T$ (tables 17A and 17B, pgs. 61 and 62; figs. 3 and 5, pgs. 65 and 67: 111 and figs. 4 and 6, pgs. 66 and 68: 112). (c) The k-values were 2.67 ± 0.32 for the NAP-group on day 3 and 3.01 ± 0.38 for the AP-group on day 3 (table 17A, p. 61).

(2) The glucose tolerance was not significantly decreased on day 7 [24 hours after partial pancreatectomy (table 17A, p. 61)].

(3) All dogs were considered to be pre-diabetic on day 18 because (a) the glucose tolerance curve did not return to normal within 60 minutes post injection (fig. 1: 311, p. 63; fig. 2: 312, p. 64). (b) The data fit the two mathematical models less well than normal dogs but the r^2 was equal for both equations (tables 17A and 17B, pgs. 61 and 62; figs. 3 and 5: 311, pgs. 65 and 67, and figs. 4 and 6: 312, pgs. 66 and 68). (c) The k-values ranged between 1.96 ± 0.33 for the NAP-group on day 18 and 2.14 ± 0.10 for the AP-group on day 18 (table 17A, p. 61).

(4) The NAP-group of dogs treated with bovine growth hormone and dexamethasone

were diabetic on day 20. There was (a) a continuously high glucose level which never returned to normal (fig. 1: 411, p. 63). (b) There was an impaired fit to both models of the glucose tolerance curve (r^2 was decreased) (tables 17A and 17B, pgs. 61 and 62; figs. 3 and 5: 411, pgs. 65 and 67). (c) The k-values ranged 1.55 ± 0.28 (table 17A, p. 61).

(5) The induction of acute pancreatitis in the pancreatic remnant rendered the AP-dogs profoundly diabetic on day 20 as shown by (a) very abnormally shaped glucose tolerance curve that remained above 300 mg% after 60 minutes (fig. 2: 412, p. 64). (b) The data had the minimum fit to the two models (tables 17A and 17B, pgs. 61 and 62; figs. 4 and 6: 412, pgs. 66 and 68). (c) The lowest k-value in the whole investigation ($k = 1.13 \pm 0.44$) (table 17A, p. 61) was obtained on this day.

(6) The glucose tolerance curve (a) returned to normal shape in the NAP-dogs (fig. 1: 511, p. 63) on day 25 whereas this did not occur for the AP-dogs (fig. 2: 512, p. 64). (b) The curve regained a fairly good fit to both models in the NAP-dogs on day 25, but the fit was better for the $Y = \alpha + \beta_1 \frac{1}{T} + \beta_2 T$ than for the $\log Y = \alpha + \beta T$ model (tables 17A and 17B, pgs. 61 and 62; figs. 3 and 5: 511, pgs. 65 and 67). The curve for the AP-dogs on day 25 did not improve very much in fit to either of the functions (tables 17A and 17B, pgs. 61 and 62; figs. 4 and 6: 512, pgs. 66 and 68). These results indicated that the hormonal diabetes apparently reverted rapidly toward normal whereas the acute pancreatitis/diabetes mellitus did not revert toward normal nearly as much. Even though normal blood glucose values were found on day 25 in the AP-group, the glucose tolerance test revealed impaired carbohydrate metabolism.

TABLE 17A

BLOOD CHEMISTRY

REGRESSION ANALYSIS OF THE H-IVGTT

$$\log Y = \alpha + \beta T$$

NAP-DOGS

Day	N	$\alpha \pm SD_\alpha$	$\beta \pm SD_\beta$	k(%)	r^2	$SS_{\log Y}$
3	8	5.99 ± 2.61	−0.0267 ± 0.0032	2.67	0.63	17.80
5	8	6.11 ± 2.00	−0.0254 ± 0.0025	2.54	0.72	14.04
7[a]	8	6.25 ± 1.80	−0.0250 ± 0.0027	2.50	0.76	12.94
10	8	6.18 ± 1.18	−0.0222 ± 0.0014	2.22	0.85	9.16
16[b]						
18	8	6.13 ± 2.63	−0.0196 ± 0.0033	1.96	0.48	12.70
19[d]						
20[c]	8	6.11 ± 1.98	−0.0155 ± 0.0028	1.55	0.47	7.03
25	7	6.14 ± 1.65	−0.0259 ± 0.0023	2.59	0.78	11.85

AP-DOGS

Day	N	$\alpha \pm SD_\alpha$	$\beta \pm SD$	k(%)	r^2	$SS_{\log Y}$
3	8	5.99 ± 2.68	−0.0301 ± 0.0038	3.01	0.67	21.21
5	8	6.13 ± 2.44	−0.0281 ± 0.0030	2.81	0.68	18.20
7[a]	8	6.18 ± 0.90	−0.0217 ± 0.0011	2.17	0.90	8.24
10	8	6.13 ± 1.45	−0.0258 ± 0.0018	2.58	0.83	12.53
16[b]						
18[c]	8	6.02 ± 1.54	−0.0214 ± 0.0019	2.14	0.76	9.51
19[e]						
20	7	6.40 ± 2.64	−0.0113 ± 0.0044	1.13	0.18	8.05
25	6	6.26 ± 1.78	−0.0167 ± 0.0036	1.67	0.48	5.70

a) 24 hours after 50 $\bar{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) Prior to surgical procedures

TABLE 17B

BLOOD CHEMISTRY

REGRESSION ANALYSIS OF THE H-IVGTT

$$Y = \alpha + \beta_1 \frac{1}{T} + \beta_2 T$$

NAP-DOGS

Day	N	$\alpha \pm SD_\alpha$	$\beta_1 \pm SD_{\beta_1}$	$\beta_2 \pm SD_{\beta_2}$	r^2	SS_Y
3	8	144 ± 415	1709 ± 261	-1.28 ± 0.90	0.82	928554
5	8	258 ± 323	1058 ± 203	-2.85 ± 0.70	0.86	701711
7[a]	8	298 ± 307	1188 ± 113	-3.24 ± 0.66	0.89	858178
10	8	345 ± 237	636 ± 149	-3.78 ± 0.51	0.90	567177
16[b]						
18	8	286 ± 744	1054 ± 468	-2.13 ± 1.61	0.47	997395
19[d]						
20[c]	8	349 ± 645	609 ± 465	-2.67 ± 1.67	0.42	671170
25	7	264 ± 323	1085 ± 232	-2.97 ± 0.80	0.85	659919

AP-DOGS

Day	N	$\alpha \pm SD_\alpha$	$\beta_1 \pm SD_{\beta_1}$	$\beta_2 \pm SD_{\beta_2}$	r^2	SS_Y
3	8	144 ± 355	1679 ± 223	-1.66 ± 0.77	0.87	934392
5	8	263 ± 437	1120 ± 275	-3.22 ± 0.94	0.80	895837
7[a]	8	328 ± 244	778 ± 153	-3.51 ± 0.52	0.90	604700
10	8	294 ± 267	811 ± 168	-3.52 ± 0.57	0.89	637172
16[b]						
18[c]	8	252 ± 316	929 ± 199	-2.42 ± 0.68	0.82	546862
19[e]						
20	7	537 ±1444	700 ±1217	-3.14 ± 4.19	0.14	2244659
25	6	344 ± 612	1153 ± 622	-2.28 ± 2.14	0.51	352254

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) Prior to surgical procedures

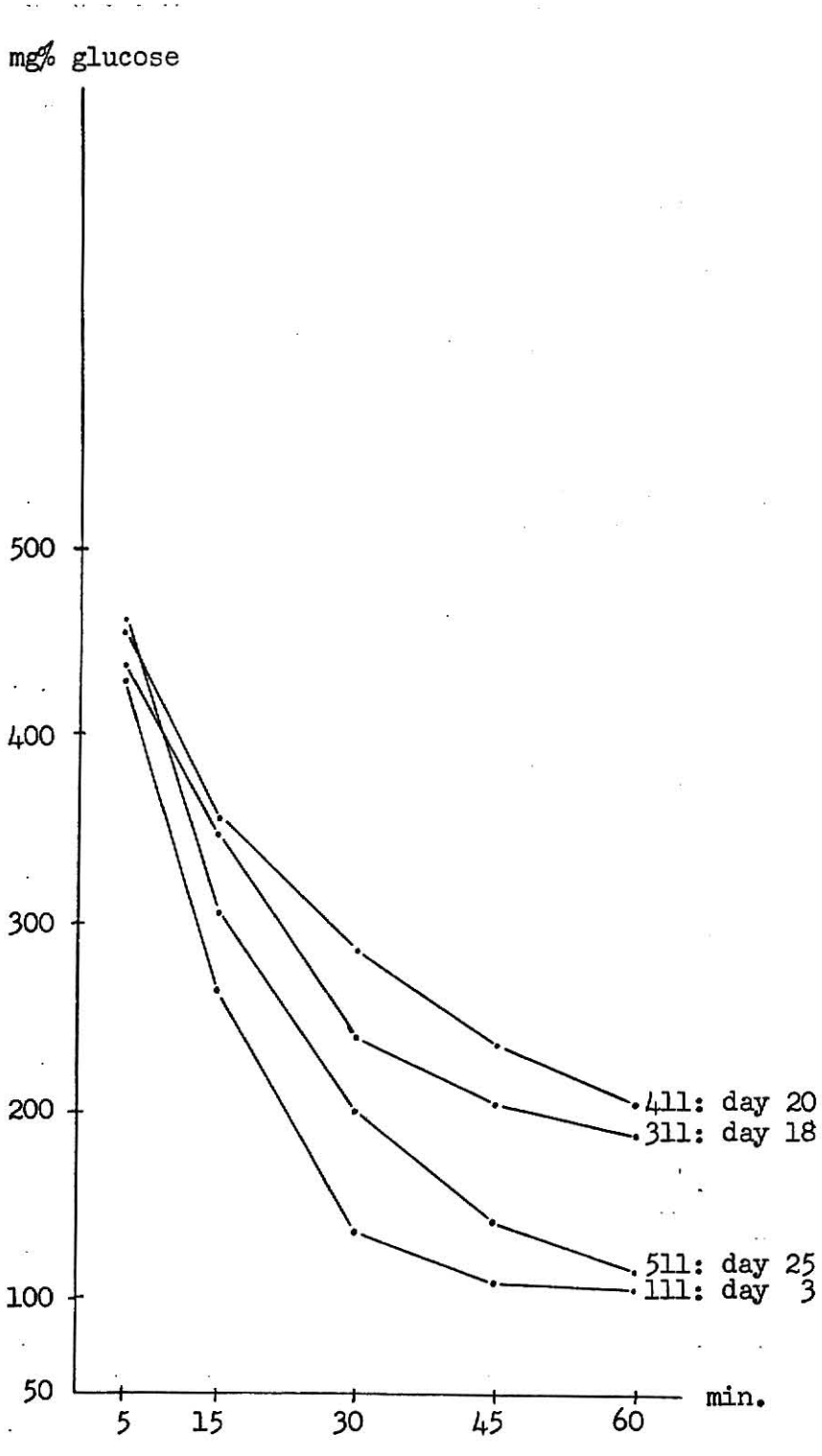


Fig. 1. NAP-dogs: The glucose tolerance curve.

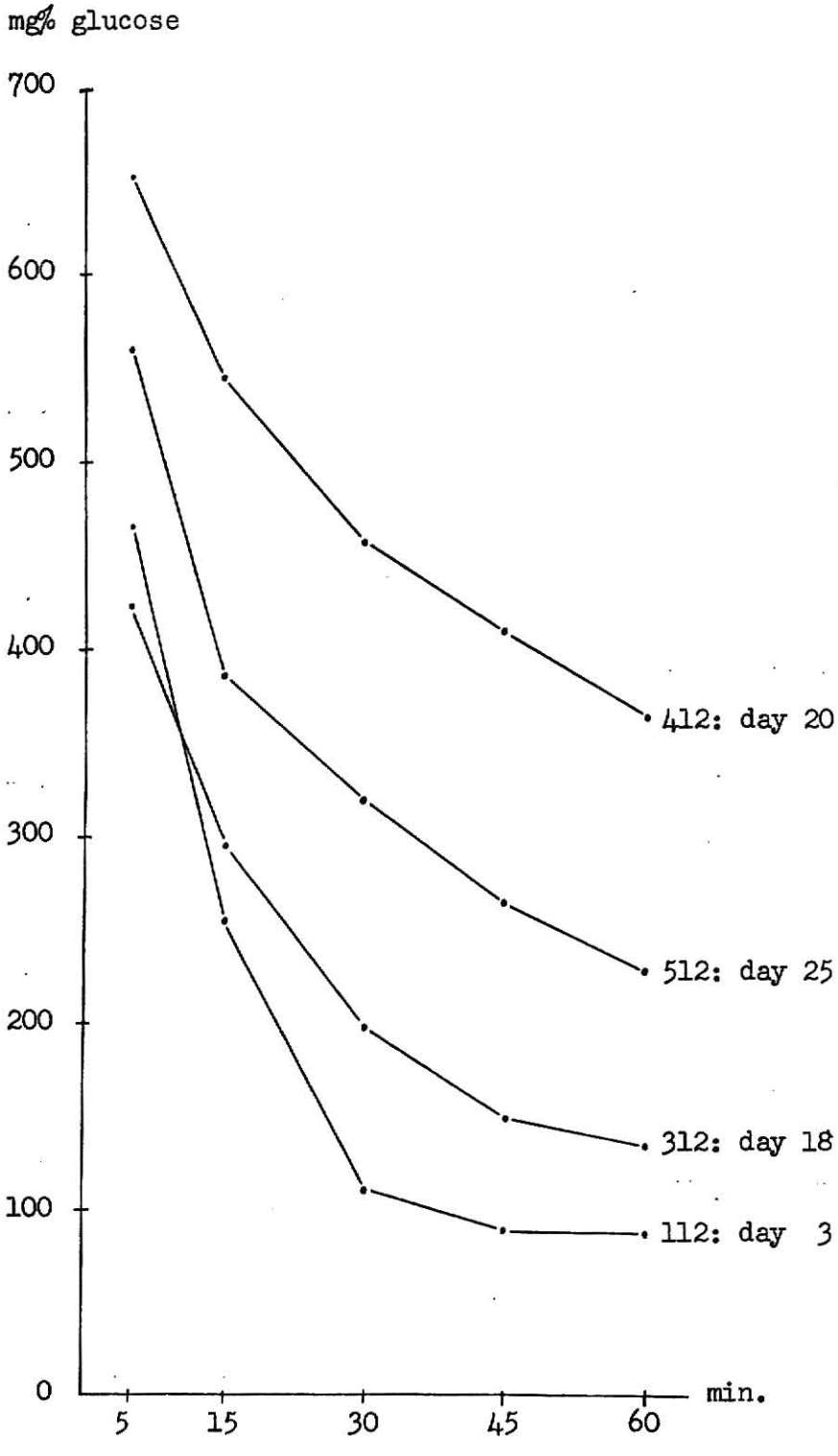


Fig. 2. AP-dogs. The glucose tolerance curve.

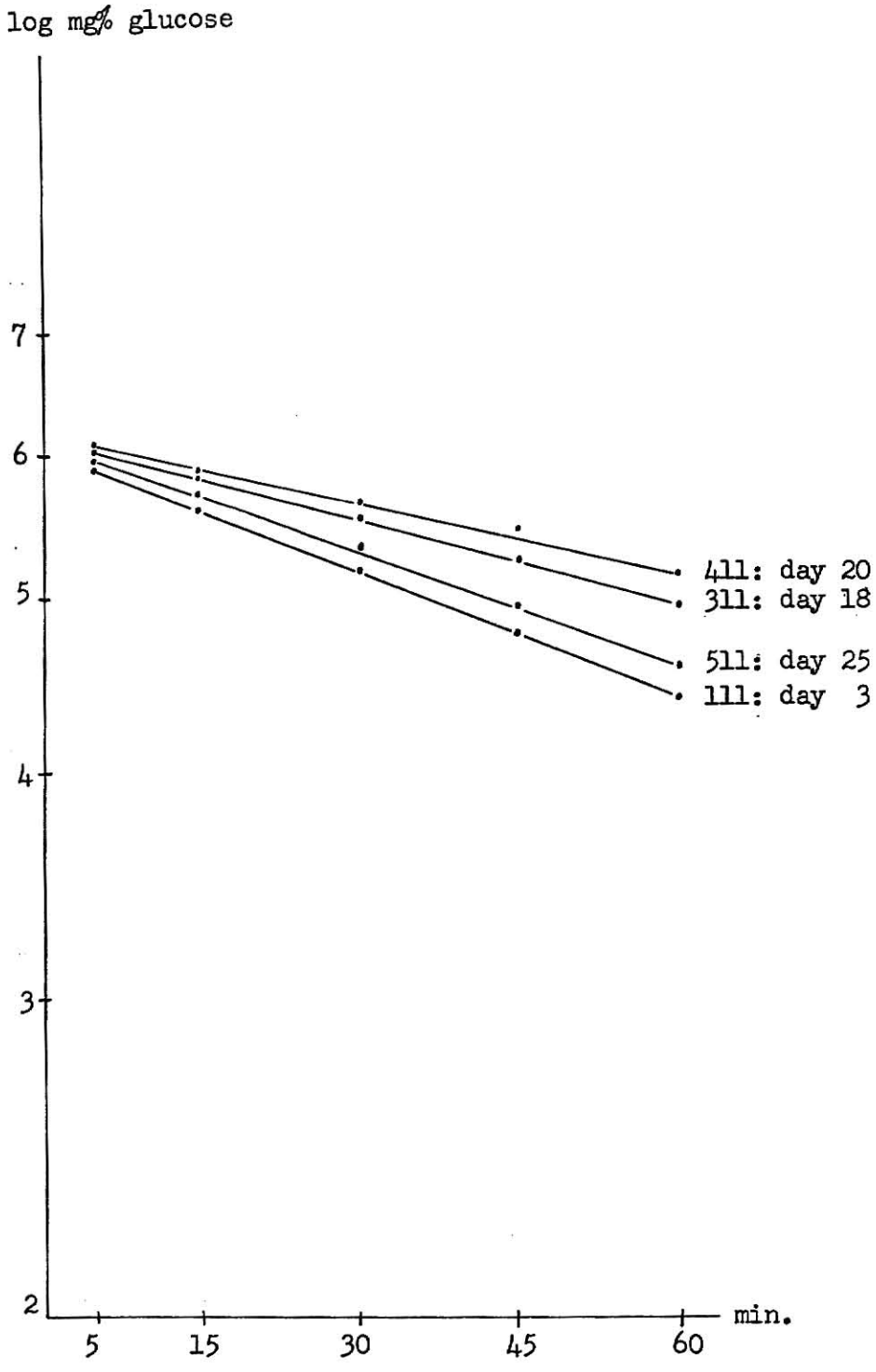


Fig. 3. NAP-dogs: The glucose tolerance curve.

Function: $\log Y = \alpha + \beta T$

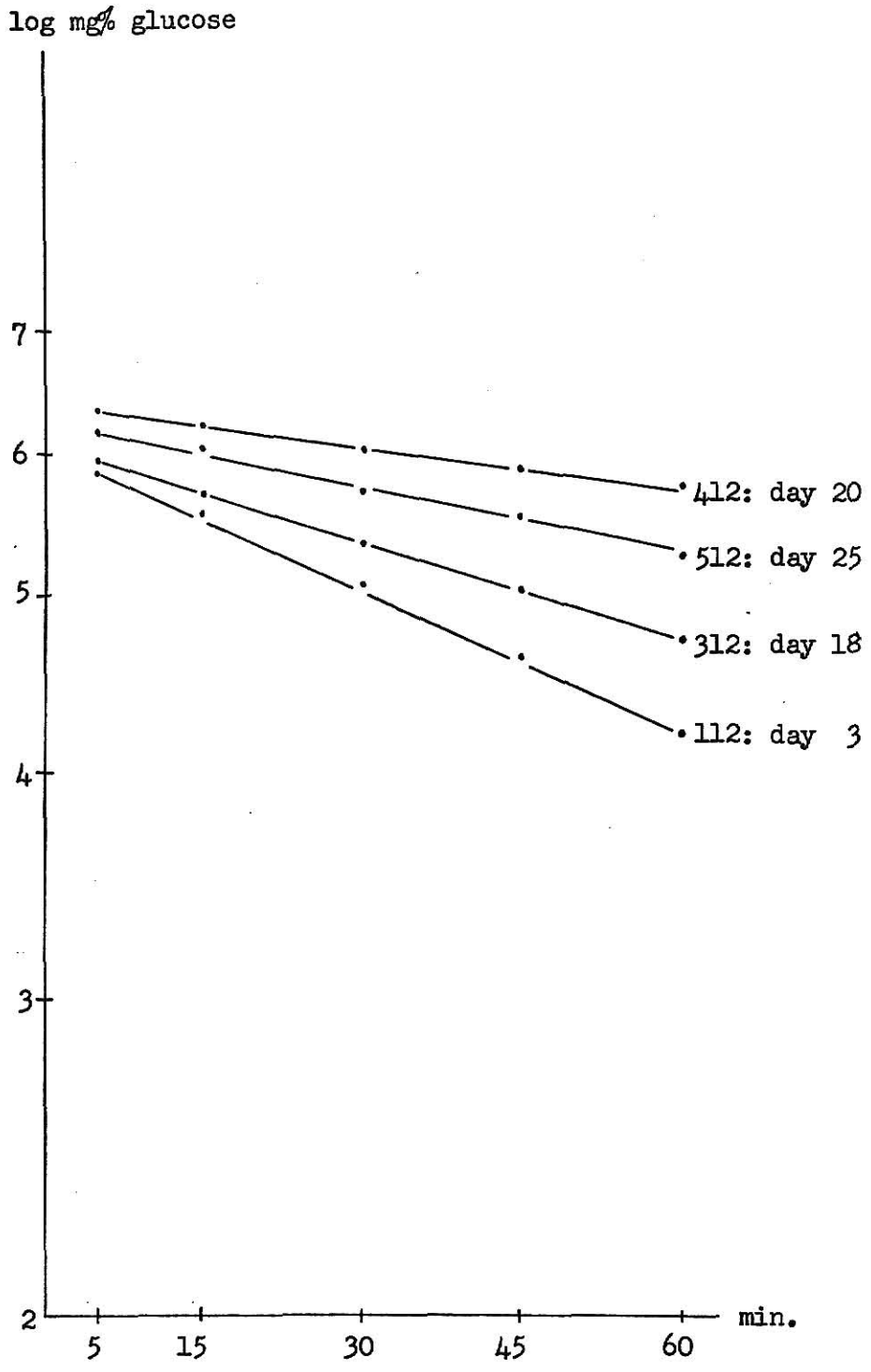


Fig. 4. AP-dogs: The glucose tolerance curve.
Function: $\log Y = \alpha + \beta T$

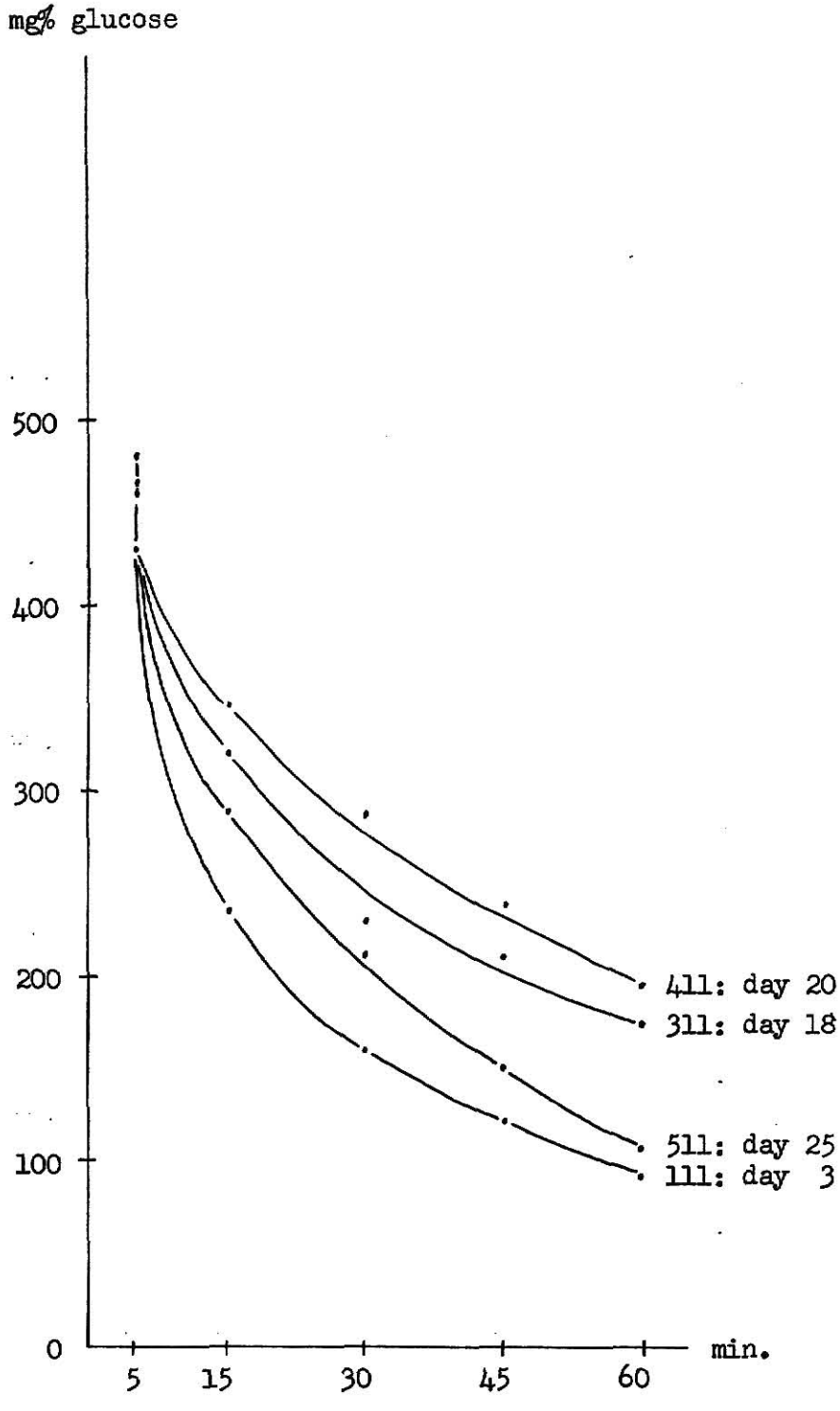


Fig. 5. NAP-dogs: The glucose tolerance curve.

Function: $Y = \alpha + \beta_1 \frac{1}{T} + \beta_2 T$

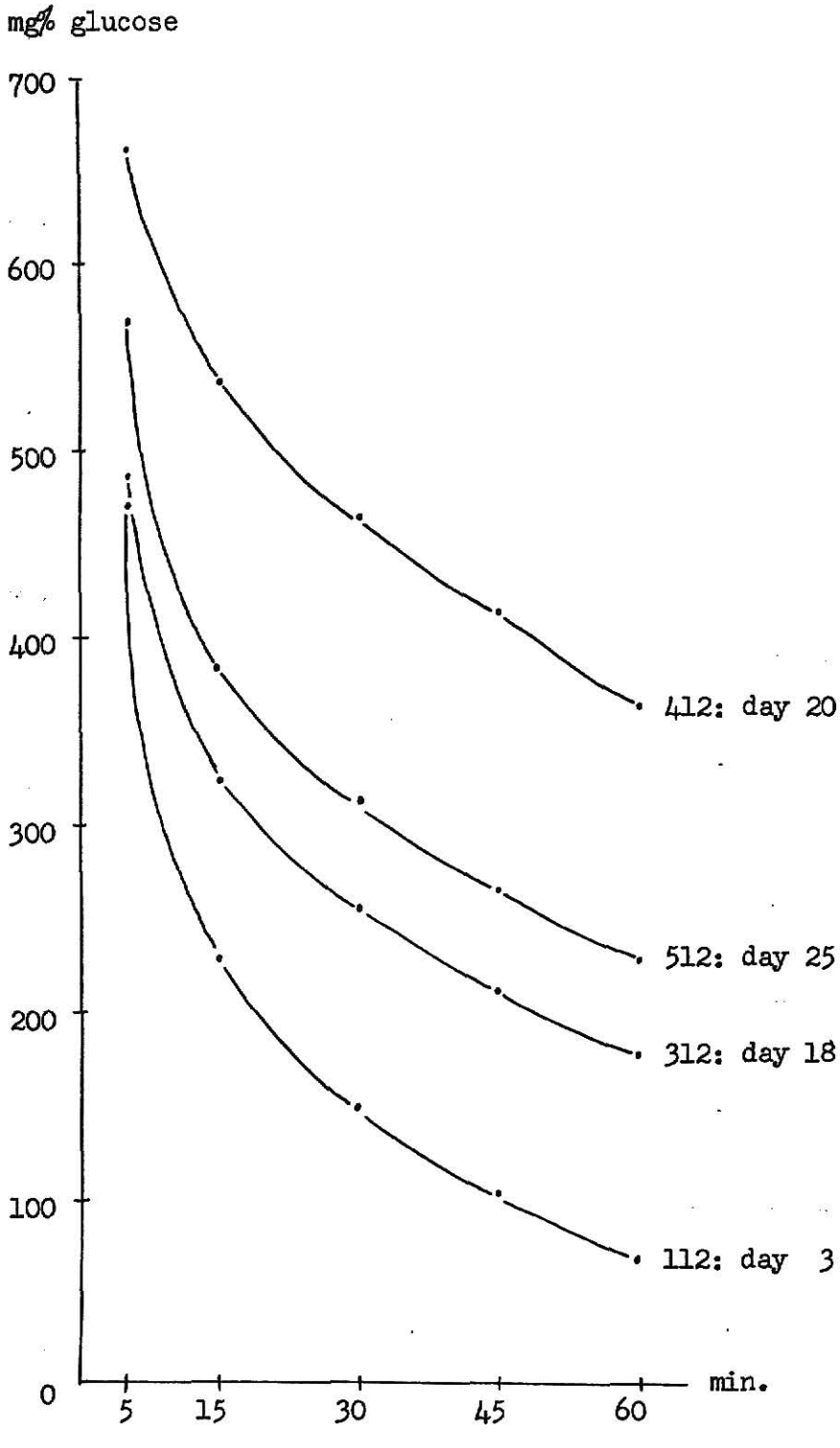


Fig. 6. AP-dogs: The glucose tolerance curve.

Function: $Y = \alpha + \beta_1 \frac{1}{T} + \beta_2 T$

Blood Glucose Concentration (mg%)

Characteristic features:

(1) Normal mean blood glucose was 95 mg% for all dogs on days 3 and 5 (tables 18 and 19, pgs. 70 and 71).

(2) Mean blood glucose following 50% partial pancreatectomy was (a) 105 mg% on day 7 (mean of all dogs, tables 18 and 19, pgs. 70 and 71) and (b) 109 mg% on day 8 (mean of all dogs, table 18, p. 70).

(3) Mean blood glucose following BGH (5 mg/kg/intramuscularly twice daily) and DX (0.02 mg/kg/intramuscularly twice daily) was (a) 114 mg% for the NAP-dogs on day 18 and (b) 213 mg% for the AP-dogs on day 19 (tables 18 and 19, pgs. 70 and 71).

(4) Mean blood glucose concentration for the AP-dogs on day 20 after partial pancreatectomy, hormonal treatment, and staphylococcal alpha-toxin infusion was 371 $\pm$ 335 mg% (table 19, p. 70).

(5) There was a statistical significant difference (α = .05) between the means of the NAP- and AP-dogs on day 20 whereas this was not true on any other day (tables 20 and 52, pgs. 73 and 123).

(6) The NAP-dogs experienced an abrupt decrease in blood glucose after cessation of treatment but the AP-dogs maintained a higher mean blood glucose.

TABLE 18

BLOOD CHEMISTRY

BLOOD GLUCOSE CONCENTRATION (mg%)

	NAP-DOGS				AP-DOGS			
Day	N	Means		S.E.M.	Day	N	Means	S.E.M.
3	8	93.3	±	3.4	3	8	95.0 ±	2.8
5	8	98.8	±	2.3	5	8	97.0 ±	3.7
7[a]	8	108.3	±	3.1	7[a]	8	102.3 ±	5.1
8	8	114.6	±	4.3	8	8	105.5 ±	3.3
9	8	105.6	±	3.2	9	8	101.8 ±	2.2
10	8	103.1	±	2.6	10	8	99.8 ±	2.8
11	8	104.0	±	3.2	11	8	98.9 ±	4.5
12	8	103.6	±	2.1	12	8	99.5 ±	3.5
13	8	99.0	±	3.6	13	8	103.4 ±	2.7
14	8	102.1	±	4.1	14	8	99.0 ±	3.8
15	8	97.3	±	3.3	15	8	97.5 ±	2.6
16[b]	8	101.6	±	4.0	16[b]	8	96.5 ±	2.2
17	8	119.3	±	6.4	17	8	114.6 ±	4.8
18	8	144.5	±	30.0	18[c]	8	134.6 ±	11.8
19[d]	8	203.5	±	41.0	19[e]	8	184.6 ±	33.8
20[c]	7	213.7	±	41.9	20	8	371.1 ±	111.4
21	7	164.4	±	28.8	21	6	155.8 ±	30.0
22	7	118.0	±	10.0	22	6	144.0 ±	28.6
23	7	97.7	±	6.3	23	6	138.5 ±	26.9
24	7	96.7	±	4.8	24	6	159.0 ±	42.0
25	7	100.3	±	2.8	25	6	154.5 ±	33.7

a) 24 hours after 50 $\bar{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) Prior to surgical procedures

TABLE 19

BLOOD CHEMISTRY

BLOOD GLUCOSE (mg%)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	93.37	92.55	9.62	3	8	94.87	75.26	8.67
5	8	98.87	67.26	8.20	5	8	97.25	120.78	10.99
7[a]	8	108.25	96.21	9.80	7[a]	8	102.62	256.55	16.01
10	8	103.12	83.26	9.12	10	8	99.87	68.12	8.25
16[b]					16[b]				
18	8	144.50	8419.14	91.75	18	8	134.62	1301.12	36.07
19[d]	8	203.60			19[e]	8	184.60		
20[c]	7	213.57	12953.61	113.81	20	7	371.14	112416.75	335.28
25	6	100.33	103.86	10.19	25	6	154.50	7372.29	85.86

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 20

LSD* PROCEDURE

BLOOD CHEMISTRY

ORDERED ARRAY OF

MEAN BLOOD GLUCOSE CONCENTRATION (mg%)

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
3	93	3	94
5	98	5	97
25	100	10	99
10	103	7	102
7	108	19	134
19	144	25	154
20	213	20	371

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

Serum Amylase Activity (Somogyi Units / cc)

Characteristic features:

(1) Normal serum amylase was below 1500 Somogyi Units/cc as measured in the NAP- and AP-dogs on days 3 and 5 (tables 21 and 22, pgs. 74 and 75).

(2) The mean serum amylase increased subsequent to partial pancreatectomy (table 21, p. 74; fig. 7, p. 79). This increase was significant for the AP-dogs (tables 22 and 52, pgs. 74 and 123).

(3) There was a sudden drop in mean serum amylase from day 7 to day 19 for both the NAP- and AP-dogs (table 21, p. 74; fig. 7, p. 79); statistically significant in both groups of dogs (tables 22 and 52, pgs. 75 and 123).

(4) The hormonal regimen (BGH and DX) did not have any obvious influence on the mean serum amylase as seen on day 19 in both the NAP- and AP-dogs (table 21, p. 74; fig. 7, p. 79).

(5) The serum amylase increased significantly from day 19 to day 20 in the AP-dogs after treatment with staphylococcal alpha-toxin (tables 21, 22, and 52, pgs. 74, 75, and 123; fig. 7, p. 79). Since the blood sample was drawn only 20 - 24 hours following the ductal infusion, it implied that amylase very abruptly and rapidly increased. A declining trend was reflected through a significant lower amylase value on day 21 (table 22, p. 75). Four days following the acute pancreatitis, amylase was normal (table 21, p. 74; fig. 7, p. 79).

TABLE 21

BLOOD CHEMISTRY

SERUM AMYLASE ACTIVITY (SOMOGYI UNITS/cc)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	912	267907	517	3	8	1346	113220	336
5	8	1300	348195	590	5	8	1173	342910	585
7[a]	8	2144	336270	579	7[a]	8	2562	984048	991
16[b]					16[b]				
19[d]	8	605	102142	319	19[e]	8	1137	1050755	1025
20[c]	8	1055	480429	693	20	8	5639	5923737	2433
21	7	1042	542283	736	21	7	4337	6543583	2557
25	6	1365	1533465	1238	25	6	1600	481228	693

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 22

LSD* PROCEDURE

BLOOD CHEMISTRY

ORDERED ARRAY OF

MEAN SERUM AMYLASE ACTIVITY (S.U.)

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
19	605	19	1137
3	912	5	1173
21	1042	3	1346
20	1055	25	1600
6	1300	7	2562
25	1365	21	4337
7	2144	20	5639

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

Serum Lipase Activity (Lipase Units / cc)

Characteristic features:

(1) Normal serum lipase was below 0.5 Lipase Units/cc as seen in the NAP- and AP-dogs on days 3 and 5 (tables 23 and 24, pgs. 77 and 78).

(2) There was an increase in mean serum lipase after partial pancreatectomy as encountered in the mean serum amylase series (table 23, p. 77; fig. 7, p. 79). The increase occurred in both groups of dogs on day 7 and was significant for the AP-dogs (tables 24 and 52, pgs. 78 and 123).

(3) The mean serum lipase dropped to normal range on day 19 prior to acute pancreatitis (table 23, p. 77; fig. 7, p. 79).

(4) Diabetogenic hormones (BGH and DX) did not alter mean serum lipase in either of the groups of dogs (table 23, p. 77; fig. 7, p. 79).

(5) There was an abrupt and statistically significant increase in the serum lipase mean following the staphylococcal alpha-toxin regimen in the AP-dogs on day 20 (tables 23, 24, and 52, pgs. 77, 78, and 123; fig. 7, p. 79). A decreasing tendency was obvious already on day 21 (table 23, p. 77; fig. 7, p. 79).

(6) Mean serum lipase and mean serum amylase increased and decreased approximately in the same ratio.

TABLE 23

BLOOD CHEMISTRY

SERUM LIPASE ACTIVITY (LIPASE UNITS)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	0.17	0.42	0.20	3	8	0.20	0.37	0.19
5	8	0.31	1.24	0.35	5	8	0.20	0.48	0.22
7[a]	8	0.96	9.02	0.95	7[a]	8	1.11	4.15	0.64
16[b]					16[b]				
19[d]	8	0.26	0.34	1.84	19[e]	8	0.37	0.99	3.15
20[c]	8	0.65	4.77	0.69	20	8	4.98	56.55	2.37
21	7	0.37	0.92	0.30	21	7	3.45	10.72	1.03
25	6	0.50	4.35	0.66	25	6	0.86	8.14	0.90

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 24

LSD* PROCEDURE

BLOOD CHEMISTRY

ORDERED ARRAY OF

MEAN SERUM LIPASE ACTIVITY (L.U.)

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
3	0.17	3	0.20
19	0.26	5	0.20
5	0.31	19	0.37
21	0.37	26	0.80
25	0.50	7	1.10
20	0.65	21	3.45
7	0.96	20	4.98

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

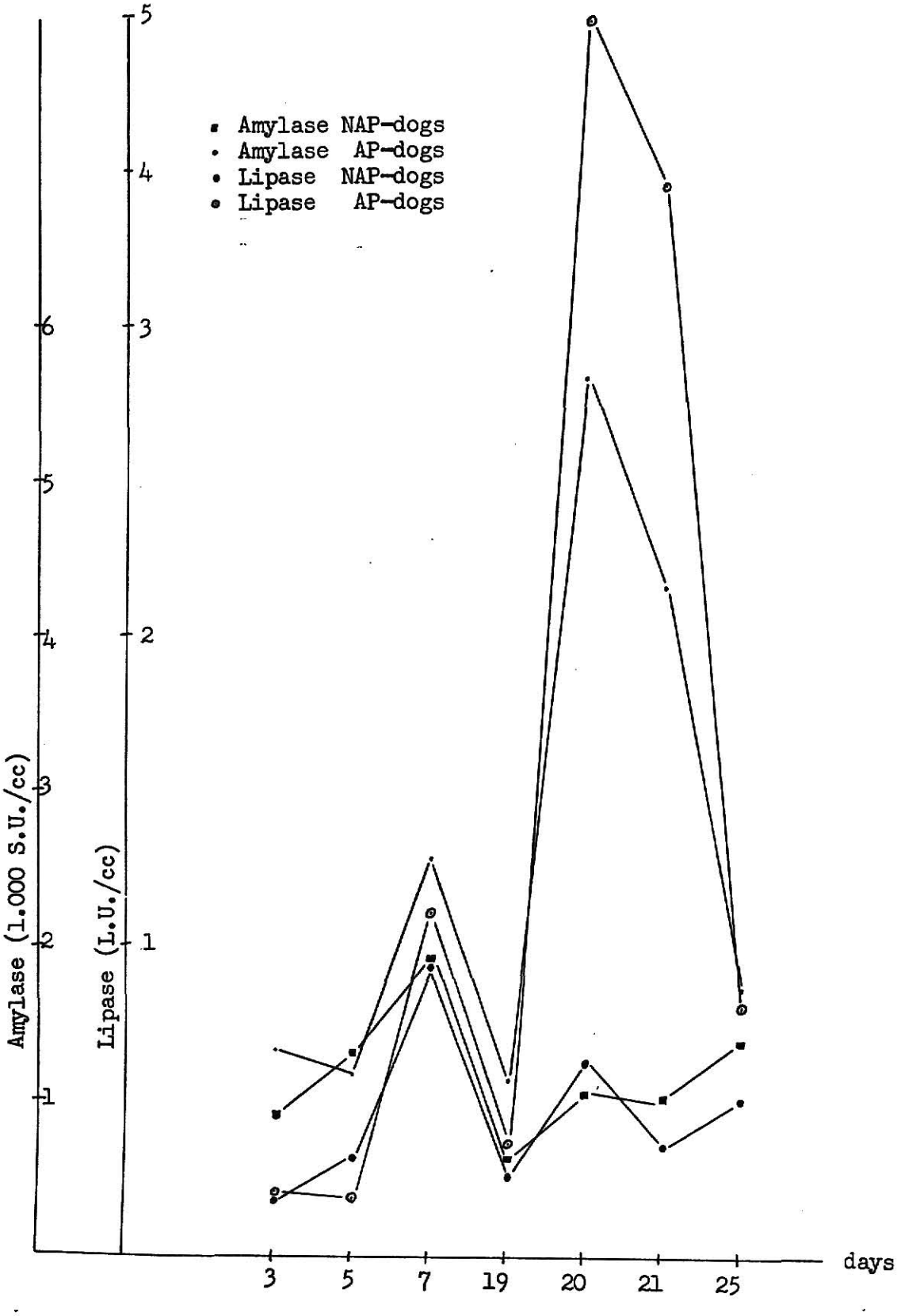


Fig. 7. Graphic presentation of mean serum amylase and lipase activities.

S-GPT Activity (Frankel Units / cc)

Characteristic features:

(1) S-GPT was a constant blood component (mean approximately 30 Frankel Units/ cc) in the NAP- and AP-dogs on days 3, 5, and 7 (tables 25 and 26, pgs. 81 and 82).

(2) BGH and DX elevated mean S-GPT in both the NAP- and AP-dogs on day 19 (table 25, p. 81). Statistical significance occurred in the NAP-dogs (tables 26 and 53, pgs. 82 and 124).

(3) The induction of acute pancreatitis in the AP-dogs on day 20 increased the mean S-GPT significantly different from day 19 (tables 25, 26, and 53, pgs, 81, 82, and 124).

(4) Neither the NAP- nor the AP-dogs resumed normal mean S-GPT on day 25 (table 25, p. 81).

TABLE 25

BLOOD CHEMISTRY

S-GPT ACTIVITY (FRANKEL UNITS/cc)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	30	1405	37	3	8	27	214	14
5	8	23	224	14	5	8	23	156	12
7[a]	8	29	127	11	7[a]	8	32	832	28
16[b]					16[b]				
19[d]	8	133	5407	73	19[e]	8	90	3389	58
20[c]	7	242	14991	122	20	7	383	30330	174
25	6	240	85599	292	25	5	206	13515	116

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 26

LSD* PROCEDURE

BLOOD CHEMISTRY

ORDERED ARRAY OF

MEAN S-GPT ACTIVITY (F.U.)

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
5	23	5	23
7	29	3	27
3	30	7	32
19	133	19	90
26	240	26	206
20	242	20	383

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

Bromsulfalein (BSP) Retention Rate (%)

Characteristic features:

(1) The mean 30-minute BSP retention rate in dogs given 5 mg sulfobromophthalein/kg body weight intravenously was close to 5% based on the NAP- and AP-dogs on day 4 (table 27, p. 84).

(2) The hormonal regimen (BGH and DX) that caused a high mean S-GPT activity did not change the mean BSP retention rate in the NAP-dogs on day 20 (table 27, p. 84).

(3) Acute pancreatitis/diabetes mellitus regimen increased the mean BSP retention rate (table 27, p. 84), indicating that the blood flow through the liver was impaired.

(4) The AP-group of dogs did not resume normal BSP retention rate on day 26 (table 27, p. 84).

TABLE 27

FUNCTION TESTS

	LIVER						KIDNEY					
	% BSP RETENTION IN 30 MIN						ENDOGENOUS CREATININE CLEARANCE (ml/min/kg BODY WEIGHT)					
	NAP-DOGS			AP-DOGS			NAP-DOGS			AP-DOGS		
Day	N	Means	S.E.M.	N	Means	S.E.M.	Day	N	Means	S.E.M.	N	Means	S.E.M.
4	8	4.7	± 0.5	8	4.5	± 0.6	4	8	2.84	± 0.2	8	3.01	± 0.3
10	8	6.4	± 1.6	8	4.3	± 0.8	10	8	2.61	± 0.2	8	2.97	± 0.3
20	6	4.5	± 0.7	6	9.6	± 1.2	20	6	2.56	± 0.3	6	2.05	± 0.3
26	6	5.4	± 0.9	5	7.0	± 2.0	26	6	3.12	± 0.4	5	2.67	± 0.3

50 $\overline{P}$ was performed on day 7

Hormonal regimen was initiated on day 16 both in the NAP- and AP-group of dogs

Hormonal regimen was discontinued (1) on day 20 in the NAP-dogs and (2) on day 18 in the AP-dogs

Sham operation was performed on day 19 in the NAP-dogs

Acute pancreatitis was induced on day 19 in the AP-dogs

Endogenous Creatinine Clearance [C_{Cr} (ml/min/kg)]

Characteristic features:

(1) *Mean endogenous* creatinine clearance (ml/min/kg) in normal dogs; i.e. the NAP- and AP-dogs on day 4 was 2.78 ± 0.25 ml/min/kg (table 27, p. 84).

(2) Hormonal treatment (BGH and DX) did not alter the creatinine clearance noticeably as seen in the NAP-dogs on day 20 (table 27, p. 84).

(3) The acute pancreatitis/diabetes mellitus regimen decreased the creatinine clearance noticeably [C_{Cr} = 2.05 ± 0.3 ml/min/kg (table 27, p. 84)].

(4) Both groups of dogs had normal endogenous creatinine clearance on day 26 (table 27, p. 84).

Plasma Creatinine Concentration (mg%)

Characteristic features:

(1) Plasma creatinine was a constant plasma constituent and below 1 mg% in the NAP- and AP-dogs on days 3 and 5 (tables 28 and 29, pgs. 87 and 88).

(2) The mean plasma creatinine was not affected of the hormonal regimen (BGH and DX) in the NAP-dogs at any day (tables 28 and 29, pgs. 87 and 88).

(3) The mean plasma creatinine changed significantly during the course of acute pancreatitis/diabetes mellitus in the AP-dogs on day 20 (tables 29 and 53, pgs. 88 and 124).

(4) The mean plasma creatinine resumed normal values in the AP-dogs on day 25 (table 28, p. 87).

TABLE 28

BLOOD CHEMISTRY

PLASMA CREATININE CONCENTRATION (mg%)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	0.86	0.04	0.20	3	8	0.87	0.06	0.25
5	8	0.87	0.01	0.14	5	8	0.88	0.01	0.13
7[a]	8	0.97	0.22	0.46	7[a]	8	0.83	0.00	0.09
16[b]					16[b]				
19[d]	8	0.95	0.02	0.15	19[e]	8	0.86	0.00	0.09
20[c]	7	0.84	0.01	0.13	20	7	1.55	0.93	0.96
25	6	0.71	0.00	0.08	25	5	0.73	0.01	0.12

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 29

LSD* PROCEDURE

BLOOD CHEMISTRY

ORDERED ARRAY OF

MEAN PLASMA CREATININE CONCENTRATION (mg%)

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
7	0.97	20	1.55
19	0.95	5	0.88
5	0.87	3	0.87
3	0.86	19	0.86
20	0.84	7	0.83
25	0.71	25	0.73

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

Urinalysis

The essential features of urinalysis appear in table 30, p. 90.

(1) Polyuria occurred in all dogs on days 18 and 19.

(2) Glycosuria occurred in 58% of the NAP-dogs and in 87% og the AP-dogs on day 20.

(3) Ketonuria occurred in the AP-dogs on days 20, 21, 22, and 23, whereas ketonuria was not seen in the NAP-dogs at any time.

(4) Oliguria was present on day 20 in the AP-dogs.

(5) The mean urinary specific gravity (S.G.) was at a minimum on day 21 for the NAP-dogs and on day 19 for the AP-dogs. Then it started to increase. The AP-dogs had a significant increase on day 20 (1.040).

(6) The urinary specific gravity remained decreased in both the NAP- and AP-dogs from day 21 to day 25.

(7) pH was measured daily and had an extreme variation.

TABLE 30

MAJOR FINDINGS IN URINALYSIS (DAYS 15-25)

NAP-DOGS							AP-DOGS						
Day	N	Polyuria %	Glycosuria %	Ketonuria %	Average SG	S.E.M.	Day	N	Polyuria %	Glycosuria %	Ketonuria %	Average SG	S.E.M.
15	8	0	0	0	1.038	± 0.014	15	8	0	0	0	1.036	± 0.005
16[b]	8	0	0	0	1.028	± 0.028	16[b]	8	0	0	0	1.035	± 0.004
17	8	0	0	0	1.026	± 0.023	17	8	0	0	0	1.031	± 0.005
18	8	100	25	0	1.022	± 0.004	18[c]	8	100	0	0	1.024	± 0.004
19[d]	8	100	38	0	1.026	± 0.003	19[e]	8	100	38	0	1.021	± 0.003
20[c]	7	85	58	0	1.019	± 0.003	20	7	0[x]	87	36	1.040	± 0.009
21	7	85	43	0	1.014	± 0.003	21	6	85	66	66	1.021	± 0.004
22	7	43	0	0	1.015	± 0.004	22	6	60	66	33	1.020	± 0.006
23	7	43	0	0	1.016	± 0.003	23	6	60	40	20	1.020	± 0.004
24	7	30	0	0	1.021	± 0.005	24	6	40	40	20	1.021	± 0.005
25	7	30	0	0	1.018	± 0.002	25	6	40	40	0	1.020	± 0.004

x) Oliguria

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) Prior to surgical procedures

Plasma Sodium Concentration (mEq/l.)

Characteristic features:

(1) Mean plasma sodium of the NAP- and AP-dogs on days 3 and 5 was 142.9 mEq/l. (table 31, p. 92).

(2) Partial pancreatectomy did not noticeably change the mean plasma sodium in the NAP- or AP-dogs on day 7 (table 31, p. 92).

(3) Four days hormonal regimen (BGH and DX) did not alter mean plasma sodium noticeably in the NAP-dogs (table 31, p. 92).

(4) Acute pancreatitis/diabetes mellitus regimen altered mean plasma sodium in the AP-dogs but not significantly (tables 31 and 53, pgs. 92 and 124).

(5) Dogs subjected to acute pancreatitis/diabetes mellitus maintained a lower mean plasma sodium than dogs treated with BGH/DX on day 25 (table 31, p. 92).

(6) Mean plasma sodium decreased at the same rate as mean plasma (H^+) increased (tables 31 and 38, pgs. 92 and 103).

TABLE 31

BLOOD CHEMISTRY

PLASMA SODIUM CONCENTRATION (mEq/l.)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	145.1	42.2	6.4	3	8	144.5	47.9	6.9
5	8	143.0	43.7	6.6	5	8	139.2	61.6	7.8
7[a]	8	144.5	33.1	5.7	7[a]	8	138.7	80.7	8.9
16[b]					16[b]				
19[d]	8	143.2	50.7	7.1	19[e]	8	141.7	17.6	4.2
20[c]	7	140.0	53.3	7.3	20	7	137.8	26.1	5.1
25	6	144.1	8.9	2.9	25	6	140.2	15.7	3.9

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

Plasma Potassium Concentration (mEq/l.)

Characteristic features:

(1) Mean plasma potassium in the NAP- and AP-dogs on days 3 and 5 was 4.37 mEq/l. (tables 32 and 33, pgs. 94 and 95).

(2) Mean plasma potassium decreased after partial pancreatectomy in the NAP- and AP-dogs on day 7 (table 32, p. 94). This alteration was significant (tables 33 and 54, pgs. 95 and 125). However, there was no significant difference between the mean plasma potassium of the NAP- and AP-dogs on day 7.

(3) Mean plasma potassium remained constant during the hormonal regimen (BGH and DX) in the NAP-dogs on days 19 and 20 (table 32, p. 94).

(4) Mean plasma potassium increased noticeably after induction of acute pancreatitis; i.e. on day 20 for the AP-dogs, but not significantly (tables 32, 33, and 54, pgs. 94, 95, and 125).

(5) Mean plasma potassium increased at the same rate as mean blood (H^+) increased (tables 32 and 38, pgs. 94 and 103).

TABLE 32

BLOOD CHEMISTRY

PLASMA POTASSIUM CONCENTRATION (mEq/l.)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	4.38	0.26	0.51	3	8	4.37	0.28	0.53
5	8	4.36	0.10	0.32	5	8	4.37	0.18	0.43
7[a]	8	3.98	0.05	0.22	7[a]	8	3.65	0.14	0.37
16[b]					16[b]				
19[d]	8	4.27	0.24	0.49	19[e]	8	4.27	0.41	0.64
20[c]	7	4.11	0.28	0.53	20	7	4.42	0.06	0.25
25	6	4.18	0.03	0.18	25	5	4.20	0.06	0.25

a) 24 hours after 50 $\bar{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 33

LSD* PROCEDURE

BLOOD CHEMISTRY

ORDERED ARRAY OF

MEAN PLASMA POTASSIUM CONCENTRATION (mEq/l.)

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
3	4.38	20	4.42
5	4.36	3	4.37
19	4.27	5	4.37
25	4.18	19	4.27
20	4.11	25	4.20
7	3.98	7	3.65

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

Plasma Chloride Concentration (mEq/l.)

Characteristic features:

(1) Mean plasma chloride in the NAP- and AP-dogs on days 3 and 5 was 108 mEq/l. (tables 34 and 35, pgs. 97 and 98).

(2) Partial pancreatectomy decreased mean plasma chloride noticeably in the AP-dogs on day 7 (table 34, p. 97) and significantly in the NAP-dogs on day 7 (tables 35 and 54, pgs. 98 and 125).

(3) The four days regimen of BGH/DX decreased mean plasma chloride noticeably in the NAP-dogs as measured on days 19 and 20 (table 34, p. 97).

(4) Acute pancreatitis/diabetes mellitus regimen decreased the actual mean plasma chloride significantly on day 20 (tables 35 and 54, pgs. 98 and 125).

(5) Animals exposed to BGH/DX treatment and acute pancreatitis/diabetes mellitus had not reestablished their normal mean plasma chloride by the 25th day (table 34, p. 97).

TABLE 34

BLOOD CHEMISTRY

PLASMA CHLORIDE CONCENTRATION (mEq/l.)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	108.1	12.6	3.5	3	8	109.6	7.6	2.7
5	8	108.3	6.2	2.5	5	8	109.3	5.6	2.3
7[a]	8	103.0	20.8	4.5	7[a]	8	104.6	28.5	5.3
16[b]					16[b]				
19[d]	8	101.3	35.4	5.9	19[e]	8	101.5	16.0	4.0
20	7	99.5	15.9	3.9	20	7	93.7	88.2	9.3
25	6	105.5	4.3	2.0	25	5	99.8	81.7	9.0

a) 24 hours after 50 $\bar{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 35

LSD* PROCEDURE

BLOOD CHEMISTRY

ORDERED ARRAY OF

MEAN PLASMA CHLORIDE CONCENTRATION (mEq/l.)

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
5	108.3	3	109.6
3	108.1	5	109.3
25	105.5	7	104.6
7	103.0	19	101.5
19	101.3	25	99.8
20	99.5	20	93.7

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

Plasma Bicarbonate (HCO_3^-) Concentration (mEq/l.)

Characteristic features:

(1) Mean plasma bicarbonate in the NAP- and AP-dogs on days 3 and 5 was 22.75 mEq/l. (table 36, p. 100).

(2) Mean plasma bicarbonate did not change after partial pancreatectomy in the NAP- or AP-dogs on day 7 (table 36, p. 100).

(3) The regimen of BGH/DX did not alter the mean plasma bicarbonate noticeably or significantly in the NAP-dogs (table 36, p. 100).

(4) Mean plasma bicarbonate on day 20 in the AP-dogs did not change significantly (table 36, p. 100).

(5) There was extreme variation in mean plasma bicarbonate of the AP-dogs on day 20 (table 36, p. 100).

(6) Considering the B.E. values on table 37, p. 101, it is obvious that many dogs had severe acidosis on day 20 as a result of the acute pancreatitis/diabetes mellitus syndrome.

TABLE 36

BLOOD CHEMISTRY

PLASMA BICARBONATE CONCENTRATION (mEq/l.)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	22.75	1.42	1.19	3	8	23.06	8.24	2.87
5	8	22.75	3.50	1.87	5	8	21.75	2.28	1.51
7[a]	8	24.00	7.92	2.81	7[a]	8	22.12	6.41	2.53
16[b]					16[b]				
19[d]	8	21.56	21.10	4.59	19[e]	8	19.68	2.42	1.55
20[c]	7	21.85	12.80	3.57	20	7	21.28	61.82	7.80
25	6	23.75	12.37	3.51	25	5	24.60	10.92	3.30

a) 24 hours after 50 $\bar{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 37

BLOOD CHEMISTRY

BASE EXCESS (mEq/l.)

	NAP-DOGS								AP-DOGS							
Day	# 1	# 2	# 3	# 4	# 5	# 6	# 7	# 8	Day	# 1	# 2	# 3	# 4	# 5	# 6	# 7	# 8
3	-3.0	-3.5	-1.0	-2.0	-2.0	-1.0	-2.0	0.0	3	-1.0	-2.0	-2.5	-6.0	-1.0	-4.0	+2.0	+3.0
5	-1.0	-3.0	0.0	-2.0	-2.0	0.0	-2.5	-0.5	5	-2.0	-4.0	-1.0	-2.0	-5.5	-1.0	-3.0	0.0
7[a]	-2.0	-3.0	+2.0	-3.0	-1.5	+4.5	+2.0	-1.0	7[a]	-1.0	-1.0	-4.0	-3.0	-6.0	+0.5	+1.0	-1.0
16[b]									16[b]								
19[d]	-6.5	-8.0	-3.5	-3.0	-1.5	+1.0	-7.5	+5.5	19[e]	-2.0	-3.5	-5.0	-4.0	-6.5	-4.0	-4.5	-8.5
20[c]	-4.0	-7.0	-1.5	-2.0	-	-1.0	-5.5	+3.0	20	+5.0	0.0	-8.5	+3.0	-	-8.0	+1.0	-28.0
25	-2.5	0.0	0.0	-1.0	-	-0.5	+5.0	-	25	+6.0	-2.0	-	0.0	-	-1.0	+0.5	-

a) 24 hours after 50 $\bar{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

Blood pH [$-\log (H^+)$]

Characteristic features:

(1) Mean blood pH for the NAP- and AP-dogs on days 3 and 5 was 7.3734 (table 38, p. 103).

(2) Partial pancreatectomy did not change mean blood pH on day 7 in the NAP- or AP-dogs (table 38, p. 103).

(3) Acute pancreatitis/diabetes mellitus regimen induced noticeable but not significant changes in mean blood pH on day 20 in the AP-dogs where mean blood pH reached its lowest values (tables 38 and 55, pgs. 103 and 126).

(4) Both the NAP- and AP-dogs resumed entirely normal mean blood pH on day 25 (table 38, p. 103).

TABLE 38

BLOOD CHEMISTRY

BLOOD pH [$-\log (H^+)$]

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	7.3675	0.0003	0.0177	3	8	7.3775	0.0007	0.0289
5	8	7.3712	0.0002	0.0170	5	8	7.3775	0.0013	0.0369
7[a)]	8	7.3900	0.0008	0.0296	7[a)]	8	7.3856	0.0017	0.0415
16[b)]					16[b)]				
19[d)]	8	7.3637	0.0015	0.0389	19[e)]	8	7.3537	0.0016	0.0407
20[c)]	7	7.3628	0.0008	0.0292	20	7	7.2985	0.0328	0.1813
25	6	7.4016	0.0009	0.0304	25	5	7.3990	0.0012	0.0352

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

Blood P_{CO_2} (mm Hg)

Characteristic features:

(1) Mean blood P_{CO_2} in the NAP- and AP-dogs on days 3 and 5 was 39 mm Hg (table 39, p. 105).

(2) 50% partial pancreatectomy and BGH/DX regimen did not change mean P_{CO_2} in the NAP- or AP-dogs (tables 39 and 55, pgs. 105 and 126).

(3) Increased mean blood P_{CO_2} was disclosed during acute pancreatitis/ diabetes mellitus regimen on day 20 in the AP-dogs (table 39, p. 105).

(4) The changes was reversed and the increased mean blood P_{CO_2} was returned to normal by the 25th day in the AP-dogs (table 39, p. 105).

TABLE 39

BLOOD CHEMISTRY

BLOOD P_{CO_2} (mm Hg)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	40.56	5.88	2.42	3	8	39.50	29.64	5.44
5	8	40.25	10.57	3.25	5	8	38.25	8.42	2.90
7[a]	8	40.87	18.48	4.29	7[a]	8	39.50	33.78	5.81
16[b]					16[b]				
19[d]	8	38.88	22.38	4.73	19[e]	8	36.18	10.42	3.22
20[c]	7	39.57	18.70	4.32	20	7	42.14	22.55	4.74
25	6	39.21	11.72	3.42	25	5	39.00	57.62	7.59

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 40

BLOOD CHEMISTRY

BLOOD P_{O_2} (mm Hg)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	37.87	31.05	5.57	3	8	32.43	50.60	7.11
5	8	32.16	81.12	9.00	5	8	30.75	45.92	6.77
7[a]	8	31.56	28.17	5.30	7[a]	8	31.31	52.13	7.22
16[b]					16[b]				
19[d]	8	32.56	27.60	5.25	19[e]	8	30.93	25.31	5.03
20[c]	7	33.52	23.25	4.82	20	7	30.60	10.72	3.27
25	6	33.15	8.66	2.94	25	5	30.28	1.44	1.20

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

Hemoglobin Concentration (g%)

Characteristic features:

(1) Mean hemoglobin in the NAP- and AP-dogs on days 3 and 5 was 14 - 16 g% (tables 41 and 42, pgs. 108 and 109).

(2) There was a continuous trend towards a lower mean hemoglobin in both groups of dogs. Significance occurred between day 7 and day 19 in the NAP-dogs (tables 42 and 56, pgs. 109 and 127).

(3) Acute pancreatitis/diabetes mellitus regimen resulted in an increased mean hemoglobin attributed to dehydration on day 20 (table 41, p. 108).

(4) No dogs resumed normal mean hemoglobin by the end of the investigation even though sampling of large amount of blood was stopped on day 20 (table 41, p. 108).

Hematocrit (%)

Characteristic features:

(1) Mean hematocrit in the NAP- and AP-dogs on days 3 and 5 was close to 45% (tables 43 and 44, pgs. 110 and 111).

(2) The variations in mean hematocrit resembled mean hemoglobin.

TABLE 41

HEMATOLOGY

HEMOGLOBIN CONCENTRATION (g%)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	16.5	2.0	1.4	3	8	16.3	11.6	3.4
5	8	15.3	5.1	2.2	5	8	14.5	3.1	1.7
7[a]	8	15.1	5.5	2.3	7[a]	8	14.3	1.4	1.1
16[b]					16[b]				
19[d]	8	12.3	1.4	1.1	19[e]	8	13.1	2.6	1.6
20[c]	7	12.4	3.9	1.9	20	7	16.0	7.3	2.7
25	6	10.6	1.4	1.2	25	5	10.8	3.2	1.7

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 42

LSD* PROCEDURE

HEMATOLOGY

ORDERED ARRAY OF

. MEAN HEMOGLOBIN CONCENTRATION (g%)

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
3	16.5	3	16.4
5	15.3	20	16.0
7	15.1	5	14.5
19	12.3	7	14.3
20	12.4	19	13.1
25	10.6	25	10.8

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

TABLE 43

HEMATOLOGY

HEMATOCRIT (PCV %)

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	47.2	12.7	3.5	3	8	44.3	13.9	3.7
5	8	44.3	39.1	6.2	5	8	42.0	19.4	4.4
7[a]	8	44.8	36.4	6.0	7[a]	8	43.0	8.0	2.8
16[b]					16[b]				
19[d]	8	36.5	9.4	3.0	19[e]	8	38.8	17.5	4.1
20[c]	7	36.5	20.2	4.5	20	7	45.8	62.1	7.8
25	6	32.1	5.3	2.3	25	5	32.4	26.2	5.1

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 44

LSD* PROCEDURE

HEMATOLOGY

ORDERED ARRAY OF

MEAN HEMATOCRIT (PCV %)

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
3	47.2	20	45.8
7	44.8	3	44.3
5	44.3	7	43.0
19	36.5	5	42.0
20	36.5	19	38.8
25	32.1	25	32.4

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

White Blood Cells (WBC) / cumm

Characteristic features:

(1) WBC/cumm in the NAP- and AP-dogs varied around 15,000/cumm on days 3 and 5 (tables 45 and 46, pgs. 113 and 114).

(2) 50% partial pancreatectomy induced a significant increase in mean WBC/cumm in both the NAP- and AP-dogs on day 7 (tables 46 and 56, pgs. 114 and 127).

(3) BGH/DX regimen exaggerated the already existent leucocytosis in the NAP-dogs on days 19 and 20 (table 45, p. 113).

(4) Acute pancreatitis/diabetes mellitus syndrome in the AP-dogs on day 20 did not change mean WBC/cumm significantly (tables 46 and 56, pgs. 114 and 127).

(5) The high mean WBC/cumm was maintained throughout the study in both the NAP- and AP-dogs. Only an imperceptible decrease took place the last five days (table 45, p. 113).

TABLE 45

HEMATOLOGY

WHITE BLOOD CELLS / cumm

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	13,813	32,698	5,718	3	8	14,387	30,621	5,533
5	8	14,743	26,291	5,127	5	8	17,025	43,879	6,624
7[a]	8	26,647	121,289	11,013	7[a]	8	24,273	54,593	7,388
16[b]					16[b]				
19[d]	8	29,675	85,264	9,233	19[e]	8	25,662	18,402	4,289
20[c]	7	33,128	46,062	6,786	20	7	29,442	152,739	12,358
25	6	27,300	424,743	20,609	25	5	27,320	117,836	10,855

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 46

LSD* PROCEDURE

HEMATOLOGY

ORDERED ARRAY OF

MEAN WHITE BLOOD CELLS / cumm

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
3	13,813	3	14,387
5	14,743	5	17,025
7	26,647	7	24,273
25	27,300	19	25,662
19	29,673	25	27,320
20	33,128	20	29,442

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

Neutrophils/cumm

Characteristic features:

(1) Neutrophils/cumm in the NAP- and AP-dogs on days 3 and 5 was between 8,000 and 10,000/cumm (tables 47 and 48, pgs. 116 and 117).

(2) The leucocytosis that occurred on day 7 in both groups of dogs following the partial pancreatectomy was predominantly an absolute neutrophilia (table 47, p. 116). The increase was significant in both groups of dogs (tables 48 and 57, pgs. 117 and 128).

(3) The maintainance and even increase in leucocytes from day 7 to day 19 in both groups of dogs was mainly due to neutrophilia (table 47, p. 116).

(4) The superimposed acute pancreatitis/diabetes mellitus on day 20 in the AP-dogs only slightly increased mean neutrophils/cumm (table 48, p. 116).

(5) Mean neutrophils/cumm decreased only slightly throughout the remainder of the study in both groups of dogs (table 47, p. 116).

TABLE 47

HEMATOLOGY

NEUTROPHILS / cumm

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	8,840	26,820	5,178	3	8	8,689	14,881	3,857
5	8	10,029	25,934	5,092	5	8	10,881	43,170	6,570
7[a]	8	24,156	107,694	10,377	7[a]	8	20,359	44,878	6,699
16[b]					16[b]				
19[d]	8	26,620	55,181	7,428	19[e]	8	21,580	10,671	3,266
20[c]	7	28,498	29,715	5,451	20	7	25,853	138,470	11,767
25	6	21,973	26,140	16,168	25	5	23,425	87,803	9,370

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 48

LSD* PROCEDURE

HEMATOLOGY

ORDERED ARRAY OF

MEAN NEUTROPHILS / cumm

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
3	8,840	3	8,689
5	10,029	5	10,881
25	21,973	7	20,359
7	24,156	19	21,580
19	26,620	25	23,425
20	28,498	20	25,853

* Fisher's least significant difference

Values lying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

Lymphocytes / cumm

Characteristic features:

(1) Lymphocytes/cumm in the NAP- and AP-dogs on days 3 and 5 was approximately 4,000/cumm (tables 49 and 50, pgs. 119 and 120).

(2) 50% partial pancreatectomy on day 6 resulted in a decreased mean lymphocytes/cumm in the NAP- and AP-dogs on day 7 (table 49, p. 119).

(3) There was a significant increase in mean lymphocytes/cumm from day 19 to day 20 in the NAP-dogs, whereas this did not occur in the AP-dogs (tables 50 and 57, pgs. 120 and 128).

(4) The NAP-dogs resumed their normal mean lymphocytes/cumm on day 25, whereas the AP-dogs remained at a lower level (table 49, p. 119).

TABLE 49

HEMATOLOGY

LYMPHOCYTES / cumm

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	3,259	1,986	1,409	3	8	3,595	4,682	2,163
5	8	2,551	1,773	1,331	5	8	3,550	2,817	1,678
7[a]	8	1,074	953	976	7[a]	8	2,153	880	938
16[b]					16[b]				
19[d]	8	1,403	2,122	1,456	19[e]	8	1,959	1,553	1,246
20[c]	7	2,644	3,846	1,961	20	7	1,541	940	969
25	6	3,276	9,628	3,102	25	5	2,408	1,024	1,012

a) 24 hours after 50 $\bar{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 50

LSD* PROCEDURE

HEMATOLOGY

ORDERED ARRAY OF

MEAN LYMPHOCYTES / cumm

NAP-DOGS		AP-DOGS	
Days	Means	Days	Means
25	3,276	3	3,595
3	3,259	5	3,550
20	2,644	25	2,408
5	2,551	7	2,153
19	1,403	19	1,959
7	1,074	20	1,541

* Fisher's least significant difference

Values tying to the left of the same vertical line are not significantly different; those lying to the left of different lines are significantly different at an alpha-level of .05

Monocytes / cumm

Characteristic features:

(1) The monocytes/cumm in the NAP- and AP-dogs on days 3 and 5 was approximately 1,000/cumm (table 51, p. 122).

(2) Mean monocytes/cumm increased noticeably in the NAP- and AP-dogs from day 7 to days 19 and 20; i.e., during the hormonal regimen (BGH/DX) (table 51, p. 122). These changes were not significant (table 57, p. 128).

(3) Mean monocytes/cumm almost resumed a normal value in both the NAP- and AP-dogs on day 25 (table 51, p. 122).

TABLE 51

HEMATOLOGY

MONOCYTES / cumm

NAP-DOGS					AP-DOGS				
Day	N	Means	Variances	Standard Deviations	Day	N	Means	Variances	Standard Deviations
3	8	1,031	445	667	3	8	863	810	900
5	8	1,031	580	763	5	8	1,071	526	725
7[a]	8	1,149	1,489	1,220	7[a]	8	1,361	2,541	1,594
16[b]					16[b]				
19[d]	8	1,951	2,132	1,460	19[e]	8	2,348	1,582	1,257
20[c]	7	1,716	4,220	2,054	20	7	1,594	1,344	1,159
25	6	1,306	2,747	1,657	25	5	1,003	562	749

a) 24 hours after 50 $\overline{P}$

b) Hormonal regimen initiated

c) Hormonal regimen discontinued

d) Sham operation

e) 12 hours after discontinuation of hormonal regimen and prior to surgical procedures

TABLE 52

MEAN SQUARE

OF THE FOURTEEN TREATMENT GROUPS

AT TIME ZERO

Source of Variation	Degrees of Freedom (D.F.)	Mean Square (M.S.)		
		BLOOD GLUCOSE (mg%)	SERUM AMYLASE (S.U.)	SERUM LIPASE (L.U.)
Treatment	13	40339.85*	15836080*	1552.24*
Error	92	9387.67	1328578	74.02

* = significance at alpha-level .05

TABLE 53

MEAN SQUARE

OF THE TWELVE TREATMENT GROUPS

AT TIME ZERO

Source of Variation	Degrees of Freedom (D.F.)	Mean Square (M.S.)		
		BLOOD CREATININE (mg%)	S-GPT (F.U.)	PLASMA SODIUM (mEq/l.)
Treatment	11	0.31*	102612*	48.7
Error	77	0.11	10861	41.9

* = significance at alpha-level .05

TABLE 54

MEAN SQUARE

OF THE TWELVE TREATMENT GROUPS

AT TIME ZERO

Source of Variation	Degrees of Freedom (D.F.)	Mean Square (M.S.)		
		PLASMA POTASSIUM (mEq/l.)	PLASMA CHLORIDE (mEq/l.)	PLASMA BICARBONATE (mEq/l.)
Treatment	11	0.38*	169.9*	12.73
Error	77	0.18	24.7	12.03

* = significance at alpha-level .05

TABLE 55

MEAN SQUARE

OF THE TWELVE TREATMENT GROUPS

AT TIME ZERO

Source of Variation	Degrees of Freedom (D.F.)	Mean Square (M.S.)		
		BLOOD pH [-log (H^+)]	BLOOD P_{CO_2} (mm Hg)	BLOOD P_{O_2} (mm Hg)
Treatment	11	0.0049	16.59	31.93
Error	77	0.0035	19.66	34.37

TABLE 56

MEAN SQUARE

OF THE TWELVE TREATMENT GROUPS

AT TIME ZERO

Source of Variation	Degrees of Freedom (D.F.)	Mean Square (M.S.)		
		HEMOGLOBIN (g%)	HEMATOCRIT (%)	WHITE BLOOD CELLS cumm
Treatment	11	28.3*	181.0*	349,083*
Error	77	4.1	22.3	86,742

* = significance at alpha-level .05

TABLE 57

MEAN SQUARE

OF THE TWELVE TREATMENT GROUPS

AT TIME ZERO

Source of Variation	Degrees of Freedom (D.F.)	Mean Square (M.S.)		
		NEUTROPHILS/ cumm	LYMPHCYTES/ cumm	MONOCYTES/ cumm
Treatment	11	427,461*	5,652*	1,568
Error	77	64,571	2,575	1,560

* = significance at alpha-level .05

D I S C U S S I O N

A COMPARISON OF SOME CLINICAL AND CLINICOPATHOLOGICAL FEATURES OF EXPERIMENTAL ACUTE PANCREATITIS/DIABETES MELLITUS AND SPONTANEOUS ACUTE PANCREATITIS/DIABETES MELLITUS IN THE DOG

Clinical findings

The most constant and characteristic clinical features of the dogs, subjected to acute pancreatitis on day 19 were (1) severe abdominal pain (100%) and (2) emesis (100%). The presence of severe abdominal pain has in most publications been reported as being characteristic in cases of acute pancreatitis in the dog (47, 48, 49, 50, 51, 54, 131) and in man (58, 73, 74, 75, 76, 77). The pain was not confined to the epigastric or supraumbilical region as reported in man, but was diffuse distributed. Whereas human individuals may be able to localize pain to certain parts of the abdomen or abdominal wall, it was not possible to detect localization in these dogs. Pain in the epigastric region will radiate to other areas and be misleading to the veterinarian with respect to the localization of organ lesions. It must be emphasized that other acute abdominal diseases can give rise to severe abdominal pain ("acute abdomen") (189); these include acute gastritis, acute hepatitis, acute gastric dilatation, and gastroduodenal foreign body. It is conceivable that some of the pain was contributed by the coexisting acidosis, Warren (77). Emesis has been reported in association with spontaneous acute pancreatitis in the dog (47, 48 49, 50, 51, 54, 131) and in man (58, 73, 74, 75, 76, 77). It may contain blood. It was characteristic that the vomited material in all acute pancreatitis/diabetes mellitus dogs was yellow-colored, implying that duodenal contents were present. The mechanism that caused the emesis was most likely (1) partial

duodenal occlusion due to impingement of the enlarged pancreas, (2) toxic or pyrogenic stimulation of the emetic center; i.e., absorption of necrotic products from the pancreas, ketone bodies, and conceivably the staphylococcal alpha-toxin. Whenever the vomited material was brown or bloody, acute hemorrhagic duodenitis was probably present. The vomiting of blood was correlated with the severity of the disease, since those dogs that vomited blood died or were severily keto-acidotic. These two clinical findings were in very sharp contrast to the NAP-dogs, where no emesis and only very slight pain and abdominal distension occurred on day 20.

Besides pain and vomiting, other signs pertinent to the gastro-intestinal tract were observed. The bloody diarrhea, which in this investigation occurred in 5 of 8 dogs (approximately 60%) with acute pancreatitis was a frequent sign. The same finding has been reported in man (58), but it is not well known if it also occurs in dogs with spontaneous acute pancreatitis. The bloody diarrhea was associated with an unfavorable prognosis in the acute pancreatitis/diabetes mellitus dogs and presumably attributed to a severe enterocolitis. If the animal was able to retain food in 2 days following the acute attack, the enteric complications disappeared. None of the NAP-dogs developed diarrhea and it was obvious that experimental acute pancreatitis significantly changed the GI-function.

Pancreatomegaly was detected by abdominal palpation in 6 of 8 dogs (75%) with acute hemorrhagic pancreatitis, implying severe involvement of the pancreatic acinar tissue. Crepitation was disclosed by abdominal palpation in 7 of 8 dogs (90%). This was taken as evidence for fibrin on the surface of pancreas. The same finding has been made rather frequently in man, but only a single case is reported in the veterinary literature (47). In the above citation, the

mass was suspected to be a pancreatic tumor, rather than a diffuse enlargement of the pancreas. Based on these observations, a finding of pancreatomegaly in dogs can be of great value, especially if crepitation is also present.

Hepatomegaly can presumably lead to a wrong diagnosis but it must be recalled that (1) hepatomegaly is diffusely distributed in the right epigastric region in contrast to pancreatomegaly where the mass is more discrete and localized and (2) crepitation will be present in a higher degree in pancreatitis than in acute hepatitis.

Signs from the circulatory system in the acute pancreatitis/diabetes mellitus varied depending on the severity of the acute pancreatitis/diabetes mellitus. When the acute pancreatitis was complicated by only slight diabetes as it occurred in group number 1 (page 42), the pulse was wiry, the perfusion time prolonged and the visible mecous membranes were hyperemic. In the second group (page 42) the mucous membranes were hyperemic or pale, the pulse wiry and the perfusion time even more prolonged. The third and comatous group (page 42) showed evidence of the most impaired circulatory function with muddy membranes and hardly sensible pulse. No perfusion time could be estimated in these cases (2 of 8 AP-dogs).

It was of great importance in the diagnosis, prognosis, and treatment of experimental acute pancreatitis/diabetes mellitus to monitor the kidney function closely. Whenever the circulatory system was impaired as described above, a considerable decrease of the blood pressure, as assessed by the femoral pulse, occurred. This would lead to severely diminished kidney function and the animal would not be able to filter metabolic and toxic products. Oliguria, anuria, and ultimately, renal "shut down" occurred. Renal "shut down",

hemoglobinuria, oliguria, and anuria always yielded a very poor prognosis in the acute pancreatitis/diabetes mellitus dogs, especially when keto-acidosis coexisted. It was characteristic that oliguria occurred on day 20 in all the acute pancreatitis/diabetes mellitus dogs. Death attributed to acute pancreatitis/diabetes mellitus undoubtedly was attributed to hypovolemia, low cardiac output, keto-acidosis, and probably renal failure. The NAP-dogs never developed any signs of cardiac or circulatory impairement.

The respiratory function was rather drastically changed in acute pancreatitis/diabetes mellitus, and it was ascribed to the acidosis. Severest involvement occurred in the dogs with coma, however, Kussmaul type of respiration was encountered in all 8 AP-dogs. The same finding is frequently recorded in human patients with acute pancreatitis and simultaneous keto-acidotic diabetes mellitus (58), whereas veterinarians seldom describe this phenomenon.

Diabetic coma in acute pancreatitis was associated with an extremely unfavorable prognosis in the AP-dogs. Diabetic coma is an exaggerated form of diabetic keto-acidosis. The pathophysiology is not well understood (123, 124) but three major mechanisms presumably contribute to the phenomenon: (1) Hypoinsulinemia and hyperglycemia, (2) hyperkalemia, hyponatemia, and acidosis, and (3) ketonemia. The hypoinsulinemia will impair the glucose utilisation in most tissues (exept the brain) and the result will be an increased oxidation of fat which will result in an excess of ketone bodies in the blood. These can, to some extent, be utilized, especially by the kidney (125), liver, and muscles, but they are accumulated at a rate exceeding the toxic limits. The hyperkalemia and hyponatremia will impair nerve transmission. The acidosis gives rise to increased ventilation and decreased oxygen saturation of the blood. The end

result is an organism where most metabolic processes are severely inhibited. Metabolic products are accumulated, accompanied by a profound water and electrolyte disturbance.

Spontaneous acute pancreatitis in dogs is usually not accompanied by coma unless the condition is complicated by keto-acidotic diabetes mellitus. In two of the 8 AP-dogs (25%), the acute pancreatitis gave rise to diabetic coma and both dogs died within 36 hours following the infusion of toxin.

On the basis of the above discussed clinical signs and the severity with which they occurred, the AP-dogs were classified into three groups:

(1) Acute pancreatitis with moderate changes in the glucose metabolism, showing evidence of moderate abdominal pain, emesis, and mild Kussmaul respiration.

(2) Severe acute pancreatitis/diabetes mellitus with predominant signs of severe abdominal pain, emesis, and pronounced Kussmaul respiration, indicating the existence of profound keto-acidosis.

(3) Diabetic coma with severe emesis, no abdominal pain and Kussmaul type of respiration.

The documentation of the existence of the acute pancreatitis of diabetes mellitus syndrome rests mainly on the following laboratory tests: (1) Serum amylase and lipase activities, (2) electrolyte and acid base content in blood. They changed considerably during the investigation period and will be discussed below.

Serum Amylase and Lipase Activities

Amylase and lipase activities in blood have been traditional methods of detecting pancreatic necrosis or inflammation (126, 127, 128). These enzymes are released from damaged pancreatic acinar cells. Although the initial events that cause pancreatic cell injury are not well understood, studies indicate that pancreatic proteolytic enzymes are of importance (64, 65a, 65b, 70, 129) and they can cause severe vascular injury by acting directly on the pancreatic micro circulation (130). Subsequently, isehemia due to vascular necrosis will be followed by further cell damage and an increased release of amylase and lipase as well as other cell constituents will be brought about by proteolysis and autodigestion (70).

The pathways of pancreatic enzymes into the blood stream has been the subject for numerous speculations. Two major routes are conceivable and probable: (1) Absorption of enzymes by venous drainage or (2) transperitoneal absorption; i.e., lymphatic drainage (131). Howard (132) studied portal and peripheral blood activities of pancreatic enzymes and concluded that the venous route of drainage was most likely. He emphasized that the increase of serum amylase and lipase activities in portal blood preceded that of the peripheral blood, indicating that portal absorption predominates. Waterman (133) implied that the transperitoneal or lymphatic absorption of amylase is most likely to occur because the peritoneal fluid activities of amylase was four times higher than that of peripheral blood. In the study reported here, amylase and lipase activities in peritoneal fluid were 2 - 3 times the corresponding blood activities in the two dogs that were tested. This tends to support the theory that transperitoneal absorption occurred at a faster rate than the venous drainage. Brobst (56) attempted to link these two concepts by arguing that the initial

rise in serum amylase and lipase activities is due to venous drainage, whereas the very abrupt peak 6 - 12 hours after the onset of the inflammation in experimental preparations is attributed to the lymphatic or transperitoneal absorption. This concept appears reasonable since the occlusion of the pancreatic veins by progressive necrosis and inflammation will impair the absorption of these enzymes.

The normal range of serum amylase and serum lipase is not fully investigated in dogs or cats and vary with the method used. In human patients, Sterkel and Kirsner (126) exhibited evidence for normal values of amylase from 60 to 200 Somogyi Units (S.U.) and for lipase below 1.0 Sigma-Tietz Units (S.-T.U.). Saxon et al (127) devised a modified saccharogenic method for amylase in man and recorded values ranging from 39 to 191 S.U. per cc serum. The saccharogenic methods were originated by Somogyi (134, 135). The above range appears to be very low compared with Small et al (52) who suggested that amylase values above 2130 Amylase Units were to be indicative of pancreatic injury, especially acute pancreatitis in the dog. This study has revealed that amylase values in normal dogs have an extremely wide range, but if the serum amylase is above 1500 S.U. the pancreas must be subjected to a closer examination of both the exocrine and the endocrine function. Amylase values from 1500 - 2500 S.U. were recorded 24 hours after partial pancreatectomy; i.e., surgically-induced subacute pancreatitis. Values of 2500 - 14000 S.U. were recorded in the 8 dogs with acute pancreatitis/diabetes mellitus 24 hours after infusion of the staphylococcal alpha-toxin. The animal with 14000 S.U. died within short time, and death was attributed to (1) pancreatitis and (2) diabetic coma.

The serum lipase appeared to be a more constant parameter than was serum amyl-

ase. The explanation for this consistency is found in the fact that pancreas acinar tissue is the principle source of lipase, whereas amylase is also present in liver and intestine. Nothman and Callow (136) investigated liver amylase and concluded that (1) normal blood amylase activity is maintained by liver rather than pancreas and (2) injury to the liver initiates hyperamylasemia although in a less degree than does inflammation of the pancreas. These statements question the use of amylase as an indicator of pancreatic inflammation and/or necrosis. Anticipating that the liver was a major source of amylase, necrosis and inflammation of the liver supposedly would initiate hyperamylasemia and a high S-GPT and a high serum amylase should occur simultaneously. The results of this investigation did not support this assumption and it can be concluded that the serum amylase activity was a good estimator of pancreatic inflammation and/or necrosis. The accepted practice of using serum amylase and lipase in the differential diagnosis of "acute abdomen" in human and veterinary medicine is considered reasonable, because there is a close connection between the severity of the clinical manifestations and the degree of pancreatic tissue reaction. However, caution is advised in interpretation of normal versus increased serum activities. Based on this study, values above 2500 S.U. were indicative of pancreatitis. It is desirable, however, to establish evidence for (1) the rate of change in serum amylase activity rather than the absolute activity and (2) the presence of other diseases. It is known that hyperamylasemia can occur in (a) renal insufficiency (52, 128), (b) ACTH treatment (52), (c) inflammation of the salivary glands (51, 128), (d) use of morphine or morphine derivatives (128), (e) biliary disorders, (f) alcoholism, (g) peptic ulcer, (h) intestinal obstruction (128, 137), (i) mesenteric thrombosis, (j) peritonitis, (k) hemorrhage of the spleen, and (l)

cerebral trauma in man (128). Some of these diseases can coexist with the acute pancreatitis and the hyperamylasemia may be attributed to a complex of diseases rather than uncomplicated acute pancreatitis. For this reason, a serum lipase activity determination should be performed concurrently in order to establish evidence for a true pancreatic involvement.

The results of this study indicated that serum lipase normally was below 1.0 L.U. and that it was a very consistent serum parameter. Values from 1.0 to 2.0 L.U. were found 24 hours after partial pancreatectomy, whereas 2.0 to 5.0 L.U. were found 24 hours after induction of pancreatitis. When serum lipase exceeded 5.0 L.U. the animal was gravely ill and the prognosis was poor.

Several authors have recorded (52, 56, 138) that hyperamylasemia preceded hyperlipasemia in the development of acute pancreatitis and that the decrease of amylase was more rapid than that of lipase. The results of this research did not justify a similar assumption. It was found that serum lipase and amylase activities varied simultaneously during the phase of acute pancreatitis and diabetes mellitus (fig. 7, p. 79). It can also be concluded that lipase was a constant serum parameter that did indicate pancreatic inflammation more safely than did amylase. There was strong evidence for relation between the severity of clinical signs and the level of pancreatic blood enzymes.

Blood Glucose

The fasting control were 95 mg%. There was a slight, transient increase (108 mg%) 24 hours after partial pancreatectomy. The blood glucose returned to normal by 96 hours after partial pancreatectomy. A further increase occurred after two days of BGH/DX treatment (167 mg%), after which surgery was performed. It was characteristic and striking that the mean blood glucose peaked very

abruptly (371 mg%) in the AP-dogs after induction of acute pancreatitis, but declined steadily in the NAP-dogs after BGH/DX treatment was discontinued. This clearly established that acute pancreatitis could render the susceptible dogs clinically and biochemically diabetic. It must also be emphasized that the variation in glucose concentration on day 20 was sizable. The urinalysis revealed simultaneous glycosuria in all dogs on day 20 (100%).

The increased glucose concentration was attributed to severe destruction of the beta-cells and subsequent insulin deficiency or insulin destruction resultant in hypoinsulinemia. Hence, the glucose utilisation in the tissues was impaired, fat oxidation increased in rate, and ketonemia ensued. In all 8 AP-dogs, ketonuria occurred on day 20 (table 30) indicating that the diabetes mellitus subsequent to acute pancreatitis belonged to the complicated type (keto-acidotic). The glucose concentration in the blood remained high in the AP-dogs, even though only one of six surviving dogs was permanently diabetic after 7 days [k-value remained low (k=1.67), mean fasting glucose exceeded 150 mg%]. The ketonuria ceased two or three days after the acute attack in four of six surviving dogs. The rapid decline of blood glucose to lower levels and the resolution of the keto-acidosis in the surviving dogs indicated that they were not permanently diabetic. It must, however, be emphasized that two of the three dogs with the severest keto-acidosis died, and thus it was not possible to obtain further data from them.

H-IVGTT

A high-dose intravenous glucose tolerance test was performed to assess changes in glucose tolerance since this change was not always reflected in the absolute glucose concentration. In the AP-dogs, it was characteristic that the maximum

change in glucose tolerance occurred 24 hours after induction of pancreatitis (k = 1.13%) and that these dogs never regained their normal glucose tolerance within 7 days. This was a feature that strongly differentiated this group of dogs from the NAP-dogs. The reason for this difference was explained through the vast inflammatory destruction of beta-cells in the AP-dogs, since the hormonal treatment was almost identical for both groups of dogs. Other factors influencing the glucose tolerance in the AP-dogs were (1) liver damage (139, 140) and (2) renal "shut down". Both factors were of extreme importance in the AP-dogs that showed oliguria and elevated S-GPT activity on day 20. Glucose tolerance tests performed in the individual dogs showed that a low k-value (below 1.15) 24 hours after induction of acute pancreatitis/diabetes mellitus was associated with an unfavorable prognosis. Thus, the k-value would seem to be of importance in the prognosis of spontaneous acute pancreatitis/diabetes mellitus syndrome in the dog.

The degree of impaired glucose tolerance and the plasma glucose concentration seemed positively correlated. The degree of hyperamylasemia and hyperlipasemia also was correlated to the degree of glucose intolerance and the absolute glucose concentration. In cases of very high serum amylase and lipase activities, decreased glucose tolerance could be expected. This statement seems reasonable since the degree of pancreatic destruction including the beta-cells is related to the blood enzyme activities.

Acid-Base and Electrolyte Status

The changes in plasma HCO_3^- and electrolytes and blood pH and P_{CO_2} in acute pancreatitis/diabetes mellitus were consistent with what one would expect in keto-acidosis. Even though the pH and HCO_3^- did not significantly change at

day 20 (alpha = .05), there was a trend toward a decrease in both parameters and it changed noticeably more in the AP-dogs than in the NAP-dogs. As the base excess [B.E. (mEq/l.)] values revealed, severe acidosis occurred in several AP-dogs 24 hours after induction of acute pancreatitis. The NAP-dogs remained entirely normal.

The mechanism of diabetic keto-acidosis involves all possible mechanisms of compensation available in the organism; i.e., the blood buffer systems, the kidneys and the lungs (141). The beta-hydroxy-butyric acid and aceto-acetic acid will tend to increase the blood (H^+) and the following buffer reaction will shift toward the right (141, 142):

$$H^+ + HCO_3^- \longrightarrow H_2O + CO_2 \text{ [catalyzed by carbonic anhydrase]}$$

As indicated, the result will then be (1) decreased plasma HCO_3^- and (2) increased blood P_{CO_2}. The P_{CO_2} will in metabolic acidosis be compensated through hyperventilation (145). The release of hyperventilation is triggered through a stimulation of the respiratory centers for CO_2 and H^+ (123, 141, 142, 143, 144, 145). The first response will be (1) increased rate and hence (2) deeper respiration. The resultant type of respiration is called Kussmaul. In contrast to the rapid pulmonary exchange of CO_2, H^+ is more slowly excreted by the kidney as (1) free H^+ and (2) NH_4^+ (141, 142). Any kidney involvement thus will impair the excretion of H^+ and exaggerate the acidosis. Increase in plasme (H^+) (decreased pH and HCO_3^-) can occur in hypoventilation (emphysema, pulmonary edema, and cardiac diseases) because the following reaction will take place (142):

$$CO_2 + H_2O \longrightarrow HCO_3^- + H^+ \text{ [catalyzed by carbonic anhydrase]}$$

In severe keto-acidosis, the increased (H^+) excretion by the kidney will cause

disturbances in sodium and potassium metabolism (141, 144): (1) Increased K^+ retention and (2) decreased sodium excretion in exchange for H^+. Besides this, the H^+ and Na^+ will replace K^+ intracellularly and this will give a further increase of plasma K^+ and a decrease of plasma Na^+. Most studies of complicated diabetes confirm this statement (144). In this study, there was no significant change in mean values of plasma (Na^+) and (K^+) 24 hours after induction of acute pancreatitis. However, the mean value for the AP-dogs did not include values for one dog that died before blood could be obtained for analysis. Cotton et al (25) found hyperkalemia and hyponatremia in spontaneous acute pancreatitis/diabetes mellitus. The animal that Cotton et al reported had been sick for considerable longer period of time on the average, than the test dogs reported here. Hyponatremia can be due to other diseases than diabetes, for example (1) vomiting (141), (2) diarrhea (143), and (3) chronic intestinal nephritis (C.I.N.).

ON THE HIGH-DOSE INTRAVENOUS GLUCOSE TOLERANCE TEST (H-IVGTT)

The response of an individual to a glucose load has generally been accepted as a good measure of glucose-metabolism; i.e., glucose tolerance. As previously cited, either an oral or an intravenous test can be performed. The use of the intravenous and the oral glucose tolerance test (IVGTT and OGTT) can be advocated whenever the diabetic condition is not made clinically obvious by polyuria and polydipsia, such as in adult diabetes mellitus in man (151). The H-IVGTT is not yet well standardized in dogs. In man, certain criteria for diabetes are established. Values below 120 mg glucose per 100 ml blood on a 24 hours fasting sample indicates that the individual is normal. Borderline

diabetics generally have fasting values from 120 - 200 mg% and above 200 mg% the condition is considered to be diabetic (146). Duncan (124), however, stated that fasting glucose values above 130 mg% and/or glycosuria are indicative of diabetes mellitus in man, and if present make the glucose tolerance test unnecessary for diagnosis. The use of the glucose tolerance test becomes most important in cases where borderline diabetes exists. It is not yet well-known whether borderline (adult-onset) diabetes occurs in dogs. When the blood glucose values are very high, the test should not be performed.

The advantages of the H-IVGTT over the OGTT are that the phase of intestinal absorption and portal transport through the liver are bypassed. Any pathologic changes disturbing absorption, such as enteritis, would decrease the reliability of the OGTT. Diabetics often have gastro-intestinal problems and, hence, in many cases, abnormal glucose absorption.

The H-IVGTT used in this study has not been reported before in detail in the dog. Veterinarians have relied on data cited for normal human individuals, borderline diabetics or overt diabetics.

The objectives of this investigation with respect to glucose tolerance were:

(1) Define the glucose tolerance curve (H-IVGTT, 45' - 60'). This curve was based on a dose of 1 g glucose per kg bodyweight given intravenously within a period of 0.5 - 1.0 minute. Samples were obtained at 0, 5, 15, 30, 45, and 60 minutes.

(2) Establish a correlation coefficient (r^2), using the two following equations:

(a) $\log Y = \alpha + \beta T$, which is the accepted equation for use in man.

(b) $Y = \alpha + \beta_1 \frac{1}{T} + \beta_2 T$, which was selected because it resembles the normal glucose tolerance curve

Test which of the models the glucose tolerance curve will fit best (max. r^2).

(3) Calculate the glucose disappearance coefficient ($k = -\beta \times [-(10)^2]$ for the glucose tolerance curve using the following formula:

$$\log Y = \alpha + \beta T$$

The above listed procedures were used in normal dogs, prediabetic dogs, transient- and overtly diabetic dogs, and in dogs with acute pancreatitis/diabetes mellitus.

The Glucose Tolerance Curve

Objective (1) above was interpreted by visualising the plotted curves 111 and 112, pgs. 63 and 64 as examples of a normal glucose tolerance curve. The peak plasma glucose concentration occurred quickly but was for convenience measured at five minutes after the beginning of the glucose infusion. Mean glucose did not exceed 500 - 550 mg% if the animal was entirely normal; i.e., had not been fed, had no history of known diabetes, and had received 1 g glucose over a periof of 0.5 - 1.0 minutes. It must be emphasized that the time period of infusion was held constant at 0.5 - 1.0 minutes. In 30 minutes, mean glucose decreased abruptly and was below 100 mg% at 45 minutes. Among 32 glucose tolerance tests performed in this study, all normal dogs attained plasma glucose concentrations below 100 mg% in 45 minutes. If the curve was plotted beyond 60 minutes, the glucose concentration rebounded. This was attributed to a

probable decrease of plasma insulin activity at 45 to 60 minutes. Studies in man can support this finding and it seems reasonable to assume that the glucose load is of importance in this mechanism (147); i.e., that the acute insulin output, not the total, is correlated (r = + 85) to the glucose load. This explains that the readily available insulin or "stored insulin" can be released very easily (147).

With continuous treatment with BGH and DX, the normal glucose tolerance curve lost its rapid decrease, whereas the 5 minute concentration remained almost constant (curves 311 and 312, pgs. 63 and 64). The characteristic features pertaining to this type of curve were (1) that it did not approach the initial glucose concentration within 60 minutes and (2) that the slope was less than normal. This latter feature appeared to be easier to visualize on the semilogarithmic paper (curves 311 and 312, pgs. 65 and 66). The type of curves represented by 311 and 312 could be called borderline diabetic or transient diabetic curves by visual inspection. Progressive treatment with the hormones impaired the glucose tolerance even more (curve 411, pgs. 63 and 65), but it did not bring about any profound changes.

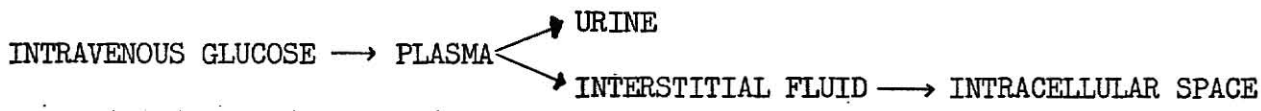
The glucose tolerance curve became very abnormal in the AP-dogs 24 hours after induction of pancreatitis (curve 412, pgs. 64 and 66). Many diabetogenic factors were operative at this stage: (1) Severe exhaustion and/or destruction of beta-cells due to acute pancreatitis, (2) gluconeogenic effect of adrenocortical activity, (3) residual effect of BGH/DX, (4) lipidosis of the liver (high S-GPT), and (5) impaired kidney function due to reduced cardiac output. Hence, it will be emphasized that the decreased glucose tolerance could be attributed in part to dysfunction of organs other than the pancreas.

Correlation Coefficient

The correlation coefficient (r^2) was calculated for both equations, as indicated in objective (2) above. It was obvious (tables 17A and 17B, pgs. 61 and 62) that the second equation (b) fit the glucose tolerance data better than did the accepted equation (a) when the dogs were normal. The reason for this can be visualized in figs. 5 and 6, pgs. 67 and 68, where the curves representing $Y = \alpha + \beta_1 \frac{1}{T} + \beta_2 T$ is plotted for days 3, 19, 20, and 25 for both groups of dogs. The tolerance curves, as previously stated, tended to rebound after 45 - 60 minutes in normal dogs and this part of the curve did not fit the logarithmic function where glucose concentration and time presumably were linearly related. Both from a physiological and a statistical point of view, this new model (b) was preferable in normal dogs. When the dogs became gradually diabetic, the r^2 revealed that the variation in expected glucose concentration (Y) attributed to regression became less pertinent to both functions. Hence, it was justified to use the log-function [equation (a)] in diabetics providing a short time period was used (e.g., 60 minutes) to avoid the rebounding of glucose which occurred after the insulin activity declined. In conclusion (1) $Y = \alpha + \beta_1 \frac{1}{T} + \beta_2 T$ could be used as an estimator of the glucose disappearance in normal dogs rather than $\log Y = \alpha + \beta T$, since r^2 was very high for the former equation, (2) either of the two equations could be used in borderline, overt diabetics, and in acute pancreatitis/diabetes mellitus (r^2 was the same for both equations in this study), and (3) the fit of the two curves became less in diabetic cases (r^2 was small) which implied that neither of these two functions were reliable in predicting shape of the curve in diabetes mellitus.

Glucose Disappearance Coefficient

Calculation of the glucose disappearance coefficient [objective (3)] expressed the speed with which the injected glucose was eliminated from the plasma to another compartment of the organism. The possible compartments receiving the glucose appear to be brain, liver, kidney, muscles, adipose tissue, and urine (148). The following diagram will illustrate that (149):



It is believed that only 3% of the injected glucose will pass through the kidney into the urine in normal individuals (149). During the course of sublatent and clinical diabetes, the uptake of glucose to the above listed body-compartments will be impaired (exept the brain) and the disappearance rate will decrease significantly (146, 148). This disappearance coefficient (k) does not estimate the fate of glucose, but it simply reflects the movement of glucose out of blood to other compartments. It is a meaningful expression when dealing with the clinical aspect of diabetes mellitus.

In man, a k-value formula has been calculated from the assumption that the glucose disappearance is an exponential function (150):

$$C_t = C_o e^{-kt}$$

or

$$BZ_1 = BZ_o e^{-kt}$$

where BZ_1 = blood glucose concentration (C_t) at time t_1

and BZ_o = blood glucose concentration (C_o) at time t_o

The k-value is isolated by transforming the equation to: $k = \frac{0.693}{t/2}$ or $k = \frac{69.3}{t/2}$ in order to get the result in percentage of blood sugar fall/min. In the above

equations t = time in minute and k = glucose disappearance coefficient (% fall/min.). This k-value or glucose disappearance coefficient is equal to the $-\beta$ comprising table 17A, p. 61, since they both represent the regression coefficient or the slope of the transformed glucose tolerance curve.

Calculation of the k-value from the above listed formula has been done in man on the basis of two different concepts: (1) Plotting the logarithm of the actual blood glucose concentration against the time or (2) plotting the logarithm of the glucose excess value above fasting against the time. The k-value derived by the first method is called the total index and was used in this study, whereas the k-value calculated using option (2) is the increment index of k. Using a low glucose load; i.e., a total dose of 25 mg or 0.5 g/kg body weight given intravenously, these two indices are quite different (151). Duncan (152) found the following k-values in man, using the low glucose load (25 g):

	Total index	Increment index
Diabetics	0.71 ± 0.16	1.83 ± 0.31
Normal	1.37 ± 0.22	3.68 ± 0.40

Amatuzio et al (153) investigated the low-dose IVGTT and concluded that the increment index of normal subjects ranged from 3.5 - 5.0, whereas diabetics showed much lower values; i.e., 0.85 - 2.42. Lundbäck (154) studied in man the total index with a standard dose of glucose of 25 g and concluded that normal subjects had a k-value above 1.05, whereas diabetics had an average k-value of 0.63. There appeared to be a relatively large overlap between healthy subjects and mild diabetics. Kienholz (150) used the total index but gave 0.35 g/kg body weight intravenously and found in man an inverse relationship between k-value and age:

Year	10-19	20-39	40-59	60-
Mean-k	2.00	1.78	1.62	1.27

The disadvantages of using the low-dose intravenous glucose tolerance test in man appear to be (1) a considerable overlap between healthy and mild diabetics as indicated by Seltzer (151) and Dyck and Moorhouse (105) and (2) a confusing difference between the total and increment indices (151). Dyck and Moorhouse (105) solved problem (1) above, by giving a higher glucose load; i.e., 50 g totally or 1 g/kg body weight intravenously within 4 minutes. This method is called the high-dose intravenous glucose tolerance test. It occurred to Dyck and Moorhouse (105) that it was a very sensitive test for mild diabetics, even more useful and sensitive than the OGTT and the Cortisone test. They found that healthy subjects had a k-value of 1.50 or above. They also stated that only slight dose dependance occurred when given a high dose intravenously.

In this investigation, k-values were calculated on the basis of (1) high glucose load; i.e., 1 g glucose/kg body weight intravenously and (2) the actual glucose concentrations, and hence the results in these dogs were only comparable to the values of Dyck and Moorhouse (105) from their study in man. It is conceivable, however, that the k-values derived from the high-dose intravenous glucose tolerance test and using the actual glucose values will resemble those obtained from the low-dose test when plotting the glucose excess (147).

From table 17A, p. 61, it is obvious that the dogs designated as prediabetics; i.e., the NAP- and AP-dogs on day 18 ($k = 1.96 \pm 0.33$ and 2.14 ± 0.19) had a considerable overlap with normal dogs; i.e., the NAP- and AP-dogs on day 3 ($k = 2.67 \pm 0.32$ and 3.01 ± 0.38) and hence a discrimination between normal

and prediabetic dogs was very difficult. The group of dogs designated as overtly diabetics; i.e., the NAP-dogs on day 20, had a k-value of 1.55 ± 0.28 and this figure did not have any overlap with the healthy dogs; i.e., the NAP-dogs on day 3 (k = 2.67 ± 0.32), whereas there was an imperceptible overlap with the prediabetic dogs; i.e., the NAP-dogs on day 18 (k = 1.96 ± 0.33). This indicated that a safe differentiation could be done between normal and overtly diabetic dogs on basis of the k-value, whereas it appeared very difficult to make a definite distinction between prediabetics and overtly diabetic dogs although it could probably be done in most cases. The acute pancreatitis/diabetes mellitus dogs revealed k-values of 1.13 ± 0.44 and hence there was (1) no overlap between this group of dogs' k-values and the k-values found in prediabetics or in normal dogs and (2) there was only slight overlap between this group of dogs and the NAP-dogs on day 20.

Since 99% of all normal dogs; i.e., the NAP- and AP-dogs on day 3 and 5, had a k-value above 2.00, it was considered that k-values of 2.00 or higher were normal, realizing that some of the prediabetic dogs invariably will be included in this category. It was not possible definitely to establish a narrow range of k-values for the prediabetic dogs. K-values below 2.00, however, were considered to be abnormal whether this included the NAP-dogs on day 20 or the acute pancreatitis/diabetes mellitus dogs (AP-dogs) on day 20. It was obvious that the latter group of dogs had a trend towards a lower level.

The findings made in this study in normal, transiently-diabetic dogs, and acute pancreatic/diabetes mellitus dogs can not be contrasted with previous studies in veterinary medicine. Meier (14) described an IVGTT in normal and overtly diabetic dogs but did not calculate k-values. Bloom and Handelsmand

(3) found reason to believe that the glucose disappearance rate was decreased in cases of diabetes mellitus, and that complicated keto-acidotic diabetes significantly changed the slope of the curve more than the simple form of diabetes.

It was realised that (1) the fit of the glucose tolerance curve to the exponential function was best in the normal animals and hence the k-value was very reliable in normal dogs and that (2) the reliability of the k-value decreased when the r^2 decreased, and hence the actual disappearance rate might have another "k"-value.

The H-IVGTT as a tool in diagnosis of diabetes mellitus in dogs

It is accepted by most veterinarians that diabetic dogs can be divided into three groups with respect to their plasma glucose concentration:

I	II	III
non diabetics	prediabetics	overtly diabetics
< 120 mg%	120 - 200 mg%	> 200 mg%

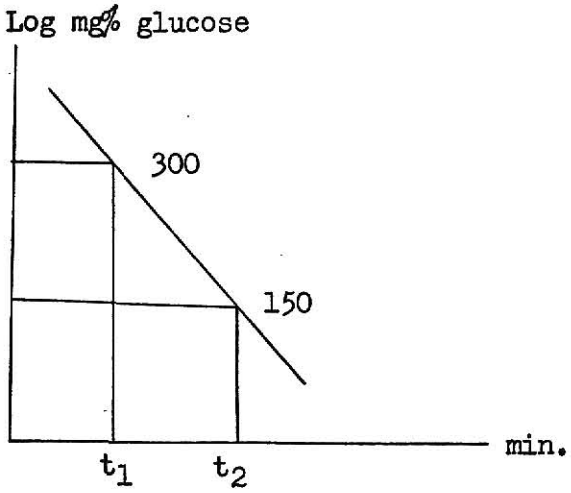
The diagnostic challenge towards an exact diagnosis of initiating spontaneous diabetes mellitus is offered by group II. It is most likely to find representatives for this type of animals among obese, spayed females of five years or more of age. They may show only faint clinical manifestations of diabetes mellitus and hence the condition will not be diagnosed or treated. They will later in their life time be endangered to develop overtly and maybe even a complicated form of diabetes mellitus. It is conceivable that a glucose tolerance test in this early stage could detect even slight impairment of the animals carbohydrate metabolism. However, until now there has been no guide

to interpretation of the high-dose intravenous glucose tolerance test in normal or in prediabetic dogs because of (1) lack of standardization of (a) gram glucose per kg body weight, (b) infusion time, (c) number of samples, and (d) duration of the test, (2) the prevalance of the OGTT over the H-IVGTT, (3) lack of a k-value or glucose disappearance coefficient in normal and prediabetics, and (4) lack of knowledge concerning the shape of the H-IVGTT curve for 60 minutes sampling (Δ 5' - 60').

Even though a high glucose concentration in dogs used in this study regularyly was related to a decreased k-value, this finding may not occur in a population of spontaneous diabetic dogs. This study provides guide lines for use of the glucose tolerance test and calculation of a k-value in order to establish evidence for the degree of glucose intolerance when the absolute plasma glucose concentration is not considerably increased; i.e., prediabetics. It is suggested to screen dogs that are old, spayed, and obese, since they are likely to have a decreased glucose tolerance that might well develop into a clinical manifest diabetes mellitus. Dogs with established juvenile atrophy of the pancreas or tumors of the beta-cells may also reveal decreased glucose tolerance (own observation).

In order to calculate an approximate k-value, the actual blood glucose concentration in mg% must be plotted as the ordinate against the time in minutes as abcissa on semilogarithmic graph-paper. From the previously derived formula $k = \frac{0.693}{t_2-t_1} \times 100$ can be calculated, when t_2 and t_1 are obtained.

If for example the glucose concentration in plasma decreases from 300 to 150 mg% and t_2 = 45 min. and t_1 = 15 min., k can be derived from the above formula:



$$k = \frac{69.3}{45-15} = \frac{69.3}{30} = 3.3\% \text{ fall/min.}$$

It must be emphasized that the diabetic glucose tolerance curve and its k-value can be misinterpreted if other diseases coexist or if other diseases are the basic reason for the impairment. In dogs this especially will be pertinent to hyperadrenocorticoism (Cushing syndrome), obesity, and pregnancy or pseudo-pregnancy. Liver cirrhosis, nephritis, and cholecystitis are also encountered in man. Hyperthyroidism which sometimes causes hyperglycemia and glycosuria does not interfere with the glucose tolerance test in man.

A COMPARISON OF SOME CLINICAL AND CLINICOPATHOLOGICAL FEATURES OF EXPERIMENTAL (HORMONAL) INDUCED DIABETES MELLITUS AND SPONTANEOUS DIABETES MELLITUS IN THE DOG

Clinical findings

The clinical features of spontaneous diabetes mellitus in the dog have been reviewed in detail previously (pgs. 3-10). The aim with this chapter was to discuss (1) the similarities between experimental, hormonal diabetes and the spontaneously occurring disease and (2) some essential concepts in the patho-

genesis of diabetes mellitus. The action and mechanism of the bovine growth hormone will be described in details later on.

The initial clinical manifestations of the spontaneous diabetes mellitus are polyuria and polydipsia (3, 4, 7, 8, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 23, 24, and 25). The same features were recorded in seven of the eight NAP-dogs, following one or two days administration of BGH/DX. The mechanism of polyuria in spontaneous diabetes mellitus involves an osmotic diuresis (155). The exaggerated water excretion can develop a hyponatremia because sodium is lost in less extent than is water. The increased tonicity of the plasma water phase will mediate thirst and water intake together with ADH release through a direct stimulation on the hypothalamus. To consume sufficient amounts of water, the animal must drink frequently, and the term "polydipsia" seems appropriate. Osmotic diuresis becomes active when the renal threshold for glucose is exceeded; i.e., hyperglycemia of 180 mg% or above (155). The increased urinary glucose can result in urine hyperosmolarity and subsequent elevation of the specific gravity (S.G.). The normal S.G. of dog urine ranges from 1.020 to 1.050 or from 500 to 1.200 mosmol per liter urine (103, 116). In diabetes it is not unusual to find a S.G. above 1.040 (3, 4, 7, 13, 103, 116). Decreased S.G., however, has been reported in progressive cases of diabetes mellitus. Most investigators agree that this low S.G. is attributed to secondary diabetic damage of the kidneys, thus, inability to concentrate the urine (3, 4, 7, 13, 103, 116). The mechanism that created polyuria in the NAP-dogs on days 17, 18, 19, 20, 21, and 22 could not solely be explained through the hyperglycemia induced by BGH/DX. If the hyperglycemia would account for this reaction, two major findings should be accomplished: (1) High urinary specific gravity and (2) hyperglycemia in higher degree. From table 30, it can be visualized that

the urinary S.G. continuously decreased and the imperceptible hyperglycemia occurring on days 17, 18, and 19 could not induce "glucose osmotic diuresis" (polyuria and polydipsia). These data implied that other pathophysiological reactions took place. A conceivable explanation for the sequence of events that lead to this initial polyuria and polydipsia appeared to be the action of the dexamethasone. As any other synthetic, potent glucocorticoid, it will increase the water clearance in the kidney and hence impose polyuria and low S.G. (156). Osbaldiston (157) recently investigated the action of strong synthetic adreno-cortocosteroids and confirmed this concept. The exact mechanism of the adreno-corticosteroids' water clearing effect is not fully understood, but it is related to hyperglycemia and/or a strong antagonism to ADH (157). The initial polyuria and polydipsia that occurred in the NAP-dogs most probably were based on the dexamethasone activity. It is conceivable that the effect of BGH was delayed and when it began to exert its action, it was responsible for elevation and maintenance of the hyperglycemia. Therefore, the BGH/DX combination was selected for this investigation and it caused hyperglycemia, glycosuria, and polyuria. In a pilot study, dexamethasone was given to 2 dogs as the only hormone in a dose of 0.02 mg/kg body weight twice daily, but was not able to initiate or maintain hyperglycemia (or glycosuria). It did, however, induce polyuria and polydipsia due to its water clearing effect. In another pilot study, BGH given alone in doses of 5 mg/kg body weight twice daily resulted in hyperglycemia, glycosuria, and polyuria.

In contrast to spontaneous diabetes mellitus where emesis frequently is noticed (4, 8, 15, 17), this feature was not recorded in dogs belonging to the NAP-group. Physiopathologic events leading to emesis are readily explained in keto-acidotic diabetes where mineral imbalance, acidosis and ketonemia will act

directly on the emetic center (123). In simple diabetes, the cause of emesis is more obscure, but could be attributed to coexisting (1) chronic pancreatitis (2) lipidosis of the liver, and/or (3) chronic nephritis. The conditions are likely to coexist when the diabetes has been present for a longer period of time. They probably did not occur in this short time study.

Diarrhea has been reported in cases of spontaneous, uncomplicated diabetes mellitus (4, 15), and was also observed in the NAP-dogs. The diarrhea occurring in spontaneous diabetes can be due to chronic pancreatic and/or hepatic dysfunction associated with coexisting kidney damage (glomerulosclerosis). Overeating was a possible explanation for diarrhea in these animals because they developed a ravenous appetite on days 17, 18, and 19.

This study was too short to measure any major changes in the weight of the dogs, and both gain and loss of weight have been reported in cases of spontaneous diabetes mellitus (15).

Dermatitis and cataract which are common complications to spontaneous diabetes mellitus (10, 21) were not recorded in this investigation.

Laboratory Findings

The two important laboratory findings in spontaneous canine diabetes mellitus are hyperglycemia and glycosuria. Tables 18 and 19 indicate that hyperglycemia was present in hormonal diabetes mellitus. Even though some NAP-dogs appeared very resistant to BGH/DX regimen, all of them developed elevation of blood glucose. The mean increase was not as high as it is common in spontaneous diabetes mellitus in the dog, where values above 400 - 500 mg% often are encountered.

The urinalysis is a powerful and necessary aid in confirming the diagnosis of

diabetes mellitus in the dog. The characteristic finding in spontaneous cases is glycosuria (3, 4, 5, 7, 9, 13, 15, 17, 19, 21, 23, 103, 116). This finding was not constant in all NAP-dogs (max. 58% on day 20), indicating that BGH/DX did not constantly produce sufficient hyperglycemia to cause glycosuria. Besides glycosuria, ketonuria regularly will occur when the glucose utilisation is severely impaired (3, 4, 7, 8, 9, 13, 15, 17, 21). The presence of ketone bodies (acetone) in the urine always indicate a poor prognosis in the dog because (1) it occurs late in the disease and (2) when present the animals condition is reversed with difficulty. This study did not reveal evidence for ketonuria or ketonemia during or after the regimen of BGH/DX in the NAP-dogs. It was therefore concluded that a short term administration of these two hormones in the 50% partial pancreatectomized animal was not able to produce a profound disturbance of the glucose metabolism. The very rapid return to normal blood glucose and the return to normal glucose tolerance supported this concept.

These features were in sharp contrast to the AP-dogs on day 20 where ketonemia, ketonuria, coma, and impaired glucose tolerance existed.

Urine pH did not reveal any special features, but in spontaneous diabetes mellitus and especially in cases complicated with ketonemia and ketonuria, the pH will tend to decrease (4, 7, 103). In order to get a more reliable expression of the urinary pH, urinary (H^+) titration should be carried out in order to estimate the titrable acid (158). This would involve an anaerobic collection of urine in order to avoid escape of CO_2 and hence an falsely increased pH.

A survey over possible urinary differential diagnostic syndromes will be given below and the listed diseases all can be misleading in the diagnosis of dia-

betes mellitus. They are presented in ordered array according to the frequency with which they are assumed to occur in the dog:

(1) Chronic nephritis (13, 15, 23, 159): however, there is low specific gravity and usually proteinuria and no glycosuria.

(2) Pyometra (13, 15, 23, 159) specific gravity is low. The urine contains no sugar or protein. The abdomen may be distended and sometimes vaginal discharge is present (159).

(3) Steroid therapy (23, 159). Polyuria and polydipsia occurs with same clinical and urinary picture as diabetes mellitus, exept that glycosuria is not present and specific gravity will more likely be low.

(4) Cystitis (159): Will give frequent urination. Often high protein and blood in urine, and alkaline pH of urine.

(5) Acute nephritis (23, 159) can be accompanied by polyuria. There is a high specific gravity, no sugar, high protein and severe abdominal pain.

(6) Cushings syndrome: Rare, low specific gravity. Increased urinary 17-hydroxy ketogenic steroids. Usually no glycosuria. No proteinuria. Bilateral alopecia. Pendulous abdomen (23).

(7) Diabetes insipidus (15, 23, 159) has low specific gravity, no sugar, no protein or ketones. The ADH test will help to prove this diagnosis.

(8) Diet (177): High carbohydrate intake.

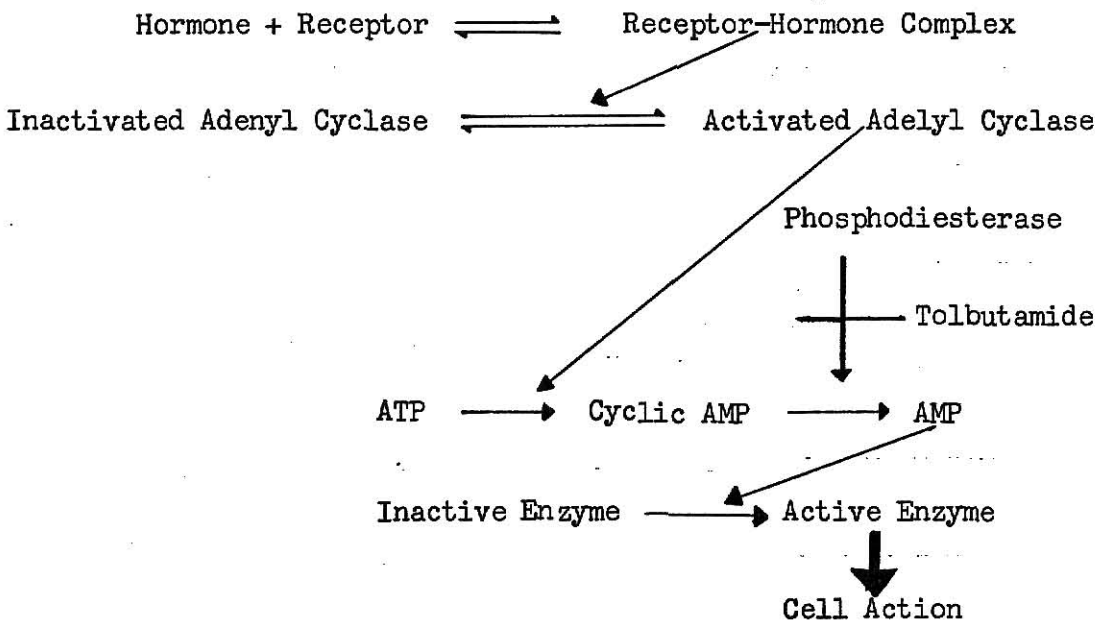
Spontaneous diabetes mellitus will often be complicated with keto-acidosis

and profound disturbances of the acid-base and electrolyte balance (25). Treatment with BGH/DX did not change any of these blood parameters considerably, indicating that this type is a simple diabetes mellitus.

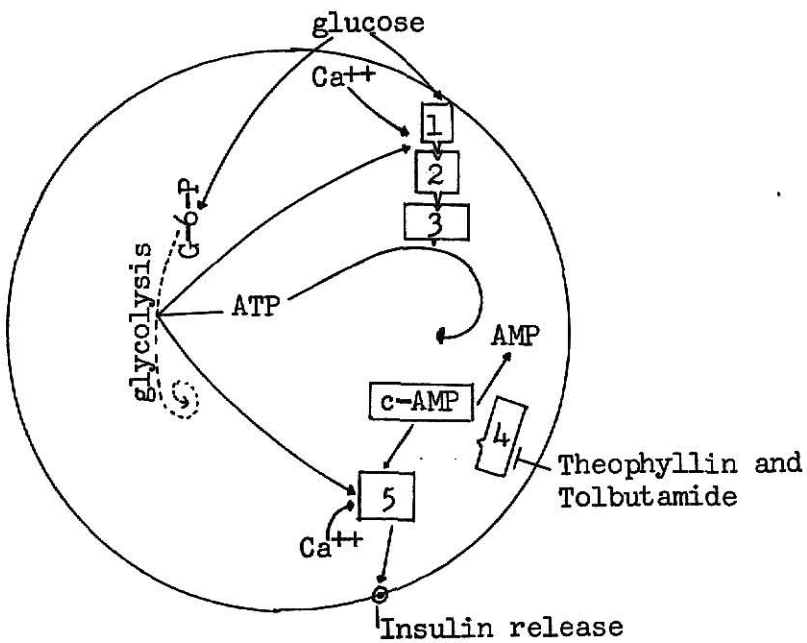
The development of diabetes mellitus

Review of the literature established evidence for acinar pancreatic involvement as an important factor in the development of diabetes mellitus. The inefficiency of insulin in controlling blood sugar can in these cases be explained through a physical reduction of the beta-cell mass and subsequent exhaustion of the remaining cells (151). This explanation, however, is not plausible when the pancreas appears macro- and microscopically entirely normal by both light- and electronmicroscopy. Especially in human medicine where both adult and juvenile diabetes occur without any acinar pancreatic involvement, considerable emphasis has been devoted to the presence of other components in the development of diabetes mellitus. The results of these investigations strongly imply that functional or biochemical diabetes exists in man. Whether this is true in dogs has not been ascertained. However, several features appear to be of importance (160).

Considerable emphasis has been put on the study of the cyclic adenyl-monophosphate or cAMP. The 3', 5' c-AMP is an essential activator in most cellular processes (160, 161, 162, 163), especially those dealing with hormones or/and hormonal reactions. A general schematic drawing is presented below, illustrating the formation and the accepted action of c-AMP (161):



It has become more and more evident that this c-AMP or 3', 5' c-AMP participates and plays a very essential role also in the insulin and glucose kinetics, participating in the release of insulin from the beta-cells. A specific drawing of the anticipated insulin release mechanism after Cerasi and Luft (164) is shown below:



1. Glucose receptor
2. Transmitter unit
3. Adenyl cyclase
4. Phosphodiesterase
5. Insulin realeasing unit

Any defect in the organism associated with (1) impaired receptor function, (2) transmitter defect, or (3) decreased adenyl cyclase activity will predispose the individual to diabetes mellitus. Today it is accepted that the receptor mechanism is the sensitive link in the pathogenesis of diabetes, both in adult and juvenile diabetes mellitus in man. The difference in the two types appear to be the degree of disturbance in the receptor mechanism or adenyl cyclase activity, which will impair or stop any insulin release or will impose on the beta-cells an inability to transfer and transform intracellular from extracellular stimulus.

This functional or biochemical defect does not exclude a possible presence of mechanical destruction via acute or chronic inflammation, but perhaps some, and maybe the majority, of diabetic dogs without demonstrable lesions have c-AMP or receptor defect.

Besides participating in the insulin release, the c-AMP is involved especially in two major hormones pertinent to the carbohydrate metabolism (162, 163, 165): (1) Phosphorylase in the liver and (2) lipase in the fat-tissues. The reaction which these hormones catalyze are diabetogenic because they tend to increase the blood glucose. Insulin, on its part, has been shown to (1) stimulate the inactivation of liver phosphorylase, (2) activate glycogen transferase, (3) inhibit the action of lipase, and (4) decrease the 3', 5' c-AMP concentration in the liver cells (162, 163). These mechanisms are well-balanced in normal individuals and slight disturbance of this balance will tend to create hyperglycemia. A profound discussion of the 3', 5' c-AMP action in the carbohydrate metabolism has been given by Sutherland (163).

It becomes more and more evident that insulin antagonists in the blood of

diabetics participates in the development of diabetes (166, 167). A compound, synalbumin, can "neutralise" proinsulin or insulin and predispose the animal for diabetes. Even though the initial output of insulin can remain sufficient for a time, it will decrease attributed to exhaustion of the beta-cells. In addition to this, the corticosteroids act like insulin antogonists by (1) stimulating glucose-6-phosphatase, (2) enhancing gluconeogenesis (165), and (3) increasing the mobilization of gluconeogenic amino acids through a not well-known enzyme reaction (165). Adrenalin is also an insulin antagonist because it activates the lipase through c-AMP (165). This activation will increase FFA in blood, increase the fat oxidation and hence increase the likelihood of accumulation of ketone bodies.

Liver insulinase plays a major role in the development of diabetes. This enzyme is responsible for insulin break down to its two major chains (117). Increased insulinase activity will impose a subclinical or clinically evident diabetes, because the insulin break down is increased. Since all insulin released from the beta-cells has to pass through the portal blood system, a great deal of insulin is destroyed in the liver prior to its peripheral action. Le Veen et al (117) achieved evidence for increased glucose tolerance in experimentally diabetic dogs if a part of the pancreatic blood flow bypassed the portal system (periportal anastomosis), indicating that a smaller amount of insulin was destroyed.

Based on the above concepts of c-AMP, synalbumin and liver insulinase, it is conceivable that the pathogenesis of diabetes is more likely based on insulin resistance; i.e., a biochemical disorder, than on an anatomical basis. BGH, which also is an insulinantagonist, is discussed in relation to glucose metabolism on pages 162 - 166.

It is still discussable whether any of the above mechanisms will participate to a noticeable extent in the development of diabetes mellitus in dogs. It is conceivable that some dogs do have defects in their c-AMP or insulinase activity and that excessive beta-cell destruction in pancreatitis can trigger the diabetes into a clinically obvious syndrome. The review of diabetic literature revealed cases where no changes had taken place in the pancreas (13), and the diabetes in such animals very likely had a metabolic basis.

BOVINE GROWTH HORMONE - DOSE, DOSE RESPONSE, AND ACTION

The literature review and the pilot study preceding this research disclosed variable recommendations concerning the dose of BGH necessary to accomplish the two stated goals: (1) To predispose the dog for diabetes mellitus without causing permanent disturbances in the glucose metabolism (short term regimen) and (2) to impose a transient or permanent diabetes mellitus using a longer term regimen. Altszuler et al (35) and Rathgeb et al (38) suggested 1 mg BGH/kg/day administered intramuscularly over a period of 5 to 14 days. Altszuler et al (37) advocated 3 mg/kg/day intramuscularly of BGH. Canine growth hormone (CGH) has recently been used in a dose of 1 mg/kg/day given subcutaneously by Rathgeb et al (39). A dose of 5 mg/BGH/kg/day given intramuscularly one half hour after a meal appeared to be suitable in this investigation when combined with .02 mg dexamethasone/kg/day. Tables 18 and 19 indicate the response of blood glucose value following 1, 2, 3, and 4 days administration. The pattern of dose response to regimen of BGH corresponds to findings in other investigations (35, 36, 37) exept it took place at a lower level than in the pilot study. There was no evidence for consistent glucose

changes beyond 4 days treatment with BGH/DX. The glucose dropped abruptly and the glucose tolerance test resumed its normal shape after BGH/DX was discontinued (35, 36, 37).

The intervention of BGH in the carbohydrate metabolism has been investigated in depth without any definite answer. It is presumed that its inhibitory effect on the glucose uptake in the peripheral tissues (muscles especially) is of importance (37). Besides this action, BGH presumably acts directly on the liver cells and inhibits specific insulin receptors on the cell membranes (191). The consequences of these events will be an increase in the glucose/insulin ratio and subsequent increase of insulin output and elevated plasma insulin activity. Besides this indirect or extra-pancreatic effect, the hormone can influence the pancreatic beta-cells directly, resulting in an increased insulin output (36). This, however, will tend to reduce the hyperglycemia but since the peripheral mechanism of insulin is blocked (muscle tissue and liver), the eventual outcome will be a continuous exhaustion of beta-cells, degranulation, and finally hyalinization. The contradictory feature of BGH action obviously is the increased output of insulin and coincidental hyperglycemia. This phenomenon is called insulin insensitivity (38). Another theory of the action of BGH has been emphasized by Rathgeb et al (38). They assumed that the hyperglycemic effect of the hormone was exerted via the fat metabolism; i.e., an increased mobilisation of FFA from the fat depots, preferable utilisation of these in the tissues for glucose and subsequent hyperglycemia. In addition to this glucose sparing effect, BGH presumably can enhance the gluconeogenesis.

An increase in blood glucose is an indication of (1) decreased insulin pro-

duction or (2) inhibition of produced insulin (hyperinsulinemia), or (3) exaggerated absorption. In the first instance, blood insulin will be decreased, e.g. pancreatic fibrosis (after chronic pancreatitis) because the reduced number of beta-cells will reduce the insulin production. The second condition will occur when insulin antagonism exists. This has briefly been discussed previously. BGH can be considered as an insulin antagonist and administration will cause significant hyperinsulinemia. Campbell and Rastogy (36) estimated the normal blood insulin to be 28 ± 3 μU/ml blood. One day subsequent to BGH administration this value was increased to 58 μU/ml blood. A maximum concentration was obtained at days 9 - 11 (278 ± 75 μU/ml blood). Altszuler et al (37) observed a similar response to BGH regimen (133 μU/ml blood after 2 - 4 days administration). Rathgeb et al (38) recorded a more moderate response to BGH (138 ± 29 μU/ml blood).

The insulin regulation involves the ratio of glucose to insulin (G/I) (36). In normal individuals, this ratio is maintained within narrow limits and the glucose has a tonic control over the insulin secretion. Increased blood glucose will change the ratio G/I, and through a direct action of the beta-cells, an increased insulin output will ensue (degranulation). To a certain extent, this mechanism will work, but when exhaustion of the beta-cell activity occurs, lack of regulation results and glucose continues to rise. Since no other hormones are known to be hypoglycemic, loss of insulin/glucose integrity will have disastrous consequences. It must, however, always be remembered that (1) some beta-cells are functioning and (2) only in very rare cases does total lack of insulin exist. Besides the tonic control exerted by the G/I ratio, a very essential point in the regulation is the inability of the beta-cells to release insulin. This occurs especially in elderly dia-

betics and the treatment with sulfonyluria is indicated. A contemporary and comprehensive review of the mechanism of tolbutamide has been given at the NIH Conference 1971 (161).

Besides participating in and partly disturbing the glucose metabolism, the BGH actively will change the fat metabolism. Campbell and Rastogy (36) anticipated, upon a vast study of blood chemical changes in dogs treated with BGH, that the FFA were greatly increased in serum after only one day treatment. The normal value of FFA in blood is estimated to 1.17 mEq/l. Maximum concentration were obtained on the third day after administration. The FFA alteration was found to precede the hyperglycemia. Other investigations (37, 39) have confirmed the above objective that serum free fatty acids will become increased as it does in spontaneous diabetes mellitus. Neither insulin nor plasma FFA were measured in the present study. It is assumed that the glucose concentration is a reliable estimator of the plasma insulin, and since hyperlipemia occurred on day 17 and 18 in both the NAP- and AP-dogs, it was concluded that the BGH imposed increased fat mobilisation and elevation of FFA in plasma. The opacity of the plasma (hyperlipemia) preceded hyperglycemia and it disappeared again on day 19, implying that the major fat mobilisation occur initially and then subsided.

The mechanism of BGH on the fat metabolism can be explained partly through its insulin inhibition in the liver and muscle cells, and partly through a direct action on the fat tissues. An increase of BGH or CGH in the plasma will mediate release of FFA from the body fat depots and the plasma becomes opaque (36, 37). The BGH does not directly increase the fat oxidation but the increased blood and tissue concentration of FFA is directly proportional to an increased glucose oxidation.

It is very essential to emphasize that the action of BGH is dependant on the nutritional status of the animal (36, 37, 38). If the animal is starving, none or very slight response can be expected in the glucose or fat metabolism.

CHANGES IN LIVER FUNCTION IN EXPERIMENTAL ACUTE PANCREATITIS/DIABETES MELLITUS

Two commonly accepted methods were chosen in order to monitor the liver function in this investigation: (1) Serum Glutamic Pyruvic Transaminase (S-GPT or PT) and (2) sulfobromophthalein (BSP) retention.

S-GPT Activity

Since S-GPT is present in very high concentration in the liver cells (168), necrosis and release of this enzyme from the dead or dying cells will result in an increased serum activity, due to a direct absorption to the blood stream and maybe also due to lymphatic absorption. A recent study (171) concluded that the S-GPT also is present in high concentration in the muscle tissue, but so far most authors (168, 169, 170, 171, 176) consider S-GPT as being a liverspecific enzyme in the dog.

The normal values of S-GPT in canine serum, measured in Frankel Units ranges from 21 $\pm$ 11 (168, 170). Moderate necrosis is considered when there is from 50 to 400 Units (170), and severe necrosis when the S-GPT is above 400 Units (170).

In this investigation was revealed a rise in S-GPT from day 7 to day 19. This elevation was significant in the NAP-dogs (from 29 to 133 Units/ml). According to Cornelius (170), these S-GPT activities would indicate moderate necrosis.

The reason for the liver damage in these dogs most likely was due to the 48 hour administration of BGH/DX, subsequent fat degeneration of the liver cells and elevation of the S-GPT (170).

The increase of S-GPT between day 19 and 20 was significant in the AP-dogs and was probably due to (1) residual effect of the BGH/DX treatment, (2) toxic hepatic necrosis due to staphylococcal alpha-toxin, (3) severely impaired glucose metabolism and following hepatic lipidosis, and (4) impaired kidney function due to hypovolemia and subsequent decreased GFR, resulting in a decreased S-GPT excretion through the urine.

The S-GPT decreased rapidly to almost 200 U at day 25 in both the NAP- and AP-dogs, but it never did regain its normal values, probably die to residual hepatic damage (fatty degeneration).

BSP Retention

By using the BSP-test, clinical medicine has available a method measuring the liver cells' ability to clear the blood of a foreign dye (170). The method appears to be superior in the detection of hepatocellular damage (170, 172, 173, 174, 175). The normal value of BSP retention in 30 minutes has been debatable. Drill and Ivy (173) recorded 2-12% retention in 30 minutes, using the infusion of a dose of 5 mg/kg intravenously. They claimed that 15% retention or above would be indicative for hepatocellular damage, using CCl_4 as toxic agent. Hoerlein and Greene (174) assumed that normal dogs would have no retention after 30 minutes, using a dose of 5 mg BSP/kg intravenously. Larsson and Morrill (175) found retention of 1.5% or less as being normal. 1.5 - 4% or above 4% was in their opinion indicative of hepatocellular damage. Cornelius (170) accepted values of 5% retention in 30 minutes and even 10%

as being fairly normal. The BSP retention in this investigation was studied using 5 mg/kg body weight of BSP injected intravenously and hence measure the percentage of retention in 30 minutes. The AP-dogs did have an increased BSP retention rate 24 hours following induction of acute pancreatitis, but it did not exceed a mean of 10%. This value did not include two of the AP-dogs since they died during the acute attack, and if they had been accounted for, other figures might have been obtained. Considering individual values on day 20, it can be concluded that high BSP occurred simultaneously with high S-GPT, indicating a trend towards simultaneous variation of S-GPT and BSP. As the S-GPT the BSP did not return to their normal ranges by day 26 in the AP-dogs and it indicated residual liver damage. Since there was no measurement of the BSP on day 19, it can not be visualized whether BGH/DX regimen could initiate any increased BSP retention rate.

The below (170) listed diseases are known to be followed by an increased BSP retention rate, and it is likely that the second and the sixth diseases were present in the AP-dogs: (1) Leptospirosis, (2) lipidosis with fat degeneration, (3) perifocal fibrosis, (4) focal hepatitis, (5) CCl_4 poisoning, (6) diabetes with lipidosis, (7) leukemia, (8) diffuse hepatic fibrosis, (9) secondary hepatic necrosis following ascites, (10) ulcerative duodenitis, (11) coccidial hemorrhagic enteritis, and (12) thallium and tetrachlorethylene poisoning.

CHANGES IN KIDNEY FUNCTION IN EXPERIMENTAL ACUTE PANCREATITIS/DIABETES MELLITUS

Plasma Creatinine

The plasma creatinine concentration is considered as being an useful parameter

in assessing the kidney function in experimental as well as spontaneous kidney diseases. The absolute concentration in plasma is dependent on the rate of production and rate of excretion, whereas it is not influenced by protein consumption (110, 177, 178) as is blood urea nitrogen (BUN). It is also assumed that the creatinine will change more rapidly that BUN in cases where the kidney function is impaired. However, creatinine concentration estimation as a measure of degree of kidney damage has been quite debatable. Kronfeld and Medway (110), Schirmeister et al (178) and Skydsgaard (190) strongly suggest the use of this compound instead of blood urea nitrogen, whereas Wilkinson (116) and Hoe and O'Shea (179) consider this parameter as being of questionable value and less reliable than the BUN ("the old method").

In view of the above, the blood creatinine was used in this investigation for two reasons: (1) To establish a normal range and (2) to find changes in blood creatinine on day 20; i.e., in acute pancreatitis/diabetes mellitus.

Medway and Kronfeld (110) suggested that 1 - 2 mg% was a normal figure for blood creatinine in most domestic animals, whereas Wilkinson (116) stated that values above 10 mg% are related to a very poor prognosis. Finco (180) published data that showed a normal creatinine value of 0.40 - 0.93 mg%. A recent study by Otto (181) reveals an increase of plasma creatinine during the course of acute pancreatitis in 14% of the cases. In 26% of the cases there was an increased BUN. These figures are only applicable to man.

It was concluded from this study that (1) the plasma creatinine values were fairly constant ranging from 0.6 to 1.0 mg% confirming Fincos results and (2a) no changes in mean plasma creatinine were observed in the hormonal treated dogs, indicating that the BGH/DX regimen did not impose severe kid-

ney damage (glomerulosclerosis) (31), and (2b) it appeared that values of 1.5 mg% or above would indicate impaired kidney function in acute pancreatitis/ diabetes mellitus, but the changes were reversible in 6 of 8 dogs, and blood creatinine returned to normal on day 26. There was a considerable variation in plasma creatinine on day 20, and several AP-dogs exceeded 2 mg%.

Endogenous Creatinine Clearance

Endogenous creatinine clearance is accepted as being a reliable figure in evaluation of the glomerular filtration rate (GFR) in man (182, 183) and in dog (103). The normal value has not been tested in a larger population of dogs but a value of 2.20 - 2.80 ml/kg/min has been given (103). Finco (180) recently investigated the endogenous creatinine clearance in normal dogs and recorded 2.93 ml/kg/min. The determination of the creatinine clearance rate enhances the value of the questionable plasma creatinine determination. The results of normal dogs obtained in this investigation did not diverge from the 2.5 to 3.1 ml/kg/min range. There was a considerable decrease in creatinine clearance (2.05 ml/kg/min) 24 hours after induction of acute pancreatitis/diabetes mellitus, indicating that there was a change in renal blood flow and in the GFR. This change in GFR will result in a decreased filtration of various plasma constituents, e.g. amylase, lipase, and thus, an increase of these parameters can be attributed to both an increased production and a decreased urinary excretion.

No previous study has been used to establish the endogenous creatinine clearance variability during the regimen of acute pancreatitis/diabetes mellitus in dogs. In man, Otto (181) recorded decreased creatinine clearance in acute hemorrhagic pancreatitis in 50 out of 70 patients (80 ml/kg/min),

whereas Mulhausen et al (184) recorded an increased endogenous creatinine clearance during acute pancreatitis.

Since the dogs used in this investigation were anesthetized with pentobarbital during the period of urine sampling, this aspect will be discussed. Aasheim (185) stated that pentobarbital anesthesia might cause a decreased blood pressure and hence a decreased GFR. Corcoran and Page (186), Glauser and Selkurt (187) and Osbaldiston (103) found no evidence for assuming that pentobarbital would have hypotensive effects. The dogs in this investigation were anesthetized for 90 minutes. The creatinine clearance was highest in the first 30 minute period and decreased noticeably in the third 30 minute period. This indicate that (1) the bladder may not have been emptied sufficiently in the last period or (2) renal blood pressure decreased during anesthesia. It seems reasonable to conclude that a 90 minute anesthesia with pentobarbital can give rise to a decreased glomerular filtration rate. Besides the hemodynamic changes in the kidney, the high glucose concentration can controbute to a decreased GFR, according to a recent work of Broechner-Mortensen (188). He injected 1 g glucose/min intravenously into normal persons and found a decreased GFR, measured by endogenous creatinine clearance. He explained the phenomenon through (1) hemodynamic changes and (2) changes in sodium transport in the cells (increased loss). Since some of the dogs used in this investigation achieved very high glucose concentration 24 hours after acute pancreatitis/diabetes mellitus, this might be a contributing factor in the decrease in GFR.

CONCLUSIONS

(1) 50% partial pancreatectomy in 16 dogs was followed by clinical and clinicopathological features characteristic for mild acute pancreatitis, whereas only transient hyperglycemia was recorded.

(2) 5 days regimen of bovine growth hormone (BGH: 5 mg/kg body weight twice daily) and dexamethasone (DX: 0.02 mg/kg body weight twice daily) in eight dogs resulted in transient diabetes mellitus [polyuria, polydipsia, hyperglycemia, glycosuria, and decreased intravenous glucose tolerance; i.e., decreased glucose disappearance coefficient (k)].

(3) Acute pancreatitis/diabetes mellitus syndrome was produced in eight dogs by treating prediabetic dogs (50% partial pancreatectomy, 3 days of BGH/DX treatment) with a pancreatic ductal infusion of staphylococcal alpha-toxin. Two of the dogs died acutely of acute ketoacidotic diabetes mellitus within 24 hours. Two other developed severe ketoacidotic diabetes mellitus; one died 48 hours after surgery and one survived. The remaining four dogs became mildly ketoacidotic but survived. One of the four dogs was still diabetic seven days after preparation. The acute pancreatitis/diabetes mellitus syndrome has the essential features of spontaneous acute pancreatitis/diabetes mellitus as reported in man and dogs.

The development of this model opens a way for the study of ketoacidotic diabetes mellitus as a complication of acute pancreatitis.

(4) The diagnosis of acute pancreatitis/diabetes mellitus was based on spe-

cific pancreatic enzyme activity in serum; i.e., serum amylase and lipase; blood glucose concentration and a high-dose intravenous glucose tolerance test (H-IVGTT). High enzyme activity corresponded to high glucose concentration and decreased glucose tolerance.

(5) The IVGTT was a useful tool in the recognition of experimentel prediabetes in dogs.

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ACUTE PANCREATITIS AND DIABETES MELLITUS. A CLINICAL AND BIOCHEMICAL STUDY IN THE DOG.

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A B S T R A C T

In man, transient or permanent diabetes mellitus may be initiated by acute pancreatitis. This sequence of events has not been described in the veterinary literature in naturally occurring cases of diabetes mellitus in dogs. The research investigated the following: (1) Whether acute pancreatitis could initiate the sequence of physiopathological events of diabetes mellitus and (2) the clinical and laboratory diagnosis of acute pancreatitis complicated by diabetes mellitus.

The syndrome was produced experimentally in dogs as follows: (1) 50% partial pancreatectomy was performed on day 6 in 16 dogs, (2) then 10 days later all dogs received for a period of 3 days two daily injections of bovine growth hormone (5 mg/kg intramuscularly) and dexamethasone (0.02 mg/kg intramuscularly) and (3a) 8 dogs continued the bovine growth hormone/dexamethasone regimen for two more days whereas (3b) the remaining 8 dogs were subjected to staphyloccoccal alpha-toxin pancreatitis.

A thorough physical examination was made daily in each dog. Laboratory investigations performed in each phase of the experiment included: (1) Total and differential WBC-count, hemoglobin concentration, and packed cell volume determination, (2) liver function tests (serum-GPT activity and BSP retention rate), (3) kidney function test (endogenous creatinine clearance), (4) pancreatic function tests (serum-amylase and -lipase activities and high dose intravenous glucose tolerance test), (5) acid-base balance determinations (serum electrolytes, blood pH, venous blood P_{CO_2}, and venous blood P_{O_2}), and (6) urinalysis.

The data showed: (1) Surgical removal of approximately 50% of the pancreas only initiated mild hyperglycemia but caused a tissue reaction in the pancreas similar to that found in naturally occurring mild acute pancreatitis, (2) when this was followed by bovine growth hormone and dexamethasone regimen of treatment, temporary hyperglycemia and hyperlipemia occurred, and (3) when the previous treatments were followed by acute pancreatitis, 2 out of 8 animals died within 16 hours in diabetic coma and the remaining 6 dogs all had impaired glucose tolerance and abnormal liver function.

The conclusion from the clinical observations strongly indicate that acute pancreatitis/diabetes mellitus syndrome constitutes an emergency situation requiring immediate treatment with chemotherapeutic agents, electrolyte solutions, and crystalline insulin. The acute pancreatitis/diabetes mellitus model appears to be readily reproducible. It opens the way for the study of keto-acidotic diabetes mellitus as a complication of acute pancreatitis. The response of this experimental model to a variety of treatment regimes may be beneficial to both man and dog.