THE CHARACTERIZATION OF SPONTANEOUS IDIOPATHIC HYPERTENSION IN A COLONY OF DOGS

By

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A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Pathology

1984

ABSTRACT

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This study documents spontaneous idiopathic hypertension in the dog but, presently, only loosely associates it with underlying pathology. The characterization of a dog model of primary hypertension was undertaken after a 5 year old female siberian husky dog was diagnosed as idiopathic hypertensive. Femoral arterial systolic, diastolic, and mean blood pressures were 200 mm Hg, 150 mm Hg, and 175 mm Hg, respectively, at the time of admission to the Veterinary Clinical Center. Other abnormalities included bilateral retinal hemorrhage with papilledema, aortic enlargement and tortuosity, and slight pulmonary arterial and cardiac enlargement.

The propositus was bred over a period of 5 years and produced several offspring. Over 10 propositus-progeny and progeny-progeny matings have taken place, producing 37 animals. Thirty of these animals were conditioned, subjected to femoral arterial blood pressure determinations, and placed into 4 groups based upon mean blood pressure

(MBP) values: group I (MBP 128±12 mm Hg, n = 4), group II (MBP 121±8 mm Hg, n = 9), group III (MBP 114±9 mm Hg, n = 8), group IV (MBP 101±9 mm Hg, n = 9). Groups I, II, and III were significantly different from group IV ($p<0.05$). Group I and group III were significantly different ($p<0.05$). However, group I was not significantly different from group II and group II was not significantly different from group III. In combined groups, there was a significant positive correlation of systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) with age, r values being 0.40, 0.47, and 0.44, respectively.

Ten animals were randomly selected from groups I, II, and III and clinically evaluated. Using the clinical tests, we have not been able to show distinct differences from group to group, but there were a few individual animals with abnormally high values of left ventricular wall thickness (LVWT), left ventricular thickness/body surface area (LVWT/BSA), and left ventricular wall thickness/body weight (LVWT/BW), upon echocardiographic examination. The only marker at present is differences in MBP from group to group. We expect the eventual unmasking of other abnormalities as time progresses.

To

My mother (Mrs. Macie Tippett),
in memory of my father (Mr. Sam Tippett),
and my brothers and sisters
(Yvonne, Kenneth, Mattie, Langford, Veronica, Glenn, Kelvin,
and Anthony).

ACKNOWLEDGEMENTS

First of all, I thank God, who through my Lord and Savior Jesus Christ, made all of this possible. I wish to express my appreciation to members of my graduate committee (Drs. Thomas Bell, Gary Blanchard, George Eyster, George Padgett, and Robert Stephenson) for their assistance in my program.

Thanks are also extended to many others who assisted me in other ways, whether in technical, financial, or inspirational capacities. The list would be too long if I included them all by name.

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LIST OF ABBREVIATIONS

BSA	Body surface area
DBP	Diastolic blood pressure
E	Epinephrine
EH	Essential hypertension
HR	Heart rate
LVWT	Left ventricular wall thickness
MBP	Mean blood pressure
NE	Norepinephrine
NSR	Normal sinus rhythm
SBP	Systolic blood pressure

INTRODUCTION

Systemic hypertension is an abnormal elevation in arterial blood pressure, which if gone unchecked, usually results in physiologic abnormalities and organ damage. It is estimated that 16% of the American human population is affected [1]. In human beings, the etiology is either primary (essential) or secondary [2] [3] [4]. Secondary hypertension constitutes approximately 5% to 10% of all known cases and includes such subcategories as renal, endocrine, neurogenic, mechanical interference, exogenous, toxemia of pregnancy, and miscellaneous causes [5] [2] [6]. Primary, essential, or idiopathic hypertension comprises 90% to 95% of all reported cases [5] [6].

The dog has long been used as an experimental model to study various forms of secondary hypertension [7] [8] [9] [10] [11] [12] [13]. However, in the dog, few cases of naturally occurring secondary hypertension have been reported [14]. No case of primary hypertension in the canine has been clinically documented in the literature.

In this study, idiopathic hypertension was diagnosed in a five year old female siberian husky dog after extensive clinical evaluation. Representatives from the resulting litters produced by the propositus were likewise evaluated

in order to identify, characterize, and further perpetuate the condition in dogs.

LITERATURE REVIEW

Hypertension in man has been studied and discussed over a period of many years. Stephen Hale, in 1711 showed that arterial pressure varied with the size of the animal, excitement, bleeding and left ventricular stroke volume, and noted the effects of hot water in relaxing and cold water, quinine, cinnamon and alcohol in constricting the small vessels [15]. Ludwig Traube, in 1856 proposed the association of contracted kidneys with hypertrophy of the left ventricle. He also noted the correlation of increased arterial pulse tension and hemorrhagic retinitis [15]. T.C. Janeway published a classic, Clinical Study of the Blood Pressure in 1904, where he placed cases of normotensive patients with atherosclerosis into the "enfeebled heart" category [15]. The syndrome of "essential hypertension" was first named by Frank in 1911 [15]. Harry Goldblatt and his coworkers became established figures in the history of hypertension by discovering a workable method for the production of experimental renal hypertension in 1934 [15]. By restricting the renal artery pulsatile blood flow instead of obstructing it entirely or damaging the kidney in other ways, they could produce "benign" or "malignant" forms of hypertension in the dog. Thus, they were responsible for the return of emphasis to the kidney and one of its chemical

products (renin) in the genesis of hypertension. By the early to mid 1900's, it was apparent to researchers that two forms of arterial hypertension existed; one form was secondary to a detected organic lesion but the second form was not. Hence, the terms "secondary" versus "idiopathic", "primary", or "essential".

Presently, hypertension has been reported worldwide and believed to affect 15-20% of all adults [5]. It has been estimated that hypertension afflicts 65 million Americans with 25 million being borderline in pressure elevation. The syndrome has been shown to cost the nation 20 billion dollars in such areas as medical bills, lost wages, and lost productivity [5]. The incidence of hypertension in the U.S. is 16%, 22% in blacks and 9% in whites [1].

There have been many defined and described secondary causes of chronic blood pressure elevations. Ten to fifteen percent of all cases of hypertension have been shown to be secondary in nature [5] with the majority of cases due to renal abnormalities. Of the other secondary causes, endocrine etiologies have been defined.

Cases of pleochromocytoma have been shown to comprise less than 1% of all the hypertensive population [16]. Sjoerdema et al. found that 10% of these tumors were malignant and necessitated the use of alpha-methyl-tyrosine to block synthesis of the increased catecholamines before hypertension could be controlled [17]. Some of the benign

tumors detected were multifocal and apparently familial [16] [18].

The adrenal cortex is an endocrine organ often incriminated in the causation of various forms of secondary hypertension. Cushings syndrome was first described by Harvey Cushing in 1932 [19]. It was held by Vetter et al. that 80% of all patients with Cushings syndrome had hypertension [20]. Mendlowitz indicated that this syndrome was associated with less than 1% of all hypertensive cases [21]. It has been shown that the blood vessels become more reactive to nonepinephrine [22] [23]. Also, there has been shown to be an increase in renin substrate and angiotension II [24]. However, the validity of this pathogenesis has been challenged [25].

In 1955, Conn first described a patient with hypokalemic hypertension due to an aldoesterone-producing adenoma of the adrenal cortex [26]. Vetter reports that primary aldosteronism is caused by an adenoma of the adrenal cortex in 70-80% of these cases [25]. Idiopathic bilateral adrenocortical hyperplasia has been thought to be the cause of primary aldosteronism in 20-30% of the patients [25]. Hypertension due to glucocorticoid suppressable aldosteronism has been shown to be amenable to glucocorticoid therapy [27].

Cases of hyperaldosteronism and hypertension have been described as being associated with extra-adrenal tumors [28] [29]. Two forms of adrenocortical hyperplasia accompanied

by hypokalemia and hypertension have been described in man: 11-hydroxylase deficiency and 17-hydroxylase deficiency [25] [30]. Virilization and excess androgens accompanied persons affected with the former disorder while amenorrhea and male pseudohermaphroditism was seen in those affected by the latter defect [31].

The prevalence of hypertension in cases of parathyroid hyperfunction ranged from 10% to 70% [32]. Nevertheless, the pathophysiologic association has not been made. In one case, an underlying renal abnormality was observed but in other studies, no linked organic abnormalities have been determined [33] [34] [35].

In a study of 458 hyperthyroid patients, Hurxtal found a systolic blood pressure of 150 mm Hg or higher in 26% of the patients overall, and in 42% of those with severe hyperthyroidism [36]. Hypertension associated with this condition was characterized by an accelerated peripheral circulation arising from a dilation of arterioles and metaarterioles [37] [38]. Other clinical signs associated with this disease state included tachycardia, arrhythmia, and high cardiac output [37] [38] [39].

The central nervous system (CNS) has also been noted to contribute to "secondary" hypertension. There has been much speculation as to what extent the CNS and specifically the autonomic nervous system play in the development and maintenance of high blood pressure. It is known that there was elevation of sympathetic activity in hypertension, thus

strongly implicating the CNS as having a role in elevated arterial pressure [40]. However, it could not be determined whether this increased activity initiated or maintained it. Cobb and Rose showed a significant correlation of increase in hypertension in occupations of intense mental activity [41]. Harris et al. showed by epidemiological data that individuals classified as tense developed hypertension more frequently than those who were not [42]. It has been documented that a specific emotional stimulus can result in transient increases in blood pressure [43] [44]. Kaplan indicated that hypertension may occur in association with increased intracranial pressure from any cause [30]. Cameron and Daig observed a paroxysmal form of hypertension in patients with tumors of the cerebellum [45]. Evans et al. observed similar results [46]. Julius listed several causes of hypertension due to neurogenic abnormalities: brain tumors, encephalitis, bulbar poliomyelitis, familial dysautonomia, acute porphyria, quadriplegia, and extra-adrenal chromaffin tumors [2].

Conditions affecting the mechanical interference with blood flow have been shown, likewise, to initiate secondary forms of hypertension. Hypertension seen in cases of patent ductus arteriosus and aortic insufficiency were shown to be due to a compensatory increase in systolic blood pressure [47]. It has been shown that coarctation of the aorta causes a rare but curable form of hypertension in children [48]. Blood pressure elevation in these cases is believed

to be caused in part by maladies within the renin-angiotension system [6]. Kaplan reported an adult form of this aortic narrowing as well as the infantile form [30].

Chobanian indicated that systolic hypertension is a common clinical problem in the elderly [49]. Pure systolic hypertension in the study was defined as a systolic blood pressure equal to or greater than 160 mm Hg and a diastolic pressure of less than 90-95 mm Hg [49]. Kannel indicated that the chief cause of excess morbidity and mortality in these hypertensives is an increased propensity to atherosclerotic disease and thus interference with blood flow [50].

Zeigler and Mast noted that arteriovenous fistulas are a rare cause of hypertension but when present are accompanied by hypertension in 45% of the cases [51]. This elevated blood pressure was thought to be due to a significant increase in the circulating blood volume or renal parenchymal ischemia causing an increase in renin release. AV fistulas in the kidney have been described as congenital or acquired.

Another condition in man which has been known to cause interference with the mechanical flow of blood and resulting in secondary hypertension is Paget's disease. This disorder has been associated with hemodynamic changes characterized by cutaneous vasodilation in the skin and subcutaneous tissue overlying involved bones. When 1/3 to 1/2 of the

skeleton was affected, the increased blood flow has been linked to high cardiac output-hypertension [52].

Several exogenous causes of secondary hypertension were listed by Julius [2]. Poisoning with heavy metals, lead and thallium, was reported to cause hypertension. Cadmium induced hypertension in rats, rabbits and dogs, either when injected intraperitoneally, or intraarterially or when administered orally [53] [54] [55] [56]. However, the significance of the relationship between cadmium and human hypertension is uncertain. Low blood levels of zinc and magnesium have been detected in some hypertensives [57] [58].

A number of unrelated drugs have also been associated with hypertension. Weber indicated that monoamine oxidase-inhibiting drugs prevented the wholesale degradation of nonepinephrine in the postganglionic nerve fiber thus potentiating the strong vasopressor response when such drugs were administered with antihypertensive drugs such as reserpine [59]. An association between the use of oral contraceptives and the occurrence of high blood pressure was reported in 1967 [60]. Since then, much discussion has taken place concerning this relationship. The actual cause of the hypertension has been suspected to be due to an increase in the renin-angiotension system with increases in renin substrate and aldosterone [61] [6]. Exogenous administration of steroids in high doses have been known to cause Cushing-like syndrome with elevation of blood pressure

and other complications [62] [63] [64]. Excess licorice ingestion has been shown to cause hypertension due to the sodium-retaining activity of glycyrrhizinic acid [65] [66].

Approximately 60% of all cases of hypertension during pregnancy has been stated to be due to another secondary form of hypertension, toxemia of pregnancy [61]. Toxemia of pregnancy has been described as a triad consisting of hypertension, edema, and proteinuria of which hypertension is the most frequently demonstrable [61] [67]. Exogenous precursor peptides formed in the placenta, renin-angiotension system, vascular spasms, prostaglandin release, intravascular coagulation, and specific glomerular renal lesions have all been suggested as having impact on the development of the hypertension.

There have been many miscellaneous causes of secondary hypertension reported in the literature. Hypertension associated with a high hematocrit has been reported in two types of patients. Gaisbock and others described a benign form of polycythemia with a hematocrit near the upper limit of normal and reduced plasma volume [68] [69] [70]. The bone marrow, white blood cell count, and platelet count were normal. While the cause is unknown, a "stress factor" was suggested as a possible etiology. In a second group of patients, polycythemia and hypertension were associated with non-neoplastic renal disease such as hydronephrosis, polycystic kidney or renal artery stenosis [71]. The specific

nature of the increase in red blood cell production and bone marrow stimulation is not known.

Lowery found sustained hypertension in 13 of 53 children with burns covering 10-75% of their bodies. The cause of the hypertension was not ascertained, however [72].

Schwartz made an association of carcinoid syndrome with essential hypertension [73]. The release of vasoactive amines were thought to be in part responsible for the elevation in blood pressure.

Many types of secondary hypertension have a renal parenchymal component. Hayduk stated that there are few types of hypertension in which primary or secondary hypertension can be excluded with certainty [74]. He further stated that the mechanism of hypertension in acute glomerulonephritis may involve sodium and water retention resulting from the glomerular lesion. In one study, 20.3% of patients with malignant hypertension were found to have associated glomerulonephritis [75]. Hypertension was found to be present in 60-75% of cases of chronic atrophic pyelonephritis [76] [77]. It has been suggested that an ischemia induced increase in renin secretion may be responsible for the hypertension in pyelonephritis [74]. Exposure of the kidneys to radiation has been shown to lead to the development of hypertension weeks and even years after the exposure [75] [78]. In one report it was indicated that a 39% incidence of hypertension was observed after irradiation [79]. Very severe hypertensive states have been known to result

from the adult form of cystic renal disease [74] [67]. Though the direct mechanism of the elevation in blood pressure is not known, ischemia due to cystic renal changes is considered possible. Sodium and water retention have been known to occur. The renal parenchymal disturbance in lupus erythematosus has also been associated with hypertension. Some authors reported a 25.2% incidence of hypertension in systemic lupus erythematosus based on an analysis of 520 cases [80]. A few cases of hydronephrosis have been associated with hypertension [81]. The speculated mechanism of hypertension could be ischemia due to pressure in the interlobular arteries and/or the loss of prostaglandin-secreting interstitial cells from the renal papilla. Similarly, several tumors within the renal parenchyma with renin-secretory function have been associated with hypertension [71] [72] [73]. These tumors, though anatomically small, have very high concentrations of renin. In addition, the non-secretory tumors, Wilm's tumor and hypernephroma, have been associated with hypertension [85] [86] [87]. Finally, hypertension is reported to be present in between 60 and 78% of patients with diabetic nephropathy [88] [89] [90].

Renovascular hypertension has been known to occur in many forms. Most patients with polyarteritis nodosa and renal involvement were shown to be hypertensive [91]. The mechanism was assumed to be due to ischemia of the areas of renal cortex which lie distal to the affected arteries. "True" renovascular hypertension, however, has been

associated with renal artery obstruction by infarct, thrombus or embolus involving the main artery or one of its branches. The major cause of obstruction of the renal artery in old age has been reported to be the presence of atherosclerotic plaques whereas in the younger patient (below age 40 years), the most frequent cause is a form of dysplasia of the renal artery [92]. Other vascular disorders of the kidney such as trauma, renal thrombosis and renal arterial dissection have been associated with hypertension [92].

All forms of hypertension for which no specific etiological agent or mechanism was determined were grouped into a second major category called primary or essential hypertension.

Essential hypertension was named by Frank in 1911 and termed "hypertensive cardiovascular disease" by Janeway in 1913 [93]. Today, it has come to designate a condition which constitutes an unidentifiable physiologic disturbance or disturbances which leads ultimately to elevation of diastolic, systolic and mean blood pressures, anatomical changes in the vascular tree, and functional impairment of involved tissues. Hypertension is perceived to be a sequela appearing during the progressive development of the disease [94]. Essential hypertension (EH) has been estimated to account for up to 90% of all cases of hypertension with the secondary type believed to comprise 10% [5]. In the

majority of the cases, the diagnosis of EH is made after the exclusion of all known secondary causes.

For years, the problem with understanding essential hypertension centered around defining it. In 1955, Perera indicated that hypertension existed if repeated recordings of casual diastolic pressures yielded values of 90 mm Hg or above [95]. Systolic blood pressure (SBP) of 140 mm Hg is generally regarded as the upper normal figure. However, the age of the individual must also be taken into consideration. Mean blood pressures (MBP) above 105 to 110 mm Hg have been regarded as hypertensive [96]. An even less definable term, "borderline hypertension" was coined by Conway et al. in 1968 [97]. It was used to designate a group of patients who had diastolic blood pressure sometimes below and sometimes above the 90 mm Hg limit. It was also regarded as a possible pre-stage to essential hypertension. A variable proportion of subjects with borderline hypertension have shown an elevation of cardiac output and heart rate [98].

As far as possible etiologies for EH, many theories have been proposed. Pickering proposed that EH may represent a quantitative rather than a qualitative deviation from the norm acquired through multifactorial inheritance and modified by environmental factors [99]. Page has supported the concept that EH is a disorder of cardiovascular regulation originating from an altered interplay of a mosaic of factors rather than in a single cause [100]. Both genetic and environmental factors have been known to play a role in

hypertension but their relative contributions are not known. In the autoregulatory hypothesis, it was proposed that the level of blood pressure was determined by the amount of blood pumped by the heart and the resistance to the flow of this blood by the vascular bed. These two factors are, in turn, affected by many other factors [3]. The sodium transport theory held that patients with EH are in a state of continuous correction of a slighty expanded extracellular fluid volume [3]. Dahl and co-workers first proposed that permanent hypertension might evolve through a genetic defect in renal sodium excretion leading to an increase in body fluid volume and, in turn, an increase in a sodium excreting hormone and hypertension [101]. In support of the concept of a sodium excreting hormone, it was suggested that increased amounts of natriuretic hormone may be involved in the pathogenesis of the disease. Other factors must also be considered as possible components of the EH syndrome. For example, alteration of pressor substances, defects in the hereditable sympathetic nervous system and related neural mechanisms, imbalances in the renin angiotension and vasodepressor systems, and obesity have all been associated with EH [3].

Since the greatest proportion of all hypertension in man is of the primary form, an animal model closely simulating EH is highly desirable. Various animals have been used to study the genetic aspects of hypertension [102]. Mice, rabbits, chickens, turkeys and dogs have been

monitored as to the contribution of strain or breed to elevated blood pressure. The most useful small animal model has been the spontaneous hypertensive rat of which several differentiated substrains have been produced. Other developed strains include the New Zealand strain of genetically hypertensive rat (GHR), Milan hypertensive strain (MHS), and Brookhaven strain of hypertensive-sensitive rats (HSR). However, the knowledge obtained from these models has been fragmentary, and the results obtained in each strain were usually concentrated on only a few aspects of the multifaceted problems of EH. In addition, each substrain had its individual, unique defect which did not include many aspects of the primary hypertensive human patient.

The dog has long been used as an experimental model to study various forms of induced secondary hypertension [7] [8] [9] [10] [11] [12] [13]. Few cases of primary hypertension have been reported and no cases have been clinically evaluated and documented. It was against this background that a case of primary hypertension in a siberian husky female dog was diagnosed. Subsequent mother-son, father-daughter, sister-brother matings have been done and colonies of affected or potentially affected animals have been produced and clinically evaluated.

MATERIALS AND METHODS

Animals

Forty-one conditioned siberian husky, golden retriever, and mixed breed (siberian husky x labrador retriever) dogs were used in the study. The dogs were free of intestinal parasites and heartworms and were vaccinated against rabies, distemper, leptospirosis, hepatitis and parvoviral infection. The colony animals colony ranged in age from 3 months to 8 years at the initiation of the study, and included 21 males and 20 females. Two unrelated siberian husky dogs (1 male and 1 female) and five golden retriever dogs (4 females and 1 male) were utilized during one phase of the experiments to establish a working normal blood pressure for siberian husky dogs. Three additional, non-colony siberian husky dogs consisting of 2 females and 1 male were used to establish normal echocardiographic values.

The propositus was bred to her male progeny and produced 5 litters. One other litter was produced as a result of a breeding to a hypertensive male labrador retriever who was diagnosed at the College of Veterinary Medicine at the University of Pennsylvania. A number of sibling matings have taken place, further enlarging the colony. The propositus and 10 colony animals were primarily selected for the present study. However, ancillary data

from other colony and non-colony animals were used on occasions.

Indwelling Catheter Blood Pressure Determinations

Three colony dogs were subjected to general anesthesia using barbiturate anesthesia and maintained on halothane gas. Surgically, the omocervical artery was isolated and an indwelling catheter was directed through the artery and into the aortic arch. The catheter contained heparin (1,000 units/ml) and crystalline penicillin (66,666 units/ml) in a saline solution. It was then externalized and secured through a skin incision on the dorsal neck. One week after the surgery, separate blood pressure and heart rate determinations were made simultaneously utilizing this catheter and the direct femoral artery puncture. Both were attached to transducers which were in turn connected to the DR8 Blood Pressure Monitoring device.

Dinamap Blood Pressure Determinations

Blood pressure determinations were obtained on colony dogs utilizing the Dinamap Research Monitor 1255[a]. Pressures were ascertained according to catalogue specifications with cuff size and gain settings corresponding to animals' limb circumference and body weight, respectively. The test was performed on awake,

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[a]Dinamap Research Monitor Model 1255, Critkon, Inc., Tampa, FL.

conscious dogs who were in left lateral recumbency. Five to ten minutes later, blood pressure determinations employing the direct method of arterial puncture were made and comparisons evaluated.

Ophthalmic Examination

The 11 animals were examined using direct ophthalmoscopy. The ocular media and retinae were evaluated for any abnormal findings suggestive of hypertension by viewing the eye grossly and by use of an ophthalmoscope. The ophthalmoscopic examination was done in a dark room with the animals being minimally restrained by an assistant.

Blood and Urine Examination

Whole blood, serum, and urine were evaluated by standard clinical methods and reported in standard units for both the propositus and colony animals semiannually. Since the data were considered ancillary, the methods, which are standardized in the Clinical Pathology Laboratory, Veterinary Clinical Center, Michigan State University, East Lansing, Michigan, are not reported. A representative set of these data is reported with the results.

Femoral Arterial Blood Pressure Determinations

The systemic arterial blood pressure for each dog was determined by femoral arterial puncture. A 22-gauge needle was attached via a heparinized saline-filled plastic tube to a Statham P23D6 pressure transducer which was in turn

connected to an Electronic for Medicine DR8 Multichannel Recorder[b]. The dogs were manually restrained in left lateral recumbency and no anesthetics were used. The mean blood pressure was electronically calculated. Diastolic, systolic, and mean blood pressures with electrocardiograms were printed on the machine oscilloscope and recording paper. Heart rates, using the ECG tracings, were determined before, during, and after arterial puncture to provide an assessment of the level of excitement. However, after no difference was found among rates in the three time periods, only the heart rate (HR) during the arterial puncture was utilized.

Nonselective Aortogram

This procedure was performed only on the propositus of the colony. Here, via a midline incision through the peritoneum, the abdominal aorta was exposed. Radiopaque dye was injected through a catheter which was placed in the abdominal aorta cranial to the branching of both renal arteries. Radiographs were taken afterwards.

Selective Left Ventricular Angiocardiogram

Each animal was anesthetized with 5 cc/lb of sodium pentobarbital intravenously. A catheter was placed via the left carotid artery into the left ventricle. With the aid

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[b]Model DR8 Recorder, Electronics for Medicine, Inc., White Plains, NY.

of fluoroscopy, contrast agent was injected and serial radiographs taken over a period of 5 seconds. Visualization of the size and shape of the left ventricular cavity, left ventricular wall, and vascular components was possible.

Thoracic Radiography and Electrocardiography

At 3 months of age, all colony dogs had routine chest radiography performed. Both ventrodorsal (VD) and lateral (L) views were taken to get some assessment of cardiac size, blood vessel size and shape, and noticeable lung lesions. At 6 months of age, they were subjected to electrocardiograms to detect heart rhythm, electrical activity, and possible cardiac enlargement.

Nonselective Venous Angiogram

This technique was utilized on the propositus, only. Fourteen ml of Hypaque M-75 was injected via the right jugular vein and radiographs were taken over a period of 9 seconds based on a technique used by Fox et al [103].

Tissue Biopsy

A wedge biopsied section of kidney from the propositus was surgically removed, fixed, and processed for light and electron microscopic examination. Five other colony animals had sections of skin and skeletal muscle similarly evaluated, as well. Wedges of skin from the left lateral flank and strips of the left external abdominal oblique muscle were sites of biopsy. The kidneys of the 5 animals

were needle biopsied during the time of wedge removal from the skin and muscle.

Plasma Catecholamine and Renin Activity Determinations

Plasma renin activity was determined by the technique described in the Angiotensin-I-Squibb Radioimmunoassay Kit[c]. During routine semi-annual evaluations, whole blood was collected from the external jugular vein and placed into pre-chilled, evacuated tubes containing EDTA. These blood-containing tubes were then centrifuged at a temperature of 0° C. The plasma was transferred into plastic tubes and immediately place on ice for analysis. Those samples not analyzed were kept frozen for later evaluation. Plasma catecholamine levels were determined utilizing the Catecholamine Radioenzymatic Kit [^{3}H][d]. Blood obtained via jugular vein puncture was collected into chilled, evacuated tubes containing EGTA and glutathione in concentrations of 90 mg/ml and 60 mg/ml, respectively. These tubes were centrifuged at 0° C for 15 minutes and the plasma was removed and stored at -20° C until used. These determinations were made on blood obtained from the caudal vena cava left renal vein and right renal vein. The methods of sample collection are described in the section, Blood Gas Analysis.

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[c]E.R. Squibb Diagnostics, New Brunswick, NJ.

[d]The Upjohn Company, Kalamazoo, MI.

Excretory Urogram

Three ml/kg of 75% Hypaque in an equal volume of 5% dextrose were administered intravenously to the propositus. Radiographs of the abdomen were taken following compression placed across the caudal abdomen. The other colony dogs subjected to this procedure received contrast agent injected from a catheter which was placed into their renal arteries via fluoroscopic guidance through the left carotid arteries.

Renal Arteriogram

In the propositus, following an abdominal incision, a catheter was placed selectively in the left renal artery. Five ml of 75% Hypaque was injected and serial radiographs taken over a 7 second period. The 10 other colony animals had the same procedure performed but with a different technique. A catheter was placed via a small incision into the left carotid artery. Through fluoroscopy, it was guided into the right renal artery and radiopaque dye injected. Radiographs were immediately taken. The same procedure was performed on the left kidney.

Echocardiographic Examination

M-mode echocardiograms were obtained using an Electronics for Medicine Honeywell Echo IV System with a 2.25 megahertz transducer[e]. The animals were awake and in left lateral recumbency. Echocardiograms were obtained from

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[e]Honeywell Echo IV System, Electronics for Medicine, Inc., White Plains, NY.

a window located in the region of the right ventricular apex. Measurements of left ventricular wall thickness were obtained from a recording taken immediately below the anterior leaflet of the mitral valve. Electrocardiograms were obtained simultaneously. In addition to colony dogs and propositus, this procedure was performed on 5 adult unrelated siberian husky dogs to give some assessment of average values for this breed.

Cerebral Spinal Fluid Examination

Ten colony dogs were anesthetized with barbiturate anesthesia, placed in right lateral recumbency and surgically prepped. After flexion of the neck, a 22 gauge spinal needle with stylet was inserted into the cisterna magnum. After the flow of spinal fluid was seen, a spinal manometer was attached and cerebrospinal fluid pressure measured. One to two ml of free flowing CSF was later collected and cytologically evaluated. Specific gravity and total protein determinations were made on each sample as well.

Blood Cadmium and Lead Determinations

Whole blood from each of 10 dogs was collected from each dog via the external jugular vein. These samples were placed into evacuated EDTA-containing tubes and submitted for cadmium and lead analysis. Each anticoagulated blood sample was separated into 100 µl aliquots and diluted with 1 ml of 0.1% HNO_3. For cadmium analysis, the solution was

directly placed via an autosampler into the graphite tube for flameless spectroscopy on a Polarized Zeeman Effect Atomic Absorption Spectrophotometer, Model 180-80 Hitachi[f]. Lead samples were first diluted 1:1 with a solution containing 2 mg/ml NH_4NO_3. Ten µl of this sample was dried using a 75 second sampling procedure with a maximum temperature of 100° C. Absorbances were compared with standards made from standardized stock solutions from Scientific Products. Cadmium was determined at 228.8 nm and lead at 283.3 nm.

Blood Gas Analysis

Ten colony dogs were anesthetized with barbiturate anesthesia and the right neck region surgically prepped for the eventual use of the right jugular vein and carotid artery. Small incisions were made in both vessels and catheters placed accordingly. Both catheters were carefully advanced and guided by fluoroscopy with continous electrocardiographic monitoring. One ml blood samples from the aorta and right atrium were taken in heparinized syringes, air removed, placed on ice, and taken to the blood gas analyzer for blood gas and pH determinations. Also, anterior vena cava, posterior vena cava, right renal vein, and left renal vein blood samples were collected through the

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[f]Hitachi Scientific Instruments, Nissei Sangyo Ltd., Mountain View, CA.

jugular vein catheter and analyzed according to previously described methods.

Data Analysis

Student's t-tests were used to analyze the data. Significance was accepted at a probability level of $\leq$ 0.05. Analysis of variance for blood pressure group designations and simple correlations for age and blood pressure comparisons were utilized and significance was accepted at a probability level of $\leq$ 0.05.

RESULTS AND DISCUSSION

Validation of Femoral Arterial Mean Blood Pressures

Mean arterial blood pressures obtained using the direct puncture technique were validated based upon a comparison in 3 dogs. Measurements of blood pressure were simultaneously monitored and recorded from the femoral artery and the aortic arch. These animals had aortic mean blood pressures of 105$\pm$7 mm Hg (number of trials [n] = 4), 103$\pm$6 mm Hg (n = 3), and 107$\pm$8 mm Hg (n = 3). Their corresponding femoral arterial mean blood pressures were 115$\pm$6 mm Hg (n = 4), 107$\pm$11 mm Hg (n = 3), and 112$\pm$16 mm Hg (n = 3), respectively. Each comparison was found to be insignificant at $p<0.05$. Average femoral arterial pressures were 6 mm Hg higher than the corresponding aortic pressures. This could have been due to transducer calibration error, as one would expect a slightly higher pressure within the aorta.

Blood Pressure Level in the Propositus

Femoral arterial blood pressures recorded upon initial examination were 200 mm Hg (SBP), 150 mm Hg (DBP), and 175 mm Hg (MBP). The pressures recorded on subsequent tables in this text are those obtained after the animal had been therapeutically maintained on diuretics and a low salt diet.

Groups, Based Upon Blood Pressure Determinations

Direct systemic arterial blood pressures were obtained in 30 dogs (excluding the propositus) over a 5 month period and the animals classified based upon their mean blood pressures (Table 1). The animals were segregated and arbitrarily placed into groups such that groups I, II, III, and IV had average MBP's of 128±12 mm Hg (range, 125-131 mm Hg); 121±8 mm Hg (range, 118-124 mm Hg); 114±9 mm Hg (range, 110-117 mm Hg); and 101±9 mm Hg (range, 91-109 mm Hg), respectively. There was at least a 7 mm Hg difference in MBP from group to group when standard deviations were not considered. Individual differences within each of the groups I, II, and III were $\leq$ 7 mm Hg when the highest and lowest values were compared. Group IV animals were removed from group III by at least 7 mm Hg. However, intra-group difference between the highest and lowest group IV values exceeds 7 mm Hg. There was no significant difference in age between the 4 groups. However, there was a positive significance correlation of age with SBP, DBP, and MBP when all groups were combined. The values for r were 0.40, 0.47, and 0.44, respectively. The mean blood pressure of Group I was not different from group II but was different from group III and group IV ($p<0.05$). There was no difference between groups II and III but there was a significant difference between groups II and IV and between III and IV ($p<0.05$). The combination of groups I and II was significantly different from the combination of groups III and IV. Two

unrelated, physically normal siberian husky dogs were tested and found to have 112±3 mm Hg (MBP), 129±6 mm Hg (SBP), 96±4 mm Hg (DBP), and 91±7 beats/min (HR) at 48 months of age. Their individual values after 5 trials were: 111±4 mm Hg (MBP), 128±6 mm Hg (SBP), 98±3 mm Hg (DBP), 97±7 beats/min (HR) and 113±3 mm Hg (MBP), 131±6 mm Hg (SBP), 95±5 mm Hg (DBP), 85±8 beats/min (HR). Based upon our previous groupings, these animals would be placed within group III. After conducting another independent study of 18 trials in 5 golden retriever dogs, MBP of 104±9 mm Hg was found. Individual mean blood pressures were: 94±7 mm Hg (n = 3), 104±3 mm Hg (n = 4), 104±8 mm Hg (n = 4), 104±11 mm Hg (n = 4), 112±14 mm Hg (n = 3). When considered as a group, these unrelated animals have an average MBP within the range of group IV. However, the one animal with a MBP of 112±14 could be placed within group III.

Dinamap Blood Pressure Recordings vs Femoral Arterial Recordings

Six animals representing groups I, II, and III had their blood pressures compared using the automatic cuff technique of the Dinamap and femoral arterial puncture. Three groups of data were collected on three separate days but a consistent number of trials using the Dinamap recorder could be obtained only on one day due to mechanical difficulty (Table 2). The utilization of the Dinamap recorder for blood pressure determination has been reported to be accurate in anesthetized animals [104] [105].

However, wide variations in SBP, DBP, MBP and HR have been a problem when conscious, unanesthetized dogs were subjected to this technique [105]. Our data (Table 2) indicates that values for SBP, DBP, and MBP were generally lower than corresponding values for femoral arterial puncture. However, heart rates obtained while utilizing the Dinamap recorder were generally higher than those obtained using the femoral arterial puncture technique. So, when considering heart rate, it would appear as if there is a higher sympathetic tone with Dinamap use. Yet, there is no resultant increase in blood pressures over those recorded using the femoral arterial puncture. Additionally, when a total of 18 MBP's were obtained by femoral puncture on three separate days and compared to 87 MBP's obtained using the Dinamap recorder over the same 3 days, there was an average standard deviation of 6 mm Hg when using the former and 12 mm Hg when using the latter method. These findings tend to indicate that the Dinamap pressures are less precise. Our values for femoral artery puncture determinations (Table 2) in this comparison are not outside the mean $\pm$ standard deviation of the individual values recorded on Table 1. These data suggest the consistency of femoral arterial puncture pressures. However, forty-three percent of all parameters measured under the femoral arterial pressures category were different from those in the Dinamap category (Table 2), being at least one standard deviation out of range when compared.

Ophthalmic Examination

Propositus - There was bilateral pupillary dilation with negative pupillary light reflex. The left eye had serous retinal elevation at the level of the optic disc. Both eyes had retinal hemorrhage and papilledema at the optic discs, as well (Figures 1 and 2). The intraocular pressures were normal.

Colony - All 10 animals examined had normal ocular structures irrespective of the various groupings (Table 3).

Blood and Urine Examination

Propositus - Whole blood, serum, and urine were evaluated and largely found to be unremarkable. The T_4 value of 8.2 ng/ml was depressed below our laboratory range of 15-40 ng/ml. However, T_3 was within normal limits (Table 4).

Colony - Tables 5, 6 and 7 depict the findings of the various groups relative to urine, chemical, and hematologic analysis. No obvious group differences existed at this time. However, individual animals had values which were slightly above or below the normally reported values.

Nonselective Aortogram

Propositus - No apparent abnormalities were observed in the distribution of the dye in the right or left kidney.

Selective Left Ventricular Angiocardiogram

Propositus - The size and shape of the left ventricular cavity appeared normal, as did the thickness of the left

ventricular wall. The aortic arch, however, was enlarged and displaced anteriorly. This enlargement extended into the brachiocephalic trunk and there was some tortuosity of the descending aorta (Figure 3).

Colony - The size and shape of the left ventricular cavity and thickness of the left ventricular wall appeared normal. No absolute statements could be made about the aortas. However, 1 animal from group I, 2 from group II, and 1 from group III appeared to have slight dilation and tortuosity of the post valvular aorta.

Thoracic Radiography and Electrocardiography

Propositus - The cardiac silhouette was slightly larger than normal. There was some evidence of right atrial enlargement as evidenced by a tall p-wave (0.6 mv) upon electrocardiographic examination.

Colony - One animal in group I had a mild generalized cardiac enlargement upon radiography but all other animals of this group were unremarkable. No significant lung changes were observed. Groups II and III had no major cardiac nor pulmonary abnormalities. Table 8 depicts a summary of the normal electrocardiographic data observed within the colony.

Nonselective Venous Angiogram

Propositus - Passage of contrast agent through the heart appeared to be unimpeded. The main pulmonary artery

was judged to be slightly enlarged. The right ventricular cavity and wall thickness appeared normal.

Renal Biopsy

Propositus - Bowman's urinary space was normal in all glomeruli examined and there was no evidence of fibrosis within Bowman's capsule. In one section, two involuted glomeruli were seen together, but associated arterioles were not in the section. In general, arteries and arterioles were well preserved with no evidence of hypertrophy.

Colony - The kidney, external abdominal oblique muscle, and skin were biopsied for histologic examination but poor tissue fixation precluded an appropriate evaluation.

Plasma Catecholamine and Plasma Renin Activity Determinations

Propositus - Norepinephrine (NE), epinephrine (E) and dopamine values were 210.1 pg/ml, 52.6 pg/ml and 21 pg.ml, respectively. Left renal vein plasma renin activity and right renal vein plasma renin activity were 2.0 ng/ml/hr and 2.6 ng/ml/hr, respectively (Tables 9 and 10).

Colony - There were no significant differences in NE, E, and dopamine levels when comparing the three groups (Table 9). These group values were also within the range reported as normal in dogs. Also, there was no significant difference in the plasma renin activity as measured in the three groups. Sodium intake was approximately the same in that the animals were fed the same laboratory chow. Sodium excretion was not measured, however.

Excretory Urogram

Propositus - Renal size and shape were normal. Filling of the diverticula and renal pelvis was achieved and the anatomy of the collecting system within the kidneys was judged to be normal. There appeared to be a slightly increased diameter to the left ureter. However, this finding may have been due to the unequal application of pressure over the abdomen (Figure 4).

Colony - Renal size and shape were normal for all animals except one dog in group III. This animal (Avalon) had one radio-dense area involving the left kidney. The area was consistent with a renal infarct, as the opaque dye was not able to penetrate, probably because of a lack of a sufficient blood supply.

Renal Arteriogram

Propositus - There was no parenchymal nor vascular architectural abnormalities observed (Figure 5).

Colony - There were no evidences of vascular abnormalities within the kidneys of these animals. However, an area consistent with an infarct was seen in the left kidney of one animal (Avalon) from group III and in the right kidney of an animal from group II (Folgers).

Echocardiographic Examination

Propositus - The propositus had values which were higher than the range for normal siberians in the categories of left ventricular wall thickness (LVWT), left ventricular

wall thickness/body surface area (LVWT/BSA), left ventricular wall thickness/weight (LVWT/weight) and septal thickness (Tables 11 and 12).

Normal Siberians - Five normal adult siberian husky dogs unrelated to our colony and weighing 18 to 25 kg were examined by echocardiography to establish normal values for this breed. Values for left ventricular wall thickness (LVWT) were indexed to weight (kg) and body surface area (M^2) by dividing LVWT by these two parameters (Table 12).

Colony - When the various groups were compared, considering LVWT, LVWT/BSA, and LVWT/weight, there was no significant difference between the groups (Tables 11 and 12, Figure 6). However, 3 animals from groups I and II had higher values than the normal siberians when LVWT was compared; 5 of 8 animals in group I and II had larger values for LVWT/BSA; and 6 of 8 dogs from groups I and II had larger values for LVWT/kg. Though there is not a significant difference for LVWT/BSA and LVWT/kg between the groups (Table 12), both groups I and II have a tendency at this time to be higher than the normal siberians and group III.

Cerebrospinal Fluid Examination

Colony - Examination of cerebrospinal fluid (CSF) pressure, cytology, specific gravity and total protein was unremarkable. All values were within the reported normal range for dogs (Table 13).

Heavy Metal Determinations

Colony - Values for lead and cadmium were within the normal range for the canine. Group differences for cadmium were insignificant and lead levels could not be detected (Table 14).

Blood Gas Analysis

Colony - No significant distinctions between the groups nor individual animals were apparent (Table 15).

Figure 1. The atapetal subalbinotic left eye showing indistinct disc margins indicative of papilledema (arrows). A pre-retinal hemorrhage (a) and deep dot retinal hemorrhage (b) are present.

Figure 2. The fundus photograph of the right eye showing papilledema lifting the retina at the disc margins (arrow) and a deep subretinal suffusion hemorrhage (c).

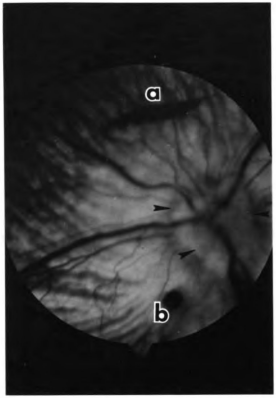

FIG 1

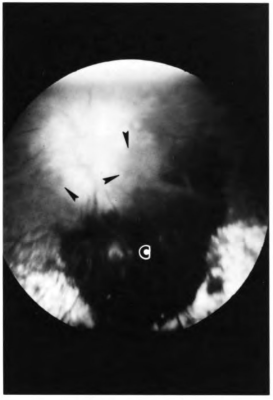

FIG 2

Figure 3. Left ventricular angiocardiogram showing aortic enlargement (open arrows) and a slight anterior displacement of the ascending aorta (closed arrows). (a) Catheter within left ventricle. (b) Normal lung field.

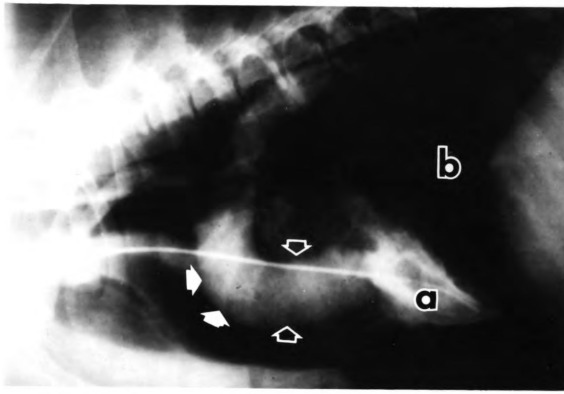

FIG 3

Figure 4. Left renal excretory urogram demonstrating that the left kidney is normal in size and shape. There is a slight increase in diameter of the left ureter (arrows), probably as a result of abdominal compression during the procedure. (a) Lumbar vertebral body. (b) 13th rib. (c) Catheter in abdominal aorta.

Figure 5. Left renal arteriogram outlining the left renal parenchyma and vascular network which appear normal. (a) Renal artery. (b) Renal cortex. (c) 13th rib. (d) Catheter within renal artery.

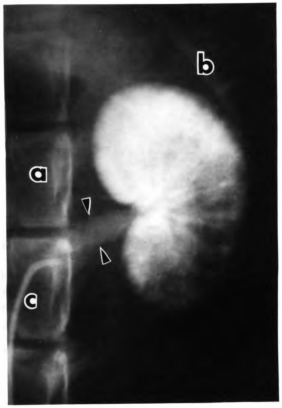

FIG 4

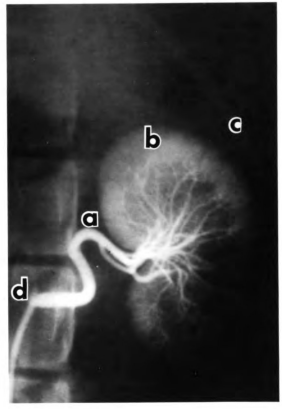

FIG 5

Figure 6. Echocardiographic analysis of normal vs colony animals showing the non-significant comparisons of representative animals from groups I, II, and III when compared to each other and to the normal control group when considering LVWT, LVWT/BSA, and LVWT/BW. Despite the non-significance between groups, individual animals from groups I and II were significantly different from the normal control group for all three parameters.

ECHOCARDIOGRAPH ANALYSIS
OF NORMAL vs. COLONY ANIMALS

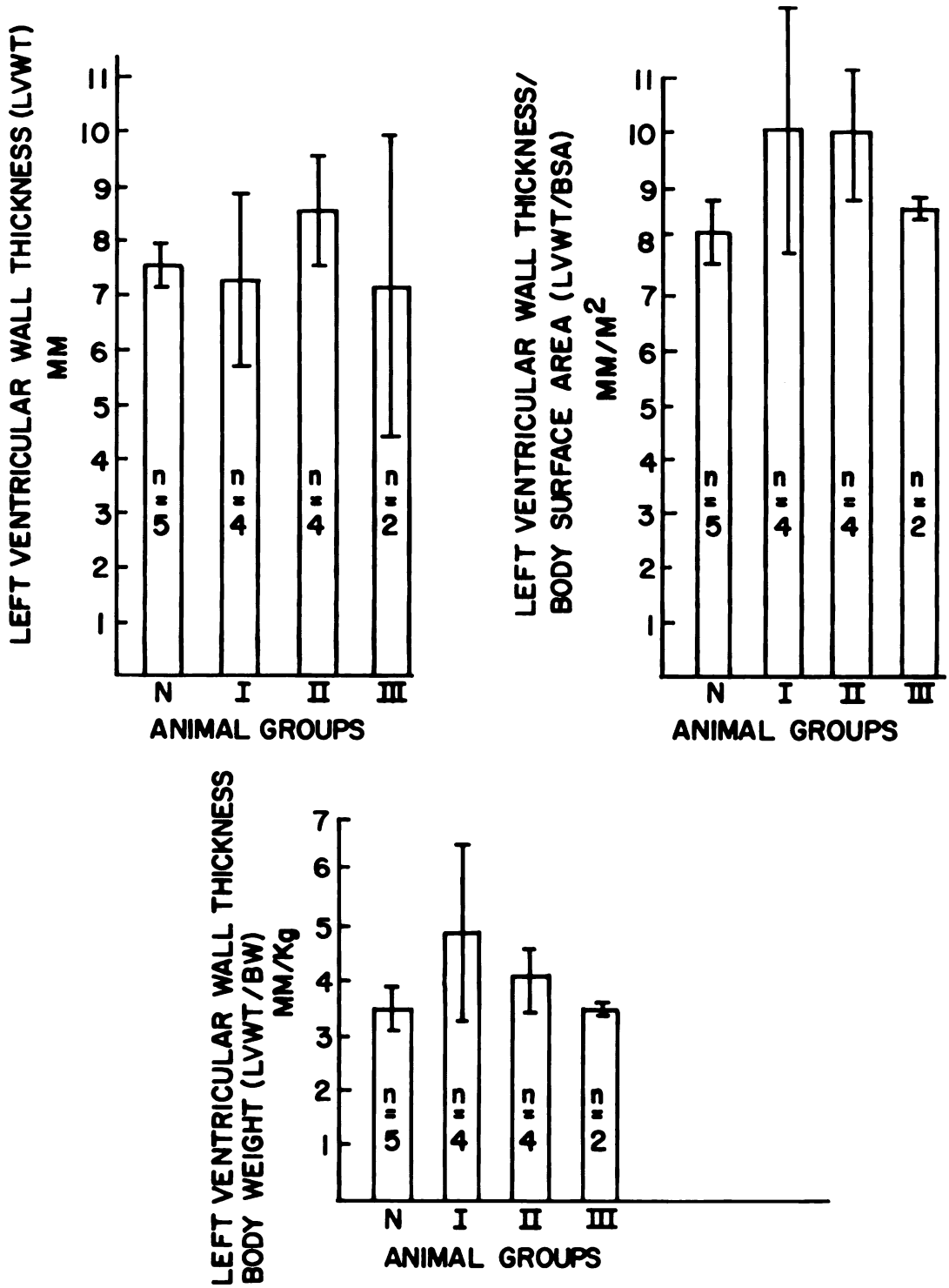

FIG 6

Figure 7. Siberian husky pedigree chart showing the familial pattern of hypertension distribution within the colony of animals. The colony consists of some related animals but with no available information, normal and affected males and females, dead or unavailable animals, and animals at the University of Pennsylvania which are maintained there by a breeding agreement. The animals are numbered individually with date of birth listed above the various litters. There was a significant positive correlation of age with SBP, DBP, and MBP within the colony.

Siberian Husky Pedigree

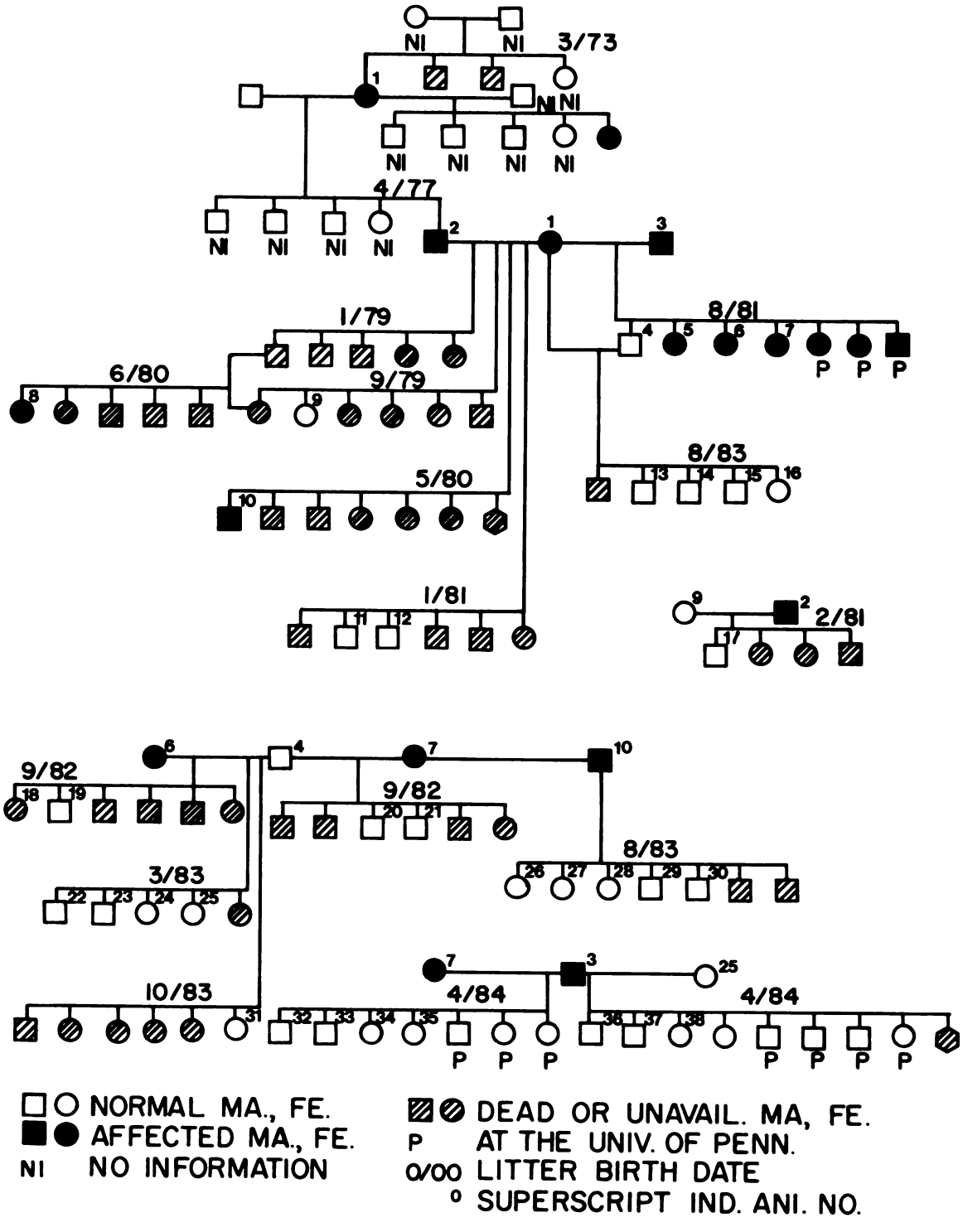

FIG 7

Table 1. Colony mean blood pressures* over a 5 month period by age and category.

Animal/Sex	Ages (months)	Heart rate (beats/min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg)	n (trials)
Group I (4 animals) - MBP 128±12						
Pistol/F	48	128±28	150±22	117±19	131±18	6
Alfreda/F	34	141±12	147±12	117±11	130±10	7
Penguin/F	34	136±21	146±13	110±7	127±8	8
A. Jacks/M	15	129±14	143±10	111±7	125±10	7
Joker†/F	132	103±15	124±6	99±5	110±5	4
Mean ± SD	33±14	133±19	146±14	114±11	128±12	7±1
Group II (9 animals) - MBP 121±8						
Yuma/M	72	132±13	143±11	108±11	124±12	9
Diamond/M	49	136±13	140±9	107±6	122±7	9
Folgers/M	41	120±14	137±13	105±7	121±9	9
Riddler/M	34	119±12	136±11	104±11	119±7	9
S. Smacks/F	15	115±50	143±4	103±4	118±4	2
Volkarye/F	10	147±29	151±17	117±22	124±5	3
Thor II/M	10	148±10	136±16	107±10	121±10	4
Volstagg/M	10	137±6	137±16	105±5	120±9	3
Hildegarde/F	10	143±13	139±9	109±11	121±10	4
Mean ± SD	28±22	133±18	140±12	107±10	121±8	6±3

*These blood pressures were obtained in awake, nonanesthetized dogs by direct femoral arterial puncture.

†Joker, the propositus was and is being maintained on a low salt diet and diuretics. Her values are not considered with group I animals.

Table 1 - Continued*.

Animal/Sex	Ages (months)	Heart rate (beats/min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg)	n (trials)
Group III (8 animals) - MBP 114±9						
Avalon/F	57	123±10	124±6	99±5	110±5	7
Sanka/M	41	114±13	134±8	97±10	113±9	9
Dion/M	40	132±20	135±8	102±7	115±6	9
Catwoman/F	34	138±8	132±18	99±10	115±14	5
Kirk/M	21	145±21	128±4	103±4	114±2	2
Goliath/M	21	155±13	136±9	104±5	117±9	4
C. Crunch/M	15	169±19	126±8	103±6	114±6	7
Hush/F	8	123±6	133±19	98±20	117±21	3
Mean ± SD	30±16	137±14	131±10	101±8	114±9	6±3
Group IV (9 animals) - MBP 101±9						
Khan/M	21	123±15	118±9	93±10	103±10	3
Trix/F	15	115±17	127±7	98±18	109±12	2
Buckwheat/M	10	150±22	118±15	89±10	102±10	4
Spanky/M	10	120±28	123±4	90±14	105±7	2
Alfalfa/M	10	113±21	120±5	92±14	102±9	3
Porky/M	10	115±13	117±9	85±9	96±9	4
Darla/F	10	118±17	108±7	79±7	91±7	4
Loki/M	10	145±10	114±6	81±8	96±6	4
Freida/F	10	140±22	123±10	94±15	108±10	4
Mean ± SD	12±4	127±18	119±8	89±12	101±9	3±1

*These blood pressures were obtained in awake, nonanesthetized dogs by direct femoral arterial puncture.

Table 2. Selected comparisons* of femoral arterial and Dinamap blood pressure determinations.

	Femoral Artery Pressures					Dinamap Pressures †				
Animal	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg)	HR (/min)	N	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg)	HR (mm Hg)	N
Penguin	144	110	130	160∫	1	156±20	127±17	134±18	139±3∫	6
Yuma	147∫	110∫	125∫	110	1	130±12∫	100±6∫	106±6∫	112±10	6
Diamond	155∫	110	130∫	120	1	134±9∫	97±4	110±7∫	134±16	6
Folgers	145∫	107	125∫	110	1	123±10∫	95±10	104±8∫	118±9	6
Riddler	135∫	95	112	120∫	1	113±12∫	93±7	100±9	137±8∫	6
Dion	132	100	108	110∫	1	125±18	81±20	95±21	129±10	6

*Animals were randomly selected as representatives from three groups; Penguin (group I); Yuma, Diamond, Folgers, and Riddler (group II); Dion (group IV).

†Three trials of Dinamap pressure determinations yielded only one complete set of data tabulated above.

∫Values in this category are outside the range (± SD) for values in the corresponding category.

Table 3. Selected comparisons* of ophthalmic examination results.

Animal	Interpretation
Group I	
Alfreda	Normal structures
Penguin	Normal structures
Joker	Retinal hemorrhage; papilledema†
Pistol	Normal structures
Group II	
Apple Jacks	Normal structures
Riddler	Normal structures
Diamond	Normal structures
Yuma	Normal structures
Folgers	Normal structures
Group III	
Avalon	Normal structures
Dion	Normal structures

*These animals were randomly selected as representatives from groups I, II, and III.

†Observed upon initial examination at MSU Veterinary Clinical Center.

Table 4. Clinical laboratory data from propositus after admission to clinic.

Hematology		Chemistry		Urinalysis	
Total protein	7.7 g/dl	BUN	10 mg/dl	Color	yellow
PCV	41.5%	Glucose	119 mg/dl	Turbidity	turbid
Hgb	14.2 g/dl	Na	142 mEq/L	Sp. Gr.	1.032
RBC	6.12 10^6/ul	K	4.5 mEq/L	pH	6.5
WBC	8200/ul	Cl	108 mEq/L	Protein	negative
Seg	76% - 6232	Ca	10.5 mg/dl	Glucose	negative
N-Seg	-- - 0	P	3.0 mg/dl	Ketones	negative
Lymph	18% - 1476	Mg	2 mg/dl	Bilirubin	moderate
Mono	2% - 164	SGPT	34 IU/L	Occ. Blood	negative
Eos	4% - 328	T_3	1.23 ng/ml	Urobilinogen	0.1
Platelets	adequate	T_4	8.2 ng/dl	WBC	negative
MCV	68 u^3	Cholesterol	189 mg/dl	RBC	negative
MCH	23 uug	Alk. Phos.	42 IU/L	Cells	few squamous
MCHC	33.9 ug/dl	Amylase	250 units	Crystals	negative
		Creatinine	0.7 mg/dl		
		Albumin	4.3 g/dl		
		Globulin	3.4 g/dl		

Table 5. Selected comparisons* of colony serum chemistry analysis.

	Group I (n = 4)	Group II (n = 4)	Group III (n = 2)
BUN	13.5±5.5	15.3±4.2	19
Glucose	70.0±3.8	76.2±10.0	86.0±6.0
Total protein	6.3±0.4	6.6±0.6	6.1±0.1
Albumin	3.5±0.2	3.6±0.1	3.5±0.1
Globulin	2.8±0.2	3.0±0.7	2.7±0.1
ALT	41.8±16.6	47.3±13.7	59.5±10.6
Alk phos	33.8±5.9	24.0±2.9	23.5±3.5
Na	147.3±1.0	147.5±1.3	147.5±0.7
Cl	114.3±0.5	114.3±1.7	117
T Co_2	18.1±1.5	18.3±1.7	16.5±2.1
Anion gap	14.5±1.9	14.3±3.2	14.5±3.5
Serum app	Clear	Clear	Clear
Ca	10.4±0.6	10.4±0.6	10.7
P	4.1±0.3	3.3±0.3	3.2±0.5
Mg	2.3±0.2	2.2±0.2	2.1±0.1
Chol	225.0±21.2	153.0±10.8	195.5±44.6
Trig	35.0±5.5	37.3±11.3	29.5±0.7
T_3	1.1±0.3	1.0±0.1	0.8±0.1
T_4	24.0±2.9	20.8±5.7	16.0±8.5
K	5.1±0.1	4.8±0.4	4.9±0.1

*The animals were randomly selected as representatives from groups I, II, and III; data collection and analysis utilizing standard units as mentioned on page 19.

Table 6. Selected comparisons* of colony urine analysis.

	†Group I (n = 3)	Group II (n = 4)	Group III (n = 2)
Color	Yellow	Yellow	Yellow
Turbidity	Clear	Clear	Clear
pH	9	7.8±1.5	7.0±1.4
Ca	2.5±1.5	2.8±0.9	3.4±1.5
P	55.6±44.9	209.0±109.9	161.0±18.38

*These animals were randomly selected from the various groups listed above; data collection and analysis utilizing standard units as mentioned on page 19.

†Only 3 animals within this group were evaluated. They included Penguin, Alfreda, and Pistol.

Table 7. Selected comparisons* of colony hematologic analysis.

	Group I (n = 4)	Group II (n = 4)	Group III (n = 2)
Plasma Tot. Prot.	6.3±27.0	6.0±0.5	6.3±0.3
PCV (spun)	46.3±6.2	48.0±1.0	42.0±1.0
WBC	10.1±2.1	10.0±2.0	8.8±0.4
RBC	6.8±0.7	7.0±0.2	6.4±0.3
Hbg	15.8±2.0	16.0±0.2	14.0±0.1
PCV	47.4±5.0	49.0±1.0	44.0±1.0
MCV	69.3±2.4	71.0±2.0	69.0±1.0
MCH	23.0±0.8	23.0±1.0	22.0±1.0
MCHC	33.2±0.9	33.0±0.4	32.0±1.0
Seg	55.0±10.0	67.0±9.0	57.0±6.0
N-Seg	-	-	-
Lymph	30.3±11.7	24.0±5.0	34.0±11.0
Mono	6.8±3.5	5.0±2.0	5.5±2.1
Eos	7.8±3.0	4.0±2.0	4.5±2.1
Baso	0.3	0	0
Platelets	Adequate	Adequate	Adequate

*Representative animals from the various groups were randomly selected and compared; data collection and analysis utilizing standard units as mentioned on page 19.

Table 8. Selected comparisons* of colony electrocardiography evaluation.

Animal	Heart rate (beats/min)	Heart rhythm	P-R interval (sec)	QRS (sec/mv)	QT (sec)	Electrical axis
Group I						
Pistol	160	NSR	0.10	0.02/1.7	0.16	+60
Alfreda	160	NSR	0.08	0.02/1.0	0.14	+60
Penguin	160	NSR	0.08	0.02/1.6	0.16	+60
Apple Jacks	200	NSR	0.08	0.02/1.1	0.14	+60
Group II						
Yuma	120	NSR	0.10	0.02/1.5	0.16	+90
Diamond	120	NSR	0.08	0.02/1.5	0.22	+60
Folgers	120	NSR	0.10	0.02/1.3	0.16	+60
Riddler	200	NSR	0.11	0.02/1.4	0.18	+60
Group III						
Avalon	160	NSR	0.10	0.02/1.2	0.16	+60
Dion	160	NSR	0.10	0.02/1.5	0.16	+60

*Animals from the various groups were randomly selected, evaluated, and compared.

Table 9. Selected comparisons* of plasma catecholamine levels between group representatives and propositus.

Animal	Dopamine (pg/ml)	Epinephrine (pg/ml)	Norepinephrine (pg/ml)
Group I	41.8±17.0†	199.8±56.4†	411.0±203.1†
Alfreda	23	207	270
Penguin	32	173	208
Pistol	54	144	629
Apple Jacks	58	275	537
Joker∫	21	53	210
Group II	38.8±16.2†	210.5±69.0†	373.5±94.9†
Riddler	36	146	284
Diamond	53	264	300
Yuma	17	156	468
Folgers	49	276	442
Group III	60.0±5.7†	191.0±79.2†	584.0±311.1†
Avalon	64	135	804
Dion	56	247	364

*Animals within the various groups were randomly selected for evaluation.

†Mean ± SD.

∫The propositus, Joker, is considered as an individual case and is not included in the calculations of group I.

Table 10. Selected comparisons* of plasma renin activity between group representatives and propositus.

Animal	Left renal vein (ng/ml/hr)	Right renal vein (ng/ml/hr)	Caudal vena cava (ng/ml/hr)
Group I	2.6±1.4†	2.2±1.2†	0.8±0.5†
Alfreda	4.3	3.7	1.5
Penguin	-	-	0.8
Pistol	1.7	1.5	0.5
Apple Jacks	1.9	1.5	0.4
Joker∫	2.0	2.6	1.2
Group II	2.0±1.4†	2.6±2.6†	0.6±0.6†
Riddler	3.9	6.4	1.5
Diamond	1.7	0.9	0.4
Yuma	1.6	1.2	0.5
Folgers	0.6	1.8	0.1
Group III	1.5±0.4†	2.6†	0.8±0.6†
Avalon	1.2	-	0.4
Dion	1.7	2.6	1.2

*The animals in the three groups were randomly selected and subjected to the above determinations.

† Mean ± SD.

∫ The propositus, Joker, was considered as an individual case and not included in the calculations of group I.

Table 11. Selected comparisons* of echocardiographic analysis of colony representatives and propositus.

Animal	LVWT (cm)	Septal thickness (cm)	Septal/LVWT	LVWT/BSA (cm/m^2)	LVWT/kg (cm/kg)	Body weight (kg)	BSA (m^2)
Group I	0.72±0.16†	0.82±0.15†	1.17±0.12†	1.07±0.23†	0.049±0.016†	15.7±5.3†	0.693±0.168†
Alfreda ∫	0.89	0.90	1.01	1.16	0.049	18.18	0.774
Penguin ∫	0.61	0.68	1.15	0.73	0.029	20.45	0.837
Pistol	0.83	1.00	1.21	1.17	0.052	15.90	0.708
Apple Jacks	0.55	0.71	1.29	1.21	0.067	8.18	0.454
Joker T	0.93	0.95	1.02	1.15	0.048	19.50	0.811
Group II	0.85±0.10†	0.87±0.04†	1.22±0.42†	0.99±0.13†	0.040±0.006†	21.4±1.1†	0.860±0.029†
Riddler	0.95	0.90	0.94	1.09	0.043	21.80	0.870
Diamond ∫	0.77	0.90	1.15	0.92	0.037	20.45	0.837
Yuma	0.75	0.81	1.84	0.84	0.033	22.70	0.898
Folgers	0.93	0.89	0.96	1.11	0.045	20.45	0.837
Group III	0.71±0.28†	0.78±0.09†	1.10±0.08†	0.85±0.02†	0.035±0.001†	20.2±0.30†	0.831±0.008†
Avalon	0.69	0.72	1.04	0.84	0.034	20.00	0.825
Dion	0.73	0.85	1.16	0.87	0.035	20.45	0.837

*The animals from the various groups were randomly selected and compared.
†Mean ± SD.
∫Values represent an average of two recordings.
TJoker, the propositus, was not included in group I calculations.

Table 12. Echocardiographic analysis of normal, non-colony Siberians.

Animal	LVWT (cm)	Septal thickness (cm)	Septal/LVWT	LVWT/BSA (cm/m^2)	LVWT/kg (cm/kg)	Body weight (kg)	BSA (m^2)
Shine	0.700	0.66	0.94	0.897	0.039	18.18	0.78
Stormy	0.785	0.85	1.08	0.809	0.031	25.00	0.96
Tammy	0.730	0.73	1.00	0.839	0.034	21.40	0.87
Clipper	0.750	0.66	0.88	0.785	0.032	23.60	0.93
Chrissy	0.800	0.50	0.62	0.740	0.039	20.50	0.85
Mean $\pm$ SD	0.75$\pm$0.04	0.68$\pm$0.13	0.90$\pm$0.17	0.814$\pm$0.06	0.035$\pm$0.004	21.73$\pm$2.66	0.87$\pm$0.07

Table 13. Selected comparisons* of colony cerebrospinal fluid examination data.

Animal	Cerebrospinal fluid pressure (cm/H_2O)	Cytologic interpretation	Total protein (mg/dl)	Specific gravity
Group I	125±18.51 †		23.5±9.26 †	1.005 †
Pistol	148	No evidence of disease	21 mg/dl	1.005
Alfreda	110	No evidence of disease	20 mg/dl	1.005
Penguin	110	No evidence of disease	37 mg/dl	1.005
Apple Jacks	132	No evidence of disease	16 mg/dl	1.005
Group II	109±20.56 †		20.5±3.11 †	1.005 †
Yuma	124	No evidence of disease	23 mg/dl	1.005
Diamond	82	No evidence of disease	21 mg/dl	1.005
Folgers	104	No evidence of disease	22 mg/dl	1.005
Riddler	126	No evidence of disease	16 mg/dl	1.005
Group III	111±1.41†		22.50±0.71 †	1.005 †
Avalon	112	No evidence of disease	22 mg/dl	1.005
Dion	110	No evidence of disease	23 mg/dl	1.005

*These animals were randomly selected from groups I, II, and III.

†Mean ± SD.

Table 14. Selected comparisons* of plasma lead and cadmium determinations.

Animal	Lead (ug/dl)	Cadmium (ug/dl)
Group I		0.50±0.20†
Pistol	0	0.24
Alfreda	0	0.69
Penguin	0	0.61
Apple Jacks	0	0.47
Group II		0.74±0.64†
Yuma	0	0.24
Diamond	0	0.41
Folgers	0	1.66
Riddler	0	0.65
Group III		0.27±0.11†
Avalon	0	0.34
Dion	0	0.19

*Comparison was made between animals from groups I, II, and III who were randomly selected for evaluation.

†Mean ± SD.

Table 15. Selected comparisons* of colony blood gas analysis.

Animal	Arterial						Venous					
	Hbg (g/dl)	pH	pCO_2 (mm Hg)	pO_2 (mm Hg)	HCO_3 (mm Hg)	SAT %	Hbg (g/dl)	pH	pCO_2 (mm Hg)	pO_2 (mm Hg)	HCO_3 (mm Hg)	SAT %
Group I												
Pistol	18.7	7.420	30.8	96.7	19.7	96.8	19.8	7.391	33.8	56.5	20.1	87.8
Alfreda	24.8	7.410	26.2	90.6	16.3	95.9	23.8	7.360	35.7	31.0	19.7	57.7
Penguin	22.4	7.435	28.9	87.2	19.2	95.9	22.1	7.395	35.2	40.3	21.2	75.0
AppleJacks	15.1	7.413	31.6	88.0	19.9	95.9	15.8	7.399	33.1	48.2	20.1	82.8
Mean±SD	20.3± 4.3	7.419± 0.011	29.4± 2.4	90.6± 4.3	18.8± 1.7	96.1± 0.5	20.4± 3.5	7.386± 0.017	44.0± 1.2	20.3± 10.9	20.3± 0.6	75.8± 13.2
Group II												
Yuma	23.3	7.466	27.1	105.0	19.4	97.6	21.3	7.447	32.4	46.8	22.1	84.1
Diamond	22.0	7.386	29.5	89.6	17.4	95.6	21.9	7.413	32.1	31.0	20.2	61.4
Folgers	21.9	7.387	31.7	77.1	18.7	94.1	20.6	7.413	29.3	47.2	18.4	82.8
Riddler	20.0	7.413	33.8	91.2	21.2	96.2	20.2	7.379	37.8	52.4	21.9	85.4
Mean±SD	21.8± 1.4	7.413± 0.038	30.5± 2.9	90.7± 11.4	19.2± 1.6	95.9± 1.5	21.0± 0.8	7.413± 0.027	32.9± 3.6	44.4± 9.3	20.7± 1.7	78.4± 11.4
Group III												
Avalon	18.6	7.383	25.3	106.7	14.8	97.1	17.3	7.331	33.6	42.8	17.3	74.3
Dion	18.5	7.418	31.3	85.7	19.9	95.6	18.1	7.409	30.9	53.9	19.2	87.2
Mean±SD	18.6± 0.1	7.400± 0.025	28.3± 4.2	96.2± 14.9	17.4± 3.6	96.4± 1.1	17.7± 0.6	7.370± 0.055	32.3± 1.9	48.4± 7.9	18.3± 1.3	80.8± 9.1

*Representative animals from the various groups were randomly selected and compared.

SUMMARY AND CONCLUSIONS

This study documents spontaneous hypertension in the dog but only loosely associates it with an underlying pathology [14]. A problem encountered when diagnosing primary or secondary hypertension in non-human species is determining a normal and an abnormal blood pressure range. In dogs many techniques of blood pressure determination have been used [14] [107] [108] but the generally accepted method in conditioned dogs has been direct arterial puncture [109]. In one study utilizing the direct arterial puncture in 21 conscious, mongrel dogs, it was determined that normal values for systolic, diastolic, and mean systemic arterial pressures were 148 ± 15.8, 87 ± 8.0, and 102.3 ± 9.4 mm Hg, respectively [110]. The propositus in our study far exceeded that reported range upon initial examination (SBP, 200 mm Hg; DBP, 150 mm Hg; MBP, 175 mm Hg). The ocular lesion as evidenced by retinal hemorrhage, a condition frequently associated with the malignant phase of hypertension in man [111] [112], was a strong indication of the significance of blood pressure elevation in the propositus.

The cardiovascular abnormalities of this animal included a slightly enlarged cardiac silhouette, right atrial enlargement, slight pulmonary artery enlargement and

tortuosity and enlargement of the thoracic aorta. However, there was no evidence of mechanical or congenital defects contributing to these changes. Increased venous return or central redistribution of blood may have contributed to an excessive right atrial filling and subsequent enlargement.

A possible increase in cardiac output and relative lack of significant renal pathology may indicate an early onset phase of hypertension. Such changes have been shown to occur in the early stages of essential hypertension in man [98]. However, the ocular pathology suggests a more advanced stage of the syndrome [111] [112].

In one study utilizing conscious alert dogs, average plasma epinephrine (E) and norepinephrine (NE) values were 144±55 pg/ml with a range of 40-241 pg/ml and 193±86 with a range of 53-405 pg/ml, respectively [113]. The value for E in the propositus was 52.6 pg/ml; lower than the average value but within the reported range. The level of NE was 210.1 pg/ml; slightly higher than the reported average but well within the accepted range. So, it doesn't appear that significant sympathetic activity causing catecholamine release was instrumental in the elevation of systemic arterial blood pressure. However, urinary catecholamine levels have not been determined.

There is insufficient available data on canine renal vein renin levels to make an assessment of the significance of our reported values. However, level of plasma renin activity in sodium replete dogs after anesthesia and surgery

was reported to be 1.2±0.1 ng/ml/hr (mean ± SD) when caudal vena cava blood samples were used [114]. The designations of "high renin", "low renin", and "normal renin" forms of hypertension, as advocated by some, could not be used because of intergroup similarities [115].

The T_4 value of 8.2 ng/ml was lower than our laboratory range of 15-40 ng/ml. However, T_3, believed to be the most metabolically active peripheral tissue hormone, was within the normal range for the dog.

Based upon the absence of known secondary causes, the propositus was diagnosed as having spontaneous idiopathic hypertension. Realizing the necessity for animal models of spontaneous primary hypertension, this animal was placed on diuretic therapy (Diuril, 250 mg/bid)[g] and fed a low salt diet (H/D prescription diet)[h] to maintain normal blood pressure and survival. The animal has been bred to other hypertensive or potentially hypertensive dogs, many of which were her offspring. Various sister-brother matings have been performed as well (Figure 7). As a result of such matings, 36 dogs have been added over a period of 5 years. Many of these animals have been on contract by placing them in homes of local residents to defray the cost of maintenance. However, periodic clinical examinations are

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[g]Diuril, Chlorothiazide, Merck, Sharp & Dohme, West Point, PA.

[h]H/D dog food, Hills Pet Products, Inc., Topeka, KS.

mandatory. Other animals have been shipped to and are owned by the University of Pennsylvania as a part of a hypertensive breeding agreement.

In essential hypertension in man, it is generally conceded that the genes play a fundamental role in blood pressure homeostasis [116]. It is also known that correlation coefficients for both systolic and diastolic blood pressures are higher within families than in unrelated individuals [3]. However, the mode of inheritance is not known. With our limited numbers of available animals from the several matings, we were not able to define a specific mode of inheritance. However, the trait does appear to be familial as 14 of 30 related animals (including propositus) have hypertension. Additionally, there were significant positive correlations of SBP, DBP, and MBP with age, r values being 0.40, 0.47, and 0.44, respectively. On the contrary, in 5 related golden retriever dogs, there was not a significant correlation of MBP with age ($r = -0.24$).

Thirty animals in which MBP was measured, were used to establish four animal groups. Group IV had the lowest MBP and contained the majority of the youngest animals. This group had pressures which were compatible with those obtained in such groups as the adult golden retriever and other mongrel dogs. Group III largely consisted of adult animals and had pressures similar to the unrelated normal siberian husky dogs which were used to establish normal adult siberian husky MBP. Group II animals appeared to be a

distinct group in that the MBP did not differ significantly from group I or group III. However, group I was significantly different from group III. This "middle" group (II) actually bridged the gap between group I and group III, similar to what is done by the "borderline" hypertensives relative to full-blown essential hypertension and normotension in man.

After group establishment, 10 animals as representatives from the three groups were further evaluated because of the possibility that secondary organic lesions could serve to further mark the condition in dogs. Upon clinical examination and evaluation, groups I and II did not differ significantly from group III, the normal siberians. There were a few individual differences upon echocardiographic analysis but no major group disparities. So, at the present stage, at least, there aren't any outstanding markers other than MBP that could be used to further segregate the groups. We feel that with time, clear group distinctions in terms of organic lesions and/or clinical manifestations will be possible as in the case with essential hypertension in man. Because of these expectations, we have developed a protocol which can be used to systematically evaluate existing colony animals as well as those which will be born into the colony (see recommendations).

RECOMMENDATIONS

Based upon our research findings, we've developed a protocol to further characterize the hypertensive state in our colony of dogs. The objective of this protocol is fivefold:

1) Provide information on blood pressure measurements so that we can continually breed for the hypertensive condition.
2) Serve as a data base for the further establishment of normal and abnormal blood pressures in dogs.
3) Monitor blood pressures beginning at an early age in the animal with the intention of tracking these animals into maturity and determining any early inclination towards hypertension development.
4) Using periodic clinical examinations to define possible contributing lesions and time of onset of such lesions.
5) To rule out or identify secondary causes of hypertension.

Table 1 should be used to screen all colony animals through the age of 5 years or at which time systemic arterial blood pressure is consistently elevated into a range compatible, at least with our group II animals. Using this table, one could detect the more prevalent secondary forms of hypertension, if present. The primary form could

also be identified by the process of eliminating the secondary forms.

Table 2 will be used to further define the hypertension diagnosed using Table 1. Using this data in Table 2, a clearer understanding of "borderline" versus full blown essential hypertension may be achieved as the more subtle changes in cardiovascular function and end organ structure and function would be identified.

Table 1. Preliminary protocol for all colony animals.

Secondary form	Age at testing (months)	Frequency of testing	Types of tests performed
Renal			
Parenchymal	3	every 6 months	urinalysis, BUN, creatinine, serum and urine Na and K
Renovascular and trauma	6	every 12 months	IVP
Endocrine			
Thyroid	3	every 6 months	T_3, T_4 levels
Adrenal	3	every 6 months	serum glucose, catecholamine, serum K, Na, plasma renin
Parathyroid	3	every 6 months	serum and urinary Ca and P
Neurogenic	6	every 12 months	blood gases, cerebrospinal fluid pressure and cytology
Mechanical interference with flow	3	every 6 months	auscultation, triglycerides and cholesterol, chest x-ray
	3	once/month until 6 months old, then every other week	femoral blood pressure
Exogenous	3	every 12 months	lead,cadmium
Miscellaneous	3	every 6 months	hematocrit, red blood cell count, white blood cell count, platelet count

Table 2. Further definition of the primary form of hypertension.

Animals	Type of tests	Frequency of tests
All hypertensive	echocardiogram	every 6 months
All hypertensive	ECG	every 6 months
All hypertensive	cardiac output/total peripheral resistance; renal arteriograms	once at hypertension diagnosis and once 36 months later
All hypertensive	funduscopic exam	every 6 months
All hypertensive	skin and skeletal muscle biopsy	every 12 months
All hypertensive	renal biopsy	every 12 months
All hypertensive	femoral arterial blood pressure	every other week

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VITAE

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