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Rates of renal gluconeogenesis were determined in intact normal dogs, and in acidotic, bicarbonate-fed, hypoglycemic, or pregnant dogs. Renal plasma flow, arterial and renal venous glucose, pH, and P_{CO_2} were measured. Renal gluconeogenesis was shown in 56% of periods from controls, 40% from acidotic, 75% from alkalotic, 39% from hypoglycemic, and 57% from pregnant dogs. Rates of renal gluconeogenesis in acidotic dogs were significantly lower than in controls. Bicarbonate-fed dogs had a higher rate than controls, but not significantly so. When compared to acidotic dogs, however, the bicarbonate-fed dogs manifested a significantly greater rate of gluconeogenesis. When clearance periods from control, acidotic, and bicarbonate-fed dogs were segregated according to the production or extraction of glucose rather than pH, it was found that periods showing production did not differ in acid-base features from those showing extraction. Hypoglycemic and pregnant dogs did not differ significantly from controls. It appears that in vivo metabolic acidosis does not significantly stimulate rates of renal gluconeogenesis.

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Renal gluconeogenesis after NH_4Cl, $NaHCO_3$, hypoglycemia, or pregnancy

DAVID M. ROXE
Experimental Medicine Division, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland 20014

ROXE, DAVID M. *Renal gluconeogenesis after NH_4Cl, $NaHCO_3$, hypoglycemia, or pregnancy.* Am. J. Physiol. 222(1): 55-60. 1972.—Rates of renal gluconeogenesis were determined in intact normal dogs, and in acidotic, bicarbonate-fed, hypoglycemic, or pregnant dogs. Renal plasma flow, arterial and renal venous glucose, pH, and P_{CO_2} were measured. Renal gluconeogenesis was shown in 50% of periods from controls, 10% from acidotic, 75% from alkalotic, 39% from hypoglycemic, and 57% from pregnant dogs. Rates of renal gluconeogenesis in acidotic dogs were significantly lower than in controls. Bicarbonate-fed dogs had a higher rate than controls, but not significantly so. When compared to acidotic dogs, however, the bicarbonate-fed dogs manifested a significantly greater rate of gluconeogenesis. When clearance periods from control, acidotic, and bicarbonate-fed dogs were segregated according to the production or extraction of glucose rather than pH, it was found that periods showing production did not differ in acid-base features from those showing extraction. Hypoglycemic and pregnant dogs did not differ significantly from controls. It appears that in vivo metabolic acidosis does not significantly stimulate rates of renal gluconeogenesis.

glucose metabolism; kidney, acid-base balance

THERE IS LITTLE EVIDENCE that in vivo renal gluconeogenesis is related to acid-base balance. It has been shown in vitro, however, that acidosis increases the rate of renal gluconeogenesis and that alkalosis decreases it (6, 8). Conflicting evidence exists as to the effects of chronic metabolic acidosis on renal gluconeogenesis in vivo (4, 19), and there is only one report of the effect of chronic metabolic alkalosis in vivo (17). Accordingly, rates of renal gluconeogenesis in intact dogs were measured in control animals and in dogs with chronic metabolic acidosis or after bicarbonate feeding.

The purpose of these experiments was to answer three questions: first, Do animals in any of the experimental conditions differ from control animals in rates of renal gluconeogenesis? second, if dogs with chronic metabolic acidosis are compared directly to dogs fed bicarbonate, do they differ in rates of renal gluconeogenesis? third, if clearance periods from acidotic, alkalotic, and control dogs are segregated according to the production or extraction of glucose rather than the acid-base condition induced, will acid-base parameters in the group of periods characterized by production of glucose differ from those in periods characterized by extraction of glucose?

The effect of insulin-induced hypoglycemia on renal gluconeogenesis was determined to study another possible control mechanism for renal gluconeogenesis.

It was found at laparotomy that two dogs were pregnant. The hormonal changes associated with pregnancy made it worthwhile to measure rates of renal gluconeogenesis in these dogs rather than to sacrifice them for no purpose.

MATERIALS AND METHODS

Both male and female dogs weighing between 15 and 24 kg were used. All dogs were wormed and immunized against rabies, distemper, hepatitis, and leptospirosis. All were shown to have a normal hematocrit shortly before shipment. They were fed standard dog chow ad libitum.

Chronic metabolic acidosis was induced by adding 10 g of NH_4Cl to the chow daily for 5 days. Chronic metabolic alkalosis was sought by adding 10 g of $NaHCO_3$ to the chow for 5–7 days. Food was withheld from the night before surgery. Water was permitted ad libitum to the time of surgery.

Each animal was anesthetized (Nembutal, 30 mg/kg, iv), intubated to permit free respiration, and given an infusion of normal saline containing 2.5 ml of 20% sodium aminohippurate per liter at 5 ml/min. *Dog 21* received Na_2SO_4 in the infusion to insure urinary acidification.

An arterial catheter was placed in the left femoral artery. A catheter was placed in the right femoral vein and passed into the vena cava to approximately the level of the right renal vein. The abdomen was opened in the midline and both ureters were exposed and catheterized with polyvinyl tubing which was tied firmly in place. The right kidney and renal vein were exposed, and the venous catheter from the right femoral vein was manipulated into the right renal vein and was tied at the femoral vein. Care was taken not to dissect away the fat and connective tissue at the junction of the renal vein and the vena cava and to avoid handling the renal artery and the kidney. When all lines were in place, the abdomen was closed with metal clips.

Rectal temperature was monitored by using a Telethermometer model 43-TA from the Yellow Springs Instrument Corp. When the temperature fell below 37°C, a heating pad under the dog was turned on.

When possible, eight 30-min clearance periods were obtained from each animal. Arterial and renal venous blood samples were collected simultaneously at the midpoint of each clearance period. When blood samples were collected,

more than 3 times the capacity of the catheter was withdrawn and set aside before obtaining the sample. The samples were then collected over approximately 30 sec in heparinized, siliconized, glass syringes. Each sample had a volume of 5–6 ml; 3–4 ml were immediately centrifuged, and the plasma was separated. The remainder was used for pH and blood-gas analysis with an Instrumentation Laboratory pH/gas analyzer, model 113. After withdrawal of the sample, the blood initially set aside was reinfused and followed by a saline flush equal in volume to the sample withdrawn.

Urine was collected from the ureteral catheter and then centrifuged for removal of any cellular material.

After the last clearance period the animal was sacrificed, the abdomen was opened, and the positions of the catheters were verified. The catheterized kidney was removed, opened, and inspected for evidence of gross abnormality; then several wedge biopsies were obtained and preserved in buffered Formalin. Hematoxylin and eosin slides were prepared and interpreted by the Division of Experimental Pathology.

Glucose in plasma and urine was determined by the hexokinase method (Boehringer). Each unknown sample was done in duplicate, and the individual value recorded was the mean of the duplicate determinations. Renal vein glucose concentrations have been corrected for the abstraction or urinary water.

The standard deviation for the method obtained from a 100 mg/100 ml standard was ± 1.38 mg/100 ml.

Para-aminohippurate in plasma and urine was measured by using the method of Smith et al. (18). Readings were made in duplicate on an Evelyn colorimeter. The extraction ratio for each clearance period was determined and was used in the calculation of renal plasma flow.

Bicarbonate values were calculated from the Henderson-Hasselbalch equation.

Statistical comparisons between groups were made by using the Student *t* test; statistical significance has been indicated when $P < .05$.

RESULTS

The control group was composed of five dogs from which a total of 34 clearance periods was obtained. The bicarbonate-fed group was not clearly alkalotic, although this group was more alkalotic than the controls or ammonium chloride-fed groups. It will be referred to as "bicarbonate-fed," or as "relatively alkalotic." Twenty-four clearance periods were obtained from the three bicarbonate-fed dogs and 20 periods from three acidotic dogs. From three animals made hypoglycemic with small doses (0.1 U/kg, iv) of regular insulin, 23 clearance periods were obtained. Fourteen clearance periods were obtained from two pregnant dogs, one of which was estimated to be about 3 weeks pregnant and the other near term.

From this total of 115 clearance periods, renal gluconeogenesis was demonstrated in 62 instances, i.e., renal vein glucose concentration exceeded arterial glucose concentration. For the entire population, then, gluconeogenesis was found 54% of the time. Gluconeogenesis was found in 56% of periods from controls, 40% from acidotic dogs, 75% from bicarbonate-fed dogs, 39% from hypoglycemic dogs, and in 57% of periods from the pregnant dogs.

In general, there was not a consistent pattern of production in a single animal; periods of production alternated with periods of extraction. Only one animal showed the same pattern for all eight periods, and that was an 18-kg male that had received $NaHCO_3$ for 5 days and showed net production of glucose during every period. A more typical pattern is demonstrated in Table 1, which shows the detailed results of *dog 21*. This was one of the control animals that did not undergo any acid-base manipulation. There was considerable variation in the renal plasma flow over the 5 hr of the experiment. Very little change occurred in acid-base status during that time. Arterial glucose stayed within a range of 109–136 mg/100 ml throughout the procedure. Renal venous glucose was somewhat more closely controlled between 110 and 133 mg/100 ml. Production was noted in three periods with 7.59 mg/min as the greatest rate. Extraction was seen in five periods, but never reached a rate of 2 mg/min. Although urinary glucose concentration varied widely, urinary glucose excretion never reached 0.3 mg/min.

The functional data for all of the groups are contained in Tables 2, 3, and 4. In Table 2 each experimental group is compared to control, and significant differences are marked by an asterisk. In Table 3 acidotic and bicarbonate-fed animals are compared; in Table 4 each of the clearance periods from the acidotic, bicarbonate-fed, and control populations is segregated according to production or extraction of glucose, and producers are compared to extractors.

The first set of comparisons is presented in Table 2. It should be noted that arterial and renal venous concentrations of glucose differ from control only in the hypoglycemic animals. The magnitude of the difference between renal venous and arterial glucose concentrations is indicated as V-A. Acidotic animals showed a negative value for this number and thereby differed significantly from controls ($P < .02$). Conversely, bicarbonate-fed animals showed a markedly positive value for this number and exceeded controls by a significant degree ($P < .025$). Another significant difference from control was noted in the rate of production of glucose expressed in micromoles per minute per kilogram. The acidotic group showed significant extraction of glucose and differed from the control group by 1.48 μmoles/min per kg. Although bicarbonate-fed animals showed a rate of production higher than controls, the difference was not demonstrably significant. Hypoglycemic and pregnant animals did not differ significantly from controls either in the value of V-A or in the rate of production of glucose. Urinary glucose concentrations varied widely in all groups and were clearly different from control values only in the hypoglycemic dogs.

There were significant variations in acid-base balance in the different groups. Arterial pH was lower than control in the acidotic dogs and higher in the bicarbonate-fed dogs. Bicarbonate was significantly lower in the acidotic group. Hypoglycemic dogs showed acidosis; pregnant dogs were alkalotic. Arterial P_{CO_2} was lower than normal in all groups including the controls. The degree of alveolar hyperventilation noted was essentially the same in all

TABLE 1. *Summary of typical experiment*

Event	A Glu, mg/100 ml	V Glu, mg/100 ml	A Glu, mg/100 ml	U Glu, mg/100 ml	Data for Right Kidney Only							A pH	A P_{CO_2}	RV pH	RV P_{CO_2}
					E*	RPF, ml/min	RPF, ml/min per kg	Glu Prodn,† mg/min	Glu Extracn,† mg/min	Glu Prodn, μmoles/min per kg	Glu Extracn, μmoles/min per kg				
Anesth. U_1															
A_1V_1	119.6	119.5	−.1		.81	42.7	2.5		.01		.03	7.40	26.5	7.40	30
U_2				22.4											
A_2V_2	120.4	132.6	12.2		.79	61.9	3.6	7.59		2.48		7.41	25	7.42	27.5
U_3				24.5											
A_3V_3	129.6	133.3	3.7		.78	58.7	3.5	2.16		0.7		7.41	24	7.44	25.5
U_4				31.1											
A_4V_4	135.9	132.9	−3.0		.87	53.3	3.1		1.55		.51	7.41	27	7.42	31
U_5				38.1											
A_5V_5	132.6	131.2	−1.4		.83	72.1	4.2		.97		.32	7.44	28	7.43	30.5
U_6				73.4											
A_6V_6	124.6	122.9	−1.7		.70	107.9	6.4		1.62		.53	7.44	24.5	7.45	24.5
U_7				65.1											
A_7V_7	120	118.7	−1.3		.79	54	3.2		.57		.19	7.45	25	7.43	27.5
U_8				61.7											
A_8V_8	109.1	110.3	1.2		.81	52.1	3.1	.69		.23		7.43	30	7.34	28
End U_8				24.5											

* Extraction ratio. † Glucose flux = A Glu × RPF-[(V Glu × RPF) + U Glu]. Positive values = extraction.

TABLE 2. *Comparison of experimental groups to controls*

Group	A Glu, mg/100 ml	V Glu, mg/100 ml	V-A Glu, mg/100 ml	U Glu, mg/100 ml	A pH	A P_{CO_2}	A HCO_3	RV pH	RV P_{CO_2}	RV HCO_3	Data for Data for Right Kidney Only					
											E	RPF, ml/min	Prodn, mg/min	Extracn, mg/min	Prodn, μmoles/min per kg	Extracn, μmoles/min per kg
Control	122.8	124.4	1.6	31.6	7.37	29.4	15.7	7.37	31.2	16.5	.81	87	1.07		.33	
Acidotic	127.3	122.3	−5.0*	38.7	7.17*	33.3	11.4*	7.23*	36.8	14.6	.81	72		3.23		1.10*
HCO_3^- fed	124	131.6	7.6*	32	7.39	28.4	16.6	7.39	31.8	18.6	81	42*	3.64		1.02	
Hypoglycemic	55*	54.7*	.3	17.7*	7.33*	28.4		7.32*	25.8		.78	54*	.15			.03
Pregnant	128.7	130.7	2.0	17.9	7.45*	20.6*		7.45*	22.6*		.76	106	2.4		.57	

* $P < .05$.

groups and, therefore, was not the result of the metabolic alterations in acid-base balance. At any rate, the degree of hypocapnea present was essentially constant in all groups and therefore should not be implicated as causing specific differences between groups.

The extraction ratios in all of the groups were essentially identical. There was a real difference in renal plasma flow, however, with significant depression of the renal plasma both the bicarbonate-fed and the hypoglycemic groups. The reasons for this are not clear; surgery was not prolonged or difficult in these dogs.

The length of the experiment and rectal temperature were also analyzed in all groups. The time from administration of anesthesia to the moment when a blood sample was drawn was noted in each clearance period. Those times were averaged for each group as a gross index indicating the duration of the procedure. There was no clear difference between any of the experimental groups and controls. Rectal temperature was recorded when bloods were drawn in as many cases as possible. All dogs were somewhat hypothermic compared to the 38.5–39 C normal value for dogs.

In summary, Table 2 compares each of the experimental groups to the control population. The acidotic dogs had a significantly lower V-A value than controls and showed significant extraction of glucose. The bicarbonate-fed population had a V-A value significantly greater than controls. The rate of net production by the bicarbonate-fed dogs exceeded the rate in the controls, but the difference was not clearly significant.

Table 3 contains the data pertinent to the second question. If dogs with chronic metabolic acidosis are compared to those fed bicarbonate, do they differ in rates of renal gluconeogenesis? Again, significant differences are marked by an asterisk. The V-A value was 12.6 mg/100 ml greater in the relatively alkalotic dogs than in the acidotic ones. Urinary glucose concentration was similarly higher. Renal

TABLE 3. *Comparison of acidotic and HCO_3^- fed dogs*

Group	A Glu, mg/100 ml	V Glu, mg/100 ml	V-A Glu, mg/100 ml	U Glu, mg/100 ml	A pH	A P_{CO_2}	A HCO_3	RV pH	RV P_{CO_2}	RV HCO_3	Data for Right Kidney Only					
											E	RPF, ml/min	Prodn, mg/min	Extracn, mg/min	Prodn, μmoles/min per kg	Extracn, μmoles/min per kg
Acidotic	127.3	122.3	−5.0*	18.7*	7.17*	35.3	11.4*	7.23	36.8*	14.6	.81	72*		3.23*		1.10*
HCO_3^- fed	124	131.6	7.6	32	7.39	28.4	16.6	7.39	31.8	18.6	.81	42	3.64*		1.02*	

* $P < .05$.

TABLE 4. *Comparison of periods showing production to periods showing extraction*

Group	A Glu, mg/100 ml	V Glu, mg/100 ml	V-A Glu, mg/100 ml	U Glu, mg/100 ml	A pH	A P_{CO_2}	A HCO_3	RV pH	RV P_{CO_2}	RV HCO_3	Data for Right Kidney Only					
											E	RPF, ml/min	Prodn, mg/min	Extracn, mg/min	Prodn, μmoles/min per kg	Extracn, μmoles/min per kg
Net production	124.6	132.9*	8.3*	31.8	7.34	29.3	15.0	7.35	32.2	17	.82	65.3	4.75*		1.39*	
Net extraction	124.0	116.8	−7.2	24.5	7.30	32.1	15.0	7.32	34.4	16.1	.80	73.2		4.68*		1.45*

* $P < .05$

plasma flow was greater in the acidotic dogs. The acidotic dogs showed net extraction of glucose; the more alkalotic dogs showed net production. The difference in rates of production is significant. The difference found in pH and P_{CO_2} of the two groups was predictable. There is essentially no difference in P_{CO_2} or P_{O_2} in arterial or venous blood in these groups. Rectal temperature was higher in the more alkalotic animals. In summary, Table 3 shows that when directly compared to each other the relatively alkalotic dogs produced significantly more glucose than the acidotic dogs, despite a diminished RPF.

The third question asked was, "If clearance periods from control, acidotic, and relatively alkalotic dogs are segregated according to the production or extraction of glucose and not according to dietary manipulation, will acid-base parameters in the producers differ from those in extractors?" The answer, as reflected in Table 4, is no. The similarities are more striking than the differences. There is no meaningful, indeed, almost no measurable, difference in arterial glucose concentration in the two groups. The extraction ratios are nearly identical. There is no significant difference in renal plasma flow. There is only a difference of .04 pH units between the groups, and those periods characterized by net extraction of glucose show the lower pH, although the difference is not statistically meaningful. Arterial HCO_3^- concentrations were identical. The higher P_{CO_2} was in the group showing extraction, but the difference of less than 3 mm Hg is probably not meaningful. When producers are compared to extractors (some dogs being producers in one period and extractors in the next), there is no difference in pH, P_{CO_2}, HCO_3^-, extraction ratio, renal plasma flow, arterial glucose concentration, urinary glucose concentration, or temperature between periods characterized by production and periods characterized by extraction.

Sections from the kidney of each dog were submitted to the Division of Experimental Pathology at the Institute for "blind" evaluation. Two animals were found to have abnormal kidneys. One of the pregnant dogs had thickening of the basement membrane of Bowman's capsule and of the glomerular tufts. The findings were thought to be compatible with a glomerulitis, but no etiology could be established. The second abnormality occurred in one of the three hypoglycemic animals and was a mild interstitial nephritis. Although this is a common abnormality in dog populations, our control and experimental groups were unusually free of canine interstitial nephritis.

In a group comparison no differences in histological appearance, and, in particular, in ischemic changes existed between groups.

DISCUSSION

After Benoy and Elliott (1) demonstrated that kidney slices were capable of carbohydrate synthesis, renal gluconeogenesis was studied because of an interest in diabetes mellitus (2) and the kidney's role in maintaining glucose homeostasis (13). It became clear that renal gluconeogenesis occurred in many species (10), and significant V-A values were demonstrated in some cases (14–16).

These observations were extended by Cohn, Katz, and Kolinsky (5) who reported in 1950 that renal gluconeogenesis occurred in intact, anesthetized dogs, the kidneys of which formed glucose in 40 of 49 clearance periods. Cohn et al. felt that the process was favored during hyperglycemia and noted that rates of renal gluconeogenesis were not related to renal plasma flow.

Subsequently, many investigators tried to discover the factors that regulate rates of renal gluconeogenesis. Concentrations of fatty acids (9), ketone bodies (9), growth hormone (7), thyroxine (7), cortisone (7), adenosine 3',5'-monophosphate (12), DL-carnitine (20), and bicarbonate (20) have been shown to affect rates of gluconeogene-

sis as have diabetes mellitus, the concentration of precursor substance (20), and the acid-base balance of the donor animal and of the medium in which the slices were incubated (6, 8). To date no one has reported an experiment in which all of the factors known to affect renal gluconeogenesis have been controlled simultaneously.

In some cases the reports of the effect of a single variable appear to be in conflict. For instance, Weideman and Krebs (20) showed that, when rat renal cortical slices were incubated in phosphate-buffered saline, increasing the concentration of bicarbonate from 2 to 25 mM increased glucose production from propionate. Conversely, Kamm, Fuisz, Goodman, and Cahill (8) showed that when rat kidney cortical slices were incubated at constant pH and the concentration of bicarbonate was increased from 10 to 70 mM, glucose production from alpha-ketoglutarate decreased. It would appear that the effect of bicarbonate concentration may depend upon the type of precursor used.

Considerations such as these may help to explain why it has not been possible to document in vivo the stimulation to renal gluconeogenesis that is clearly seen in acidotic conditions in vitro. The response in vitro has been shown in several laboratories. The response in vivo has been slight, at best, as reported by Steiner, Goodman, and Treble (19). They found a significant increase in rates of gluconeogenesis in acidotic dogs, but the increase amounted to only 0.25 mg/100 ml and was detectable only with a sophisticated analytical system for glucose determination. Churchill and Malvin (4) did not find an increase in rates of gluconeogenesis in dogs that had chronic metabolic acidosis. They did demonstrate an increase in gluconeogenesis following lactate infusion, and it would be expected that lactate infusion would be an alkalinizing procedure. Roxe, DiSalvo, and Balagura-Baruch (17) did not find any increase in net rate of renal gluconeogenesis in dogs that had chronic metabolic acidosis, and in most cases did not find significant V-A values in dogs in the control or experimental populations.

The present study represents the third report that chronic metabolic acidosis does not increase rates of renal gluconeogenesis in intact dogs. In fact, V-A values were lower than control in the acidotic dogs and higher than control in the more alkalotic dogs. Control animals had significantly higher rates of renal gluconeogenesis than acidotic animals. These results, obtained from acidotic, control, and bicarbonate-fed dogs, indicate that chronic metabolic acidosis does not increase the rate of renal gluconeogenesis in intact dogs and that chronic metabolic alkalosis does not depress it. Because there were no meaningful acid-base differences between periods showing production and those showing extraction of glucose acid-base status does not seem an important regulating factor for renal gluconeogenesis. Other factors must have a more important role than acid-base balance in regulating the rate of this process in vivo.

It seemed logical to consider whether arterial hypoglycemia was a potent stimulus to renal gluconeogenesis. The data did not support the contention that it is. Although arterial glucose levels were halved, there was no significant increase in rates of renal gluconeogenesis, and the frequency of gluconeogenesis was decreased. It did not appear that this degree of hypoglycemia represented a significant stimulus to renal gluconeogenesis.

Because pregnancy is associated with increased levels of circulating hormones and a tendency to manifest glucosuria, rates of renal gluconeogenesis were examined in the two pregnant dogs. One was approximately 3 weeks pregnant, the other near term. No significant increase in rates of renal gluconeogenesis was found, and there was no significant increase in urinary glucose concentration.

A third factor considered was renal plasma flow. No correlation between renal plasma flow and rates of renal gluconeogenesis was demonstrable. The group with the highest rates of gluconeogenesis had the lowest renal plasma flow and was the most alkalotic. Cohn, Katz, and Kollinsky (5) also found that renal plasma flow did not correlate with rates of renal gluconeogenesis. Steiner, Goodman, and Treble (19) found that there was not a significant difference in renal plasma flow between their control and acidotic groups, although there was a significant difference in rates of gluconeogenesis. Roxe et al. (17) likewise found no correlation between the two. The data presented here confirm those earlier reports.

There is another factor that conceivably could affect the rates of gluconeogenesis, and that is the structural integrity of the renal parenchyma. Dogs are susceptible to an interstitial nephritis, and it has been reported that in animals over 8 years of age, nephritis is the rule rather than the exception (3). The prevalence of this nephritis was reviewed some years ago. The pathology of this and related canine nephritides has been well described (11). It would be anticipated that in a random population of mongrel dogs the prevalence of this condition would be high. It was surprising to note that it was so low in the present series; not one animal in the control, acidotic, or alkalotic population showed evidence of interstitial nephritis. Since the metabolic consequences of canine interstitial nephritis have not been defined, it seems worthwhile to screen for the presence of this common disease in some fashion.

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The experiments were conducted according to the principles enunciated in "Guide for Laboratory Animal Facilities and Care."

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