

Urine Sodium Concentrations are Predictive of Hypoadrenocorticism in Hyponatremic Dogs: A Retrospective Pilot Study

E.M. Lennon¹, DVM PhD DACVIM, J.B. Hummel², DVM DACVIM, S.L. Vaden³, DVM PhD DACVIM

¹ University of Tennessee College of Veterinary Medicine, 2407 River Dr, Knoxville TN 37996;
elennon1@utk.edu

² IDEXX Diagnostics, Cary, NC; James-Hummel@idexx.com

³ North Carolina State University College of Veterinary Medicine, 1060 William Moore Dr,
Raleigh NC 27607; slvaden@ncsu.edu, (919)513-6235

Short title: Urine Sodium Concentrations Predict Hypoadrenocorticism

Corresponding author: Shelly Vaden, North Carolina State University College of Veterinary
Medicine, 1060 William Moore Drive, Raleigh NC 27606; slvaden@ncsu.edu

Abbreviations:

HypoNa Hyponatremic

This study was presented in abstract form at the 28th annual Forum of the American College of
Veterinary Internal Medicine, Anaheim CA.

Summary

Objectives: To determine if a urine sodium concentration could be used to rule out hypoadrenocorticism in hyponatraemic dogs.

Methods: Review of medical records of hyponatraemic dogs (serum sodium < 135 mmol/L) that had recorded urine sodium concentrations. Twenty hyponatraemic dogs were included; 11 diagnosed with classical hypoadrenocorticism and nine with non-adrenal causes of hyponatraemia. A Wilcoxon sum rank test was used to compare results between groups.

Results: No dog with hypoadrenocorticism had a urine sodium concentration < 30mmol/L. Urine sodium concentration in dogs with hypoadrenocorticism was significantly higher (median 103 mmol/L, range: 41-225), than in dogs with non-adrenal illness (median: 10 mmol/L, range: 2-86) ($p < 0.0005$). Serum sodium concentrations were not significantly different between dogs with hypoadrenocorticism and dogs with non-adrenal illness.

Clinical Significance: These results suggest that urine sodium concentrations can be used to prioritise a differential diagnosis of hypoadrenocorticism in hyponatraemic dogs. A urine sodium concentration < 30 mmol/L in a hyponatraemic dog makes classical hypoadrenocorticism an unlikely cause of the hyponatraemia. Nevertheless, because of the small sample size our results should be interpreted with caution and a larger follow-up study would be valuable.

Keywords

hypoadrenocorticism, aldosterone, hyponatraemia, urine sodium

24

25 **Introduction**

26 Classical primary hypoadrenocorticism is a syndrome that is often challenging to
27 diagnose due to its vague clinical signs and lack of pathognomonic clinicopathologic data.
28 Many dogs with hypoadrenocorticism are critically ill and require expensive care and
29 hospitalisation before a definitive diagnosis is made. Serum cortisol is usually measured by
30 reference laboratories, typically with a waiting period from the time a sample is collected.
31 Therefore, a test available in an emergency setting that could be used to help to prioritise
32 the differential diagnosis of hypoadrenocorticism in a critically ill patient would have value in
33 providing a tentative prognosis prior to expensive care and hospitalisation.

34 In classical hypoadrenocorticism, aldosterone deficiency results in renal sodium
35 wasting and potassium retention, resulting in hyponatraemia and hyperkalaemia (Willard et
36 al., 1982, Melian and Peterson, 1996, Rakich and Lorenz, 1984, Haviland et al., 2016, Adler
37 et al., 2007). Dogs with classical hypoadrenocorticism become total-body volume- and
38 sodium-depleted, which can result in severe neurologic and cardiovascular complications
39 (Melian and Peterson, 1996, MacMillan, 2003, Brady et al., 1999).

40 In a hypovolaemic hyponatraemic state, the renal tubules should actively resorb
41 sodium, resulting in minimal loss of sodium into the urine (Tyler et al., 1987, Kamel et al.,
42 1989, Spasovski et al., 2014, Ball and Iqbal, 2016, Fenske et al., 2010). However, in the
43 case of renal sodium wasting, which occurs with aldosterone deficiency or renal tubular
44 injury, high urine sodium concentrations (greater than 30-40 mmol/L) can result despite
45 hypovolaemia or hyponatraemia (Milionis et al., 2002, Waldrop, 2008, Buffington and
46 Abreo, 2016). In human medicine, urine sodium concentrations are an important part of
47 the diagnostic algorithm for hyponatraemia (Spasovski et al., 2014, Ball and Iqbal, 2016,
48 Fenske et al., 2010). The diagnostic utility of urine sodium concentrations are not well

documented in veterinary patients, although extrapolation from humans has been suggested (Waldrop, 2008). Based on findings in humans, expected urine sodium concentrations in hyponatraemic dogs with classical primary hypoadrenocorticism should be > 30 mmol/L, while dogs with hyponatraemia due to most other common causes (hypovolaemia, vomiting and diarrhoea, sepsis, and effusions) should have renal conservation of sodium, resulting in small amounts of sodium in the urine (< 30 mmol/L). Therefore, measurement of a urine sodium concentration may be a useful diagnostic tool to prioritise the likelihood of hypoadrenocorticism in cases with consistent history, physical examination, and serum chemistry findings.

Although many clinicians are familiar with measurement of fractional excretion of electrolytes, where the electrolyte is normalised to creatinine, the absolute measurement of electrolyte concentrations can provide useful information even in the absence of normalisation to creatinine. Urine sodium excretion has been described in normal dogs, but expected ranges have not been established for dogs with hyponatraemia (DiBartola et al., 1980, Hartenbower et al., 1974). In the case of total body hyponatraemia and normal renal tubular function, sodium is highly conserved; almost all sodium is resorbed from the renal tubule, resulting in very small amounts of sodium in the urine, regardless of the degree of urine concentration as measured by the urine specific gravity or the urine creatinine concentration (Ball and Iqbal, 2016, Spasovski et al., 2014).

In humans, there are limited causes of hyponatraemia with absolute urine sodium concentration > 30 -40 mmol/L. These situations include the syndrome of inappropriate ADH secretion (SIADH), classical primary hypoadrenocorticism, osmotic diuresis, hypothyroidism, diuretic usage, renal tubular damage and some causes of vomiting with hypochloraemic alkalosis (Milionis et al., 2002, Ball and Iqbal, 2016, Spasovski et al., 2014, Verbalis et al., 2013). Of these aetiologies, those that occur with relative frequency in the dog are

hypoadrenocorticism, diuretic usage, hypothyroidism, vomiting with hypochloraemic alkalosis and renal tubulopathy.

Therefore, in patients in which hypoadrenocorticism is suspected based on physical examination, complete blood count, serum chemistry, (especially when hyponatraemia is present), and urinalysis, a test to prioritise the likelihood of hypoadrenocorticism before obtaining the results of an adrenocorticotrophic hormone (ACTH) stimulation test would be valuable.

The purpose of this study was to determine if urine sodium concentrations could be used to exclude hypoadrenocorticism as a cause of hyponatraemia in dogs. We hypothesised that a high urine sodium (expected > 30-40 mmol/L based on studies in humans) could exclude classical hypoadrenocorticism as the cause of hyponatraemia in dogs. This may help owners with financial limitations make informed decisions about pursuing treatment for their pet and may help clinicians prioritise differential diagnoses, which may result in an earlier initiation of treatment such as glucocorticoids and mineralocorticoids and limited diagnostic testing.

Materials and Methods

Case identification

A retrospective search for hyponatraemic dogs that had urine sodium concentrations measured contemporaneously was performed by searching a computerised clinical pathology database for urine sodium results from 2003 - 2008, and a paper file of urine sodium results before 2003. Dogs with a serum sodium concentration less than 135 mmol/L (reference range 140-166 mmol/L) in a serum chemistry panel at the time of hospital admission were included in the study.

Medical records were reviewed, and all medications administered as well as final diagnosis were recorded. Final diagnosis was made by the attending clinician at the time the case was treated in the hospital, and available medical records were reviewed to ensure agreement. Exclusion criteria included a diagnosis of diabetes mellitus, administration of intravenous or subcutaneous fluids for greater than 12 hours before collection of urine, or any administration of diuretics, hypertonic saline, mitotane (Lysodren; Bristol Myers Squibb), trilostane (Vetoryl; Dechra), mineralocorticoids, aminoglycosides, contrast media, or chemotherapeutics before collection of urine. Twelve hours was chosen as the cutoff time prior to collection of urine in order to mimic a clinical situation, where urine from critically ill dogs is often not collected before initial stabilisation. Dogs were assigned to one of two groups depending on the final diagnosis documented in the medical record by the clinician managing the case. Dogs were diagnosed with hypoadrenocorticism if they had a pre- and post-ACTH cortisol $< 2\mu\text{g/dl}$ without a history of corticosteroid administration.

Urine sodium measurement

Urine sodium was measured using an indirect ion-selective electrode (indirect potentiometry). Instruments used to perform the measurements included Instrumentation Laboratory Genesis 21, Instrumentation Laboratory Monarch, and Roche Cobas system in a university veterinary clinical pathology laboratory. All instruments were validated for use on urine and at a low dynamic range of sodium concentration. Quality control was performed in accordance with manufacturer instructions.

Statistical analysis

A Wilcoxon Sum Rank test was used to evaluate differences between groups and sensitivity and specificity were calculated according to standard methodology. Positive and negative predictive values were calculated using a prevalence of 13%, which is the average

of three previously published studies (Gold et al., 2016, Lennon et al., 2007, Kemppainen et al., 1983).

Results

Forty-one dogs had hyponatraemia and urine sodium concentrations available. Of those, 13 dogs were excluded because of intravenous or subcutaneous fluid administration before collection of urine, five were excluded because of furosemide administration, one was excluded because of mitotane administration, one was excluded because of administration of mineralocorticoids before urine collection, and one was excluded because of hyperglycaemia. In total, 20 dogs were included in the study.

Of the 20 dogs included in the study, 11 had a diagnosis of hypoadrenocorticism (presumed to be classical hypoadrenocorticism due to the presence of hyponatraemia and, in many cases, hyperkalaemia), and the remaining nine dogs had non-adrenal causes of hyponatraemia. Non-adrenal causes of hyponatraemia were effusions (n=4), pyelonephritis (n=1), distemper (n=1), sepsis (n=1), urethral obstruction (n=1), and uncharacterised intracranial disease (n=1).

There was no statistical difference in serum sodium concentration between the dogs with classical hypoadrenocorticism, (median 127, range 106-134) and the dogs with non-adrenal illness (median 131 mmol/L, range 121-133) (Figure 1). Median urine sodium concentration was significantly higher in dogs with hypoadrenocorticism (median 103 mmol/L, range: 41-225 mmol/L) than dogs with non-adrenal causes of hyponatraemia (median 10 mmol/L (range: 2-86 mmol/L), $p < 0.0005$) (Figure 2). Based on widely used cut-offs in human medicine as well as the results of this study, 30 mmol/L was chosen as a cut-off value (Spasovski et al., 2014). None of the dogs with hypoadrenocorticism had a urine sodium concentration < 30 mmol/L. One dog with a non-adrenal cause of

hyponatraemia had a urine sodium concentration > 30 mmol/L. This dog had clear evidence of pyelonephritis documented in the medical record (pyuria and bacteriuria with granular casts and azotaemia).

Sensitivity of a urine sodium > 30 mmol/L to support of a diagnosis of hypoadrenocorticism was 100% (95% confidence interval: 71.51%-100%), and specificity was 88.89% (95% confidence interval: 51.75% to 99.72%). Assuming a prevalence of 13% based on the average of previously published rates,(Lennon et al., 2007, Bovens et al., 2014, Gold et al., 2016) positive predictive value was 61.38% (95% confidence interval: 45.18% to 77.58%) and negative predictive value was 100% (Table 1).

Discussion

The results of this study suggest that urine sodium concentrations might be useful to help prioritise the likelihood of hypoadrenocorticism in hyponatraemic dogs. The finding of a single urine sodium concentration < 30 mmol/L in a hyponatraemic dog indicates that hypoadrenocorticism is unlikely, and other causes of hyponatraemia should be considered. However, a larger study would be necessary to determine if a urine sodium can be used to exclude hypoadrenocorticism as a differential diagnosis using a urine sodium concentration. A urine sodium concentration > 30 mmol/L in a hyponatraemic dog is supportive of, but not diagnostic for, hypoadrenocorticism as a cause of the hyponatraemia (*i.e.* classical hypoadrenocorticism).

In this study, all 11 dogs with hypoadrenocorticism had inappropriately high urine sodium concentrations (> 30 mmol/L) despite serum hyponatraemia, indicating a failure of efficient resorption of sodium in the renal tubule due to a lack of sufficient aldosterone.

One dog in the non-adrenal illness group had a urine sodium concentration > 30 mmol/L. This dog had a diagnosis of pyelonephritis. Primary or secondary renal tubulopathies are also a common cause of elevated urine sodium (> 30 mmol/L) in human patients because of renal salt wasting (Spasovski et al., 2014). In human patients, other causes of hyponatraemia with a urine sodium concentration > 30 mmol/L include the syndrome of inappropriate ADH secretion (SIADH), osmotic diuresis, hypothyroidism, diuretic usage, renal tubular damage and some causes of vomiting with hypochloraemic alkalosis. Therefore, these differential diagnoses should be considered in the case of urine sodium > 30 mmol/L (Ball and Iqbal, 2016, Spasovski et al., 2014). In contrast, 8/9 of the dogs with non-adrenal illness had urine sodium concentrations < 30 mmol/L, as would be expected in the case of other causes of hyponatraemia, such as hypovolaemia, in which sodium is conserved (Spasovski et al., 2014).

Therefore, a urine sodium concentration < 30 mmol/L can be used to support the exclusion of classical hypoadrenocorticism as the cause of a dog's hyponatraemia. Specifically, a dog with hyponatraemia due to hypoadrenocorticism would be expected to have an inappropriately high urine sodium concentration. If urine sodium concentration is < 30mmol/L, hyponatraemia is unlikely to be due to hypoadrenocorticism or other primary or secondary tubulopathies. Other differential diagnoses that should be considered include sepsis, other causes of hypovolaemia, effusions, and vomiting and diarrhoea.

The measurement of a urine sodium concentration could potentially be performed on in-house chemistry analysers since the technology to measure sodium in urine samples, ion-selective electrodes, are available in these machines. However, many available in-house analysers are not validated by the manufacturers for use on urine. If manufacturers offered this validation, this test would provide rapid, in-house results, enabling clinicians to prioritise a differential diagnosis of hypoadrenocorticism as a cause of hyponatraemia before receiving results of an ACTH stimulation test.

A limitation of this study is the small sample size and retrospective nature. A larger prospective clinical study which measured serum and urine sodium as well as aldosterone would be useful in order to evaluate the utility of this test to rule out a diagnosis of hypoadrenocorticism. Another limitation of this study was that serum aldosterone concentrations were not measured to confirm that the dogs had classical hypoadrenocorticism but hyponatraemia (serum sodium < 135 mmol/L) was used as a surrogate marker.

Urine sodium concentrations have not been investigated in atypical hypoadrenocorticism in dogs with normal serum sodium concentrations; if hypoadrenocorticism is highly suspected, an ACTH stimulation test should be performed. In this study, we have only evaluated urine sodium concentrations in hyponatraemic dogs, so the expected value in normonatraemic dogs with hypoadrenocorticism are unknown.

In conclusion, the authors propose that measuring urine sodium may be used to exclude hypoadrenocorticism with aldosterone deficiency as a cause of hyponatraemia, but a larger prospective study is necessary to further evaluate the utility of this test. A urine sodium concentration < 30 mmol/L in a hyponatraemic dog indicates that classical hypoadrenocorticism an unlikely cause of the hyponatraemia.

Figure Legends

Figure 1: Serum sodium concentrations are similar between dogs with hypoadrenocorticism and dogs with non-adrenal causes of hyponatraemia (Other HypoNa). $p=0.37$

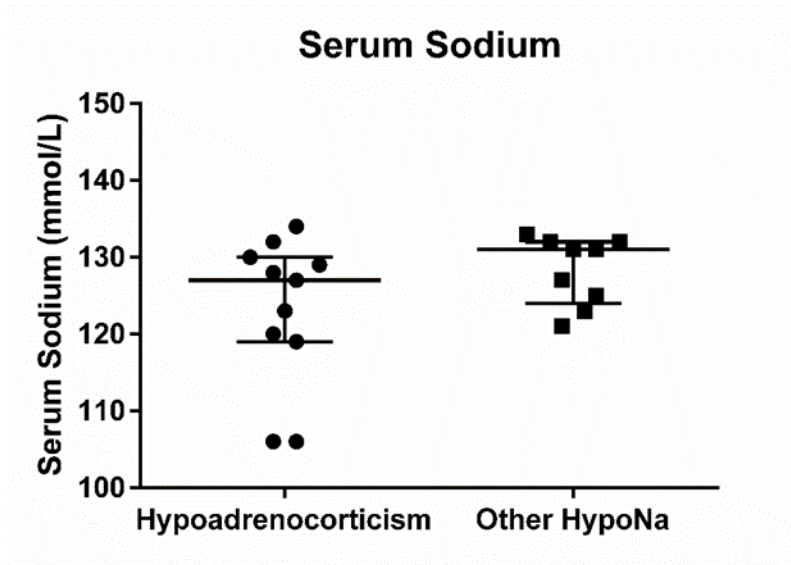


Figure 2: Urine sodium concentrations are higher in dogs with hypoadrenocorticism than non-adrenal illness (Other HypoNa). No dogs with hypoadrenocorticism had a urine sodium < 30 mmol/L, indicated by the dashed line. $p < 0.0005$.

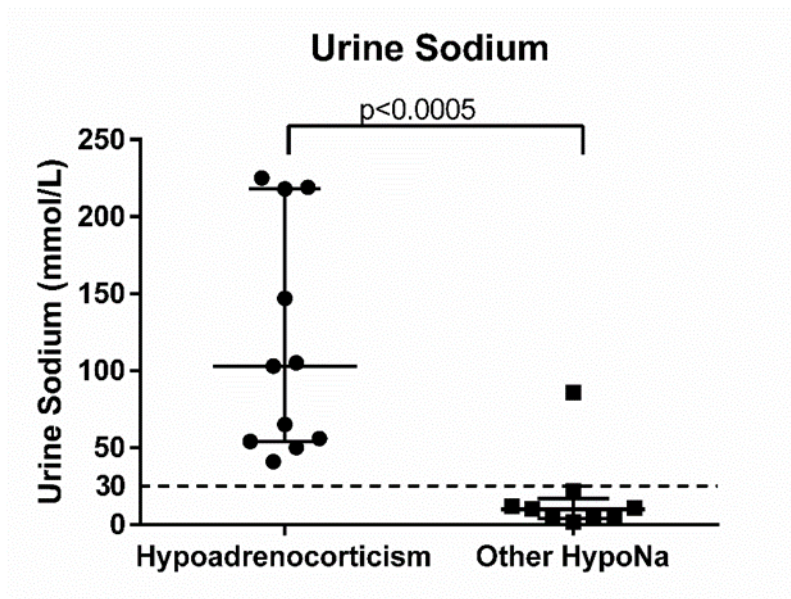


Table 1. Sensitivity and specificity of a urine sodium concentration for ruling out hypoadrenocorticism in hyponatremic dogs.

	Hypoadrenocorticism	Non-adrenal illness
Urine sodium > 30	11	1
Urine sodium < 30	0	8

Sensitivity: 100% (95% CI: 71.51%-100%); specificity: 88.89% (95% CI: 51.75% to 99.72%). Positive predictive value: 61.38% (95% CI: 45.18% to 77.58%); negative predictive value: 100%, assuming a prevalence of 13%.

No conflicts of interest have been declared.

- ADLER, J. A., DROBATZ, K. J. & HESS, R. S. 2007. Abnormalities of serum electrolyte concentrations in dogs with hypoadrenocorticism. *J Vet Intern Med*, 21, 1168-73.
- BALL, S. G. & IQBAL, Z. 2016. Diagnosis and treatment of hyponatraemia. *Best Pract Res Clin Endocrinol Metab*, 30, 161-73.
- BOVENS, C., TENNANT, K., REEVE, J. & MURPHY, K. F. 2014. Basal serum cortisol concentration as a screening test for hypoadrenocorticism in dogs. *J Vet Intern Med*, 28, 1541-5.
- BRADY, C. A., VITE, C. H. & DROBATZ, K. J. 1999. Severe neurologic sequelae in a dog after treatment of hypoadrenal crisis. *J Am Vet Med Assoc*, 215, 222-5, 210.
- BUFFINGTON, M. A. & ABREO, K. 2016. Hyponatraemia: A Review. *J Intensive Care Med*, 31, 223-36.
- DIBARTOLA, S., CHEW, D. & JACOBS, G. 1980. Quantitative urinalysis including 24-hour protein excretion in the dog. *Journal of the American Animal Hospital Association*, 16, 537-546.
- FENSKE, W., MAIER, S. K., BLECHSCHMIDT, A., ALLOLIO, B. & STORK, S. 2010. Utility and limitations of the traditional diagnostic approach to hyponatraemia: a diagnostic study. *Am J Med*, 123, 652-7.
- GOLD, A. J., LANGLOIS, D. K. & REFSAL, K. R. 2016. Evaluation of Basal Serum or Plasma Cortisol Concentrations for the Diagnosis of Hypoadrenocorticism in Dogs. *J Vet Intern Med*, 30, 1798-1805.
- HARTENBOWER, D. L., FRIEDLER, R. M., COBURN, J. W., MASSRY, S. G. & SELLERS, A. 1974. Spontaneous variations in electrolyte excretion in the awake dog. *Proc Soc Exp Biol Med*, 145, 648-53.
- HAVILAND, R. L., TOAFF-ROSENSTEIN, R. L., REEVES, M. P. & LITTMAN, M. P. 2016. Clinical features of hypoadrenocorticism in soft-coated wheaten terrier dogs: 82 cases (1979-2013). *Can Vet J*, 57, 387-94.
- KAMEL, K. S., MAGNER, P. O., ETHIER, J. H. & HALPERIN, M. L. 1989. Urine electrolytes in the assessment of extracellular fluid volume contraction. *Am J Nephrol*, 9, 344-7.
- KEMPPAINEN, R. J., THOMPSON, F. N. & LORENZ, M. D. 1983. Use of a low dose synthetic ACTH challenge test in normal and prednisone-treated dogs. *Res Vet Sci*, 35, 240-2.
- LENNON, E. M., BOYLE, T. E., HUTCHINS, R. G., FRIEDENTHAL, A., CORREA, M. T., BISSETT, S. A., MOSES, L. S., PAPICH, M. G. & BIRKENHEUER, A. J. 2007. Use of basal serum or plasma cortisol concentrations to rule out a diagnosis of hypoadrenocorticism in dogs: 123 cases (2000-2005). *J Am Vet Med Assoc*, 231, 413-6.

- MACMILLAN, K. L. 2003. Neurologic complications following treatment of canine hypoadrenocorticism. *Can Vet J*, 44, 490-2.
- MELIAN, C. & PETERSON, M. E. 1996. Diagnosis and treatment of naturally occurring hypoadrenocorticism in 42 dogs. *J Small Anim Pract*, 37, 268-75.
- MILIONIS, H. J., LIAMIS, G. L. & ELISAF, M. S. 2002. The hyponatraemic patient: a systematic approach to laboratory diagnosis. *Cmaj*, 166, 1056-62.
- RAKICH, P. & LORENZ, M. 1984. Clinical signs and laboratory abnormalities in 23 dogs with spontaneous hypoadrenocorticism. *Journal of the American Animal Hospital Association*, 20, 647-649.
- SPASOVSKI, G., VANHOLDER, R., ALLOLIO, B., ANNANE, D., BALL, S., BICHET, D., DECAUX, G., FENSKE, W., HOORN, E. J., ICHAI, C., JOANNIDIS, M., SOUPART, A., ZIETSE, R., HALLER, M., VAN DER VEER, S., VAN BIESEN, W. & NAGLER, E. 2014. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol*, 170, G1-47.
- TYLER, R. D., QUALLS, C. W., JR., HEALD, R. D., COWELL, R. L. & CLINKENBEARD, K. D. 1987. Renal concentrating ability in dehydrated hyponatraemic dogs. *J Am Vet Med Assoc*, 191, 1095-100.
- VERBALIS, J. G., GOLDSMITH, S. R., GREENBERG, A., KORZELIUS, C., SCHRIER, R. W., STERNS, R. H. & THOMPSON, C. J. 2013. Diagnosis, evaluation, and treatment of hyponatraemia: expert panel recommendations. *Am J Med*, 126, S1-42.
- WALDROP, J. E. 2008. Urinary electrolytes, solutes, and osmolality. *Vet Clin North Am Small Anim Pract*, 38, 503-12, ix.
- WILLARD, M. D., SCHALL, W. D., MCCAWE, D. E. & NACHREINER, R. F. 1982. Canine hypoadrenocorticism: report of 37 cases and review of 39 previously reported cases. *J Am Vet Med Assoc*, 180, 59-62.