Polydipsia in the Dog—Symposium 1, 2 & 3

The Differential Diagnosis of Polyuric Syndromes in the Dog

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Abstract—The clinical and pathological criteria employed for the analysis of polyuric syndromes in the dog are described. The diabetes insipidus syndrome is defined and its causes are discussed. It is suggested that there may be a disturbance in several of the systems responsible for water conservation in cases of diabetes insipidus, including a disturbance of thirst regulatory mechanisms. The factors responsible for polyuria in cases of Canine Cushing’s syndrome are discussed, and it is concluded that these are at present obscure.

INTRODUCTION

In the course of evolution from an aquatic to a terrestrial environment, vertebrates were confronted with a major problem: the conservation of precious water and sodium if they were to avoid fatal dehydration. Thus sensitive mechanisms were developed, aimed at water and salt conservation which centred on the so-called hypothalamo-neurohypophysial-renal axis and the adrenal cortex. It is with some of the disturbances of these mechanisms, their pathogenesis and differential diagnosis, that this paper is concerned.

Several canine diseases are known to be associated with a marked and persistent disturbance of water metabolism resulting in polyuria and polydipsia. The main diseases characterised by persistent polyuria, together with some known potential disorders of water metabolism, which have not as yet been unequivocally identified in the dog, are listed in Table 1.

Diabetes mellitus, chronic interstitial nephritis and the cystic hyperplasia-pyometra complex of bitches have been well documented (Wilkinson, 1962; Hoe and O'Shea, 1965; Dow, 1957; Asheim, 1963), and are not considered in detail here.

On the other hand, the diabetes insipidus syndrome is little understood, the nomenclature is confused, and both human and veterinary medical literature describe many cases which would not satisfy the minimal clinical and pathological

<table>
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<th>Clinical condition</th>
<th>Aetiology</th>
<th>Principal functional abnormality responsible for polyuria</th>
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<tr>
<td>Diabetes mellitus syndrome</td>
<td>Complex and variable, associated with a relative or absolute lack of insulin</td>
<td>Renal insensitivity to action of vasopressin arising from an osmotic diuresis due to glycosuria. Renal insensitivity to action of vasopressin arising probably from renal tubular damage due to bacterial toxins (Asheim (1963)).</td>
</tr>
<tr>
<td>Pyometra—endometritis complex of bitches</td>
<td>Complex: hormonal imbalance and inflammatory. (Dow (1959))</td>
<td>Renal insensitivity to action of vasopressin arising from— (a) Osmotic diuresis (increased solute output per residual nephron) (b) Lowered permeability of residual renal tubules and collecting ducts (c) Structural alterations of renal vasculature (d) Structural damage to interstitial tissue of renal medulla</td>
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<tr>
<td>Chronic interstitial Nephritis</td>
<td>Inflammatory</td>
<td>Similar to chronic interstitial nephritis but unassociated with raised blood urea levels. (Congenital tubular defects leading to nephrogenic diabetes insipidus have not yet been recognised in the dog). Inadequate secretion of vasopressin. (Resistance of hypothalamic osmoreceptors to plasma hypertonicity may possibly occur but has not yet been described in dogs). Possibly associated with excessive inactivation of vasopressin.</td>
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<td>Diabetes insipidus syndrome</td>
<td>4 main variants— (1) Nephrogenic: e.g. arising from renal medullary fibrosis</td>
<td><strong>Note:</strong> (b), (c) and (d) interfere with production of hypertonic medullary interstitial fluid. <strong>Note:</strong> Inadequate secretion of vasopressin. (Resistance of hypothalamic osmoreceptors to plasma hypertonicity may possibly occur but has not yet been described in dogs). Possibly associated with excessive inactivation of vasopressin.</td>
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<td>(2) Hypothalamo-neurohypophysial e.g. arising from destruction of neurones of supraoptic and paraventricular nuclei.</td>
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<td>(3) Cases of uncertain pathogenesis associated with liver damage.</td>
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<td>(4) Possible but unestablished variants in dogs</td>
<td>(i) Lesions of thirst centre causing excessive thirst with or without adequate neurohypophysial function. (ii) Acquired habitual (psychogenic) Renal insensitivity to action of vasopressin arising from impaired sodium transport in loop of Henle. Renal insensitivity to action of vasopressin associated with lesions in renal tubules</td>
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<td></td>
<td>(a) Compulsive (Primary) Polydipsia (Richards &amp; Sloper 1969)</td>
<td>Inadequate levels of circulating vasopressin Inadequate levels of circulating vasopressin</td>
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<td></td>
<td>(b) Potassium deficiency e.g. in chronic diarrhoea</td>
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<td>(c) Hypercalcaemia and hypercalciuria</td>
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<td>(d) Antibody to vasopressin (Roth, Glick, Klein and Petersen, 1966)</td>
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<td></td>
<td>(e) Inherited biochemical disorder of vasopressin synthesis in certain strains of rat. (Valtin et al., 1962)</td>
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<tr>
<td>Canine Cushing's syndrome</td>
<td>Hyperadrenocorticism associated with adrenal cortical hyperplasia, or neoplasia (autonomous or ACTH dependent)</td>
<td>Inadequately understood (? Abnormal electrolyte metabolism) (? Liver damage)</td>
</tr>
</tbody>
</table>
criteria suggested by Richards and Sloper (1969). In fact only two recently described cases of canine diabetes insipidus (Henry and Sieber, 1965; and Wirth, 1966) have satisfied the clinical criteria and none, apart from the cases reported by Richards and Sloper (1964) and Sloper, Karim and Richards (1967) have satisfied both clinical and pathological diagnostic criteria.

Polyuria is also known to be associated with the so-called canine Cushing's syndrome, and recently some well documented cases have been described by Capen, Martin and Koestner (1967), and Siegel, O'Brien, Pyle and Schryver, (1967). Although the criteria for diagnosis of this syndrome are clearly outlined, these cases do not unfortunately satisfy the criteria necessary for a full analysis of polyuric syndromes.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

In contrast to the relative lack of adequate clinical and pathological data on the diabetes insipidus syndrome, the last three decades have witnessed numerous far-reaching advances in knowledge relating to the physiological control of water

![Diagram of a sagittal section through the hypothalamo-neurohypophysial system of the dog. (Modified from Rothballer and Skoryna, 1960).](image)
metabolism and the anatomical sites relevant to this control. (See Sloper, 1966; and Pickford, 1966). This knowledge forms the basis of the modern approach to the clinical and pathological analysis of polyuric disorders in the dog.

Current concepts regarding the role of the hypothalamo-neurohypophysial-renal axis and the adrenal cortex in water and salt conservation can be briefly summarised as follows—water resorption by the kidney occurs by three interrelated processes; the first mechanism, by which the bulk (approximately 85 per cent) of the water of the glomerular filtrate is passively resorbed, is dependent on the active secretion of sodium by the proximal convoluted tubules and ascending loops of Henle. (Pitts, 1963). The second process determines the excretion or resorption of the remaining fraction of the tubular filtrate and depends on the permeability of the distal convoluted tubules and collecting ducts, and is under the control of antidiuretic hormone (ADH—vasopressin). Thus, under conditions of hydropenia the plasma tonicity (osmolality) rises, a process which stimulates hypothalamic “osmoreceptors” (Verney, 1947; Jewell and Verney, 1957), resulting in secretion of anti-diuretic hormone by neurones situated in the supraoptic (S.O.N.) and paraventricular (P.V.N.) nuclei of the hypothalamus (see Fig. 1), (Bargmann and Scharrer, 1951), thereby increasing the distal tubular and collecting duct permeability to water (Orloff and Handler, 1965). The third mechanism, which is directly concerned with the maintenance of blood volume and sodium levels is under the corticosteroid hormone aldosterone, the secretion of which is controlled by the “renin-angiotensin” system (Brown, Fraser, Leven and Robertson, 1968).

Further fundamental advances in the understanding of the elaboration and secretion of posterior pituitary principles by the hypothalamo-neurohypophysial system (H.N.S.) stemmed from the cytochemical and radioisotope incorporation studies of Sloper, (1954, 1955); Sloper and Adams (1956); and Sloper, Arnott and King (1960).

CLASSIFICATION OF THE DIABETES INSIPIDUS SYNDROME

Frank (1794) originally defined diabetes insipidus as a condition characterised by severe polyuria, unassociated with either renal disease or with glycosuria, and this broad definition was widely accepted throughout the 19th century. Following the discovery of the role of the neurohypophysis a tendency arose to restrict the term to those cases with evidence of neurohypophysial damage. A more recent trend has been to use the term in a broader sense to embrace other conditions such as “vasopressin-resistant”, “vasopressin-inactivation” and “nephrogenic” diabetes insipidus. Further confusion is apparent by the exclusion from the syndrome of cases suffering from a primary (compulsive) polydipsia arising from a disturbance of the thirst centres, even though cases in man at least, often exhibit some degree of renal resistance to vasopressin and may also show a diminished ability to secrete vasopressin (Barlow and de Wardener, 1959).

Moreover, in man, comparable dysfunctions have been postulated in association with potassium deficiency (Kleeman and Maxwell, 1959); while in association with hypercalcaemia, Fourman and Leeson (1959) have suggested that there may be not only some degree of vasopressin resistance but also a primary polydipsia.

With these considerations in mind, and following a detailed analysis of 5 cases
of canine diabetes insipidus Richards and Sloper (1969) proposed that the term diabetes insipidus could reasonably be used to embrace all conditions which exhibit severe persistent polyuria and polydipsia, in which the urinary concentration is low and in which there is no uraemia or glycosuria. They suggested that recent attempts to ascribe the pathogenesis of the syndrome in individual cases to the dysfunction of one of the several mechanisms responsible for water conservation to the exclusion of others, had tended to conceal the complexity of the syndrome. They concluded that in diabetes insipidus the possibility should be entertained of a disturbance in several of the systems responsible for water conservation. These provisos do not, however, preclude classification of the syndrome according to the nature of the basic dysfunction into four main variants as listed in Table 1.

**DIAGNOSTIC CRITERIA IN DIABETES INSIPIDUS**

These are listed in Table 2.

**A. Clinical**

1. **Minimal criteria for recognition of the syndrome**

   Following a thorough clinical and biochemical examination, an essential step in the analysis of polyuric disorders is the measurement of water intake and urine output. However, in assessing the history of individual cases it should be remembered that such factors as excessive exercise and high ambient temperatures will lead to increased water loss and a compensatory thirst.

   Water intake and urine output should be measured over a period of at least 24 hours in view of the possibility of diurnal variations in fluid consumption. Measurements are made by placing the dog in a metabolism cage which need

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**Table 2. Diagnostic Criteria for Diabetes Insipidus**

(A) Minimal criteria for the recognition of the syndrome.

1. Renal and hepatic function tests on blood and urine.
2. Haematology.
3. Evidence of—
   (a) Excessive fluid intake (polydipsia) (e.g. greater than 5 ml/Kg./hour)
   (b) Excessive urine output (polyuria) (e.g. greater than 3.8 ml/Kg./hour) with urine of low concentration (Specific Gravity less than 1.012 or osmolality less than 400 m./Osm/Kg.)

(B) Minimal criteria for differentiation of the main variants of the syndrome.

Clinical

1. Study of the effect on urine concentration (specific gravity or osmolality) of—
   (a) Water deprivation causing a 3–5 per cent fall in body weight.
   (b) Intramuscular injection of a ‘saturating’ dose of vasopressin tannate in oil (5–10 units) in the hydrated state.
2. Estimation of serum or plasma osmolality during free access to water.

Pathological

1. Study of serial sections of the hypothalamo-neurohypophysial system and of distribution of cystine-rich neurosecretory material.
2. Examination of sections of adenohypophysis, liver, kidney, adrenals, pancreas, thyroid and gonads.
not be elaborate in design, and the environmental temperature and humidity should be controlled as far as possible. If the dogs are fed during the period of measurement, the water content of the food—which may be considerable—and the amount of food ingested should be taken into account in estimating the 24 hour fluid balance.

It is known that stress acts as a potent stimulus for the release of vasopressin (Verney, 1947), and for this reason it is preferable whenever possible, to make two or three 24 hour estimations so as to allow the patient to become accustomed to the environment.

The 24 hour output of urine is collected in a suitable container and precautions should be taken to avoid undue losses arising from evaporation. This output is measured and the concentration is determined with a hydrometer, specific gravity column (Kabat and Mayer, 1948) or an osmometer.

(Note (a) Hydrometers are standardized for use at 16°C. A correction should therefore be made if the urine is warm or cold; for each 3°C above or below 16°C, 0·001 should be added or subtracted to or from the observed value.

(b) Osmolality is an index of the number of particles contained in 1 Kg. of solvent. It is measured with an osmometer, a cryoscope which determines the freezing point of a solution. Since the freezing point of water is depressed below 0°C by 1·86°C for each 1000 milliosmols, a reading is obtained expressed in milliosmols/Kg. The advantage of osmolality over specific gravity for the assessment of the renal ability to concentrate urine is discussed by de Wardener (1961).

2. **Minimal criteria for the differentiation of the main variants of the syndrome**

It is not yet possible to estimate satisfactorily low or even normal levels of circulating vasopressin (Sawyer, 1966). At present, therefore, reliance must be placed on indirect evidence of a patient’s ability to produce vasopressin by the study of the effects on urine concentration of two tests:

1. the water deprivation test.
2. the ‘pitressin’ test.

(Note. The following description of the tests is designed primarily for the study of water balance in clinical cases and not for the experimental study of water balance which requires very exacting procedures).

(1) **Water deprivation test**

This test measures the ability of the H.N.S. to produce vasopressin under the stress of dehydration. Injections of nicotine and infusions of hypertonic saline are also sometimes employed to stimulate vasopressin secretion.

When performing the water deprivation test it is important to avoid excessive dehydration by ensuring that weight loss at the end of dehydration does not exceed 3–5 per cent of the initial body weight. Cases with renal failure should not be subjected to the test.

**Procedure**

(i) The dog must be fully hydrated before commencing the test, that is, the
patient must be allowed free access to water for at least six hours before dehydration commences. The dog should be encouraged to urinate frequently during the preliminary period of hydration so as to ensure that the urinary bladder is not distended with urine at the commencement of the test. A urine sample is obtained at this stage, either by catheter or free-flow collection, and its concentration is measured.

(Note. Recurrent catheterization is best avoided, but whenever this measure is employed strict aseptic precautions should be taken. It is often possible to collect urine samples by applying pre-pubic pressure).

(ii) After weighing, the dog is placed in a metabolism cage and deprived of food and water until a weight loss of between 3 to 5 per cent of the initial weight is achieved. This weight loss may sometimes be reached in under 6 hours in dogs with severe polyuria. If the dog is not passing urine in the cage the bladder should be emptied at regular hourly intervals to avoid dilution of the final specimen taken at the end of the test.

(iii) When the required weight loss is achieved, the test is discontinued, a final urine sample is collected and its concentration is determined. The urine flow during the test in ml/Kg. body weight/hr. is calculated on the basis of the initial body weight.

(2) 'Pitressin' test
This simple test measures the ability of the kidney to respond to vasopressin and concentrate urine.

This test should follow the water deprivation test after a period, preferably 24 hours, during which the dog is fed and allowed free access to water.

Procedure
(i) Before the dog is placed in the metabolism cage a urine sample is obtained and the body weight is determined. If possible, the urinary bladder should be emptied at this stage. Five to ten units of vasopressin-tannate-in-oil (Pitressin—Parke Davis) is administered by deep intramuscular injection. It is essential that the vial should be warmed and well shaken before its contents are injected, to ensure an even suspension of the active principle.

(ii) The dog is placed in a metabolism cage and no food is given during the course of the test which should be continued for at least 7 to 8 hours after injection. Water is withheld only during the initial stages of the test, for it is important to maintain the weight of the dog as constant as possible by weighing the dog at regular hourly intervals and replacing measured urinary losses with equivalent amounts of water. Urine samples for estimation of concentration should be obtained at regular hourly or two-hourly intervals. As in the water deprivation test, similar precautions should be taken to avoid over-filling of the bladder between the collection of samples.

(iii) After a period of at least 7 hours, but preferably after 12 hours, the test is discontinued, a final urine sample is collected and its concentration is determined. The urine flow during the test is calculated as before.

B. Pathological Criteria
These are listed in Table 2. The post-mortem examination must include the
entire endocrine system and the body weight and weights of the endocrine glands should be recorded. Serial sections of the entire hypothalamo-neurohypophysial system limited anteriorly by the optic chiasm and posteriorly by the mammillary bodies should be examined. Special attention should be paid to the morphology and the number of surviving secretory neurones in the S.O.N. and P.V.N. (Fisher, Ingram and Ranson, 1938; Pickford and Ritchie, 1945). It is essential to study the distribution of cystine-rich neurosecretory material using selective cytochemical techniques (Sloper 1966).

The reaction of neurosecretory cells to various forms of stress and injury has been described by Sloper et al. (1967).

In addition to lesions involving secretory neurones and their tracts, the possibility of damage to other sites in the brain concerned with the regulation of water metabolism should be considered. These sites include the so-called “osmoreceptors” situated close to the preoptic region and paraventricular nuclei (Jewell and Verney, 1957), and thirst centres situated in the lateral hypothalamus as reviewed by Fitzsimons (1966).

Particular attention should be paid to the histological state of the liver and kidneys.

**INTERPRETATION OF CLINICAL FUNCTIONAL TESTS (10 cases)**

The water intake, urine output and response to water deprivation and vasopressin administration in 10 cases of canine diabetes insipidus, compared with findings in normal dogs is shown in Table 3.

1. **Nephrogenic Diabetes Insipidus** (1 case)

   In the single case which exhibited renal insensitivity to vasopressin the urine concentration following water deprivation and pitressin remained below that of plasma, that is below 300 m.Osm./Kg. or Sp. Gravity 1.010. The results of the two tests in this case are shown in Fig. 2 and indicated a total renal insensitivity to vasopressin.

2. **Hypothalamo-neurohypophysial cases** (6 cases)

   **Water deprivation**

   Apart from one case which achieved a urine concentration of 1160 m.Osm./Kg. in which there was possibly an additional element of primary polydipsia arising from disturbed function of thirst centres, the remaining five neurohypophysial cases showed only a slight rise in urine concentration at the end of dehydration, which in all cases was below 304 m.Osm./Kg.

   **Pitressin Test**

   On the other hand, following the administration of vasopression, the urinary concentrations achieved by these cases was considerably higher than in the single case of nephrogenic diabetes insipidus.

   The response to water deprivation and vasopressin in one case of hypothalamo-neurohypophysial diabetes insipidus is shown in Fig. 3.

3. **Cases of Uncertain Pathogenesis** (3 cases)

   In 3 cases listed in Table 3 the pathogenesis of the syndrome was obscure.
TABLE 3. Results of Functional Tests in 10 cases of naturally occurring diabetes insipidus in the dog. Comparison with values in normal dogs.

<table>
<thead>
<tr>
<th>Variety of Case</th>
<th>Water intake m./Kg./hour/ml.</th>
<th>Output ml./Kg./hour</th>
<th>Effect of dehydration (Weight loss: 3-5 per cent) m.Osm/Kg.</th>
<th>Effect of intra-muscular injection of vasopressin (5-10 u.) m.Osm/Kg.</th>
<th>Concentration during free access to water. m.Osm/Kg. or Specific Gravity</th>
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<tr>
<td>Normal</td>
<td>1.73 ± 0.38</td>
<td>0.72 ± 0.24</td>
<td>1060-1180^a</td>
<td>1600-1693^a</td>
<td>546-799^a</td>
</tr>
<tr>
<td>Hypothalamo-neuro-hypophysial (6 cases)</td>
<td>6.0-29.7 (Average: 16.4)</td>
<td>4.5-25.7 (Average: 12.6)</td>
<td>145-304 and 1160^a</td>
<td>665-1020 and 1100</td>
<td>74-187</td>
</tr>
<tr>
<td>Nephrogenic (1 case)</td>
<td>18.1</td>
<td>13.4</td>
<td>130</td>
<td>148</td>
<td>SG. 1.001</td>
</tr>
<tr>
<td>Complex Pathogenesis all with liver damage (3 cases)</td>
<td>7.9-12.0</td>
<td>6.4-8.0</td>
<td>345-552</td>
<td>405-790^4</td>
<td>78-123</td>
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</table>

3. Value of 1160 m.Osm/Kg. recorded in a dog in which there may have been an element of primary polydipsia, superimposed on neurohypophysial inadequacy.
4. Peak reached in 3-4½ hours after injection of vasopressin, instead of 5½-24 hours (average time interval: 12 hrs) in hypothalamo-neurohypophysial cases.
Fig. 2. Response to water deprivation and the administration of 10 units of
vasopressin tannate in oil (Pitressin, Parke Davis) in a case of nephrogenic diabetes insipidus.

Fig. 3. The response to water deprivation and injection of 10 units of vasopressin tannate in oil (Pitressin, Parke Davis) in a case of hypothalamo-neurohypophysial diabetes insipidus.

The urine concentrations achieved following dehydration were higher than in the single case with nephrogenic diabetes insipidus and the cases with neurohypophysial inadequacy.
These results indicated, firstly, that these 3 cases were able to secrete at least some vasopressin and, secondly, that the kidney was partially sensitive to this secretion.

When vasopressin was injected, the peak urine concentrations were lower than in normal dogs and lower than the average peak concentration achieved by dogs with neurohypophysial diabetes insipidus. Moreover, the peak concentrations were reached 3 to 4½ hours after injection, whereas in the 6 neurohypophysial cases the peak was reached after an average time interval of 12 hours. These findings led Richards and Sloper (1969) to postulate that in some cases of diabetes insipidus excessive vasopressin inactivation may be involved in the pathogenesis of the syndrome.

Cases of compulsive polydipsia, hypokalaemia, hypercalcaemia and canine Cushing's syndrome have yet to be analysed using these tests.

PATHOLOGICAL FINDINGS (11 cases)

Nephrogenic Diabetes Insipidus (1 case)

So far only one case has been reported in the dog (Sloper et al. 1967), details of which are shown in Table 3. The kidneys showed diffuse medullary fibrosis which extended to the capsule in the form of narrow bands or wedges sparing extensive areas of the renal cortex (Fig. 4). The glomeruli and renal tubules in these spared areas were apparently normal which probably accounted for the normal blood urea levels found in this case (average value of 7 samples: 37·4 mg. per 100 ml.). Serial sections of the hypothalamo-neurohypophysial system, and sections of endocrine glands and liver revealed no abnormality.

Hypothalamo-neurohypophysial Cases (7 cases—1 incompletely studied clinically)

The pathological findings in 7 dogs with neurohypophysial inadequacy have been described by Sloper et al., 1967. In all there was a reduction in the number of neurones in the S.O.N. and P.V.N., associated with a variety of lesions. In 4 cases there was a chronic meningo-encephalitis, associated in one case with a moderate degree of internal hydrocephalus (Fig. 5). Two cases had adenohypophysial adenomas, one of which shown in Fig. 6., had invaded the median eminence. This case with a urine intake of 13 ml./Kg./hour and a urine output of 9 ml./Kg./hour was, however, able to achieve a urine concentration of 1160 m.Osm/Kg. following dehydration. In fact although much of the hypothalamo-neurohypophysial system including the P.V.N. was destroyed, numerous secretory neurones survived in the anterior S.O.N. These findings raised the possibility of an element of primary polydipsia in this case.

In one case, details of which are discussed by Richards and Sloper (1964), serial sections of the hypothalamo-neurohypophysial system revealed a granuloma situated in the zona externa of the median eminence in which was embedded a nematode larva, probably *Toxocara canis* (Fig. 7).

Capen et al. (1967), described 26 cases in dogs with neoplasms of the adenohypophysis in which diabetes insipidus was the most consistent finding. No details are given regarding the number of surviving secretory neurones in the S.O.N. and P.V.N. but the authors concluded that the disturbances in water balance appeared to arise.
from interruption of the hypothalamo-neurohypophysial nerve tracts. In 16 cases there was also bilateral enlargement of the adrenal glands.

Koestner and Capen (1967) described the ultra-structural changes in the hypothalamo-neurohypophysial system in 6 dogs with diabetes insipidus associated with pituitary neoplasm. In five of these cases there was evidence of hyperadrenocorticism.

In the case described by Henry and Sieber (1965) a diagnosis of traumatic diabetes insipidus following cerebral concussion was made, but no gross or microscopic lesions were seen in the brain or pituitary of this dog, and they postulated that the probable site of the lesion was in the S.O.N. and P.V.N.

Grieg (1963) reported on 3 cases of diabetes insipidus in the dog in which no significant lesions were found at post mortem examination.

Valtin, Schroeder, Benirschke and Sokol (1962) discovered a strain of rats with diabetes insipidus which appeared to secrete oxytocin but little or no vasopressin and was associated with an inherited biochemical disorder of secretory neurones. This discovery raises the possibility that a similar disorder may be responsible for the syndrome in the dog and other species.

Cases of uncertain pathogenesis (3 cases)

In the 3 cases listed in Table 3 in which the pathogenesis of the syndrome was obscure, the pathological findings were variable and difficult to interpret. All had adrenal cortical adenomata, the clinical significance of which was questionable. In addition, hepatic lesions were present in all 3 cases. These lesions differed slightly in each case, the first showing a widespread focal infiltration with inflammatory cells composed of lymphocytes, neutrophils and occasional plasma cells; the second widespread vacuolation of hepatic cells unassociated with fatty change or glycogen infiltration, and in the third there was widespread local vacuolation of hepatic cells, some of which were shown to contain sudanophilic lipid, and in some areas there were conspicuous aggregations of mononuclear cells, mainly lymphocytes (Fig. 8). In 2 cases there was no evidence of damage to the hypothalamo-neurohypophysial system; in the third case an adenohypophysial adenoma had partially destroyed the hypothalamo-neurohypophysial system. However, at least 50 per cent of the secretory neurones in the S.O.N. and P.V.N. had survived. It is therefore unlikely that the disturbance in water balance in this case was due entirely to the neurohypophysial lesion.

**CANINE CUSHING'S SYNDROME**

This condition arises from hyperactivity of the adrenal cortex. This may be due to—

(i) excessive secretion of adrenocorticotropic hormone (ACTH) arising from hypothalamic or adenohypophysial dysfunction, e.g. in cases with functional adenohypophysial adenomas, as described in 16 dogs by Capen et al. (1967).

(ii) excessive secretion of ACTH by neoplastic tissue at other sites, a phenomenon well recognised in man (Ross 1968) but as yet unrecognised in the dog.

(iii) autonomous secretion by a functional adenoma or carcinoma of the adrenal cortex (Siegel et al., 1967).
Fig. 4. Renal cortex in a case of nephrogenic diabetes insipidus showing wedges of fibrous tissue (A) sparing extensive areas in which glomeruli and renal tubules are apparently normal. H & E × 60.

(facing p. 662)
FIG. 5. Moderate degree of internal hydrocephalus in a 4 month old male Boxer puppy with evidence of hypothalamo-neurohypophysial diabetes insipidus.
FIG. 6. Adenohypophysial adenoma (A) in a 6 year old Boxer bitch associated with symptoms of neurohypophysial inadequacy, and possibly of compulsive (primary) polydipsia. (Scale in centimetres.)
Fig. 7. Nematode larva embedded in a granuloma situated in the median eminence in a 2½ year old Great Dane dog with clinical evidence of neurohypophysial inadequacy. Haematoxylin and eosin x 800.
Fig. 8. Liver showing local vacuolation of parenchymal cells associated with a focal infiltration with mononuclear cells, mainly lymphocytes, in a 12 year old male Border Terrier with diabetes insipidus. H & E x 300.
The clinical and biochemical findings in 16 cases of hyperadrenocorticism in the dog have been described by Capen et al. (1967). The main symptoms were polydipsia, muscular weakness, bilaterally symmetrical alopecia, obesity, abdominal distension and hyperpigmentation and mineralization of the skin. The most consistent urinary and haematological alterations in these cases were low urine concentration (average Sp. gravity 1.007) and a marked reduction in the numbers of circulating eosinophils and lymphocytes.

The serum corticosteroids were significantly elevated (average value 18 μg/100 ml.) in the 4 cases in which this measurement was made. The average 24 hour excretion of 17-hydroxycorticosteroids in the 5 cases in which this determination was made, was significantly raised (10.7 mg/24 hr.) above the value of 2.08±0.7 mg./24 hr, reported by Siegel (1965) in the normal dog. Siegel et al. (1967) reported the clinical and biochemical findings, including the results of ACTH and metapyrone tests in a dog with a unilateral adrenal cortical carcinoma.

Additional tests, which in future should be applied in cases of suspected hyperfunction of the adrenal cortex in the dog, include the estimation of cortisol or corticosterone production rates, plasma ACTH levels, and dexamethasone suppression tests (James and London, 1968).

DISCUSSION

The nephrogenic and hypothalamo-neurohypophysial variants of the diabetes insipidus syndrome in the dog can generally be differentiated by employing relatively simple functional diagnostic tests designed to determine firstly the patient’s ability to secrete vasopressin, and secondly the renal response to injected vasopressin. These tests, however, have their limitations as discussed below. Concerning the validity of dehydration as a test of neurohypophysial function, it may be claimed that this procedure might fail to differentiate cases in which the secretory neurones are normal but in which the essential abnormality is a failure of “osmoreceptor” function. At present, however, the only recognised forms of hypothalamo-neurohypophysial diabetes insipidus involve (a) impaired vasopressin synthesis by secretory neurones in certain strains of rat (Valtin et al., 1962), and (b) loss or destruction of secretory neurones in the hypothalamo-neurohypophysial system. Both these abnormalities result in impaired secretion of vasopressin detectable by the water deprivation test (Sloper et al., 1967). Nevertheless, this test is only an indirect measure of the ability of the neurohypophysis to secrete vasopressin and will eventually be replaced by direct measurements of circulating vasopressin levels, but the methods at present available are insufficiently sensitive for this purpose (Sawyer, 1966).

The pitressin test, designed to measure the renal sentitivity to vasopressin, also has its limitations. For example, it cannot discriminate between moderate degrees of renal insensitivity arising from structural alterations in the kidney from that arising following the continued ingestion of large quantities of water as described by de Wardener and Herxheimer (1957), and in human patients with compulsive (primary) polydipsia (Barlow and de Wardener, 1959). In this respect, it is possible that the partial renal insensitivity to vasopressin observed in dogs with hypothalamo-
neurohypophyseal diabetes insipidus may result from the large amounts of water ingested by these animals.

Both the water deprivation and pitressin tests are of limited value in determining the essential abnormality in cases of uncertain pathogenesis, especially in those cases in which there may be an element of excessive vasopressin inactivation, possibly associated with liver damage. They are also of limited value in assessing the degree to which primary polydipsia may be a contributory factor in the pathogenesis of canine diabetes insipidus. The contribution of this factor has yet to be analysed fully; even in man in which the syndrome is well recognised, no cases have been examined at necropsy, but Silverstein et al. (1961) described a strain of rats with primary polydipsia. In affected females no lesions were found in the brain, pituitary, or kidneys, although hydronephrosis was present in males.

Compulsive (primary) polydipsia arises from disordered function of the so-called hypothalamic thirst centres, resulting in a primary polydipsia and a secondary polyuria. The physiological mechanisms involved in thirst control are still obscure (Fitzsimons, 1966). It has long been held that there is a hypothalamic thirst satiety centre, destruction of which leads to primary polydipsia (Nothnagel, 1881; Molitor and Pick, 1925, cited by Fisher et al., 1938). This concept was supported by the work of Smith and McCann (1962), who claimed that injuries to the basal tuberal region of rats caused a polydipsia. This observation raised the possibility that polydipsia in cases with neurohypophyseal damage could be due as much to injury to this area as to injury of the neurosecretory system in view of their close proximity to one another. Furthermore, "thirst" or "drinking centres" have been postulated, destruction of which leads to adipsia or hypodipsia. Stimulation of these centres leads to thirst, as demonstrated by Andersson, Larsson and Persson (1960) in the goat. In the human cases of compulsive polydipsia described by Barlow and de Wardener (1959) the essential dysfunction appeared to be one of thirst regulation, but many patients exhibited a secondary renal insensitivity to vasopressin and in some there was evidence of an impaired ability to secrete vasopressin. Diagnosis in man is usually based on the presence of psychotic symptoms, lowered plasma osmolality and fluctuance of the polyuria and polydipsia. The ability of these patients to produce a concentrated urine following dehydration was significantly greater than in patients with neurohypophyseal diabetes insipidus.

In none of the 10 cases of diabetes insipidus listed in Table 3 was there any evidence of gross overhydration resulting in lowered serum sodium or osmolality values, and symptoms of water intoxication were absent. Nevertheless it was not always possible to correlate the degree of polyuria with the degree of neurohypophyseal damage, an observation which led Richards and Sloper (1969) to postulate that there may be an element of primary polydipsia in diabetes insipidus, regardless of the cause. Indeed, the earlier observation of Kunstmann (1933) quoted by Fisher et al. (1938), lends support to this concept, for he found that after ingesting large quantities of water (up to 10 litres per day) for many days, he suffered from torturing thirst when he attempted to discontinue the experiment.

The main problem appears to lie in the assessment of the degree to which disorders of thirst are superimposed on other forms of diabetes insipidus. Before this assessment can be made in clinical cases in the dog, suitable control preparations of
chronically over-hydrated dogs, with and without experimental lesions of the neurohypophysis and thirst centres, will have to be devised and studied.

Although the association between polyuria and canine Cushing's disease is well established, the factors responsible for the polyuria are not clear. In the series reported by Capen et al. (1967) the polyuria was ascribed mainly to interruption of the hypothalamo-neurohypophysial nerve tracts by "invasive" adenohypophysial adenomas. However, in a subsequent detailed study of these cases, Koestner and Capen (1967) commented that they were not always able to correlate the degree of polyuria with the extent of neurohypophysial damage. In these cases, they postulated that the excessive quantities of ACTH produced by functional adenohypophysial adenomas might be responsible for the development of polyuria, quoting the observations of Sharkey, Perry and Ehni (1961) who noted that cortisol had a diuretic effect.

The pathogenesis of polyuria in cases of Cushing's syndrome is undoubtedly complex. Sirek and Best (1952) noted that dogs treated with cortisone daily for 4–14 days developed a marked polyuria and polydipsia, unassociated with changes in fasting blood sugar levels or glucose tolerance tests. Another factor to be considered is the possible relevance of hypokalaemia in cases of Cushing's syndrome, an abnormality which is known to result in renal tubular lesions and polyuria. Furthermore, Dingman and Despointes (1960) noted that gluco-corticoids appear to suppress the nicotine induced release of vasopressin.

It is evident that further detailed studies will have to be made before the significance of these factors can be assessed.

The role of liver in the pathogenesis of diabetes insipidus is difficult to assess, but along with other tissues, in particular the kidney, the liver contains enzymes which will inactivate vasopressin (Heller and Urban, 1935; Birnie, 1953). In 3 dogs with diabetes insipidus described by Richards and Sloper (1969) (see Table 3), there was a hepatic disturbance suspected clinically because of an elevation of the serum levels of glutamic pyruvic transaminase, alkaline phosphatase and cholesterol and later confirmed post-mortem. It was suggested that the rapidity with which the peak urinary concentration was reached after the administration of vasopressin indicated an increased rate of inactivation of vasopressin, possibly associated with the release of enzymes from damaged hepatic cells. Interestingly enough, Capen et al. (1967) noted enlargement of the liver, associated with macroscopic evidence of fatty change in 14 of the 16 cases with clinical signs of diabetes insipidus and hyperadrenocorticism; however, details of the histological state of these livers was not given.

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POLYDIPSIA IN THE DOG—SYMPOSIUM


Résumé—L'auteur décrit les critères cliniques et pathologiques de l'analyse du syndrome polyuridipsique chez le chien. Il définit le syndrome du diabète insipide et en examine les causes, en formulant l'hypothèse suivante laquelle ce syndrome comporterait éventuellement un désordre des mécanismes déterminant la conservation hydrique, notamment le mécanisme régulateur de la soif.

Zusammenfassung—Die klinischen und pathologischen Kriterien, die für die Analyse der polyurischen Syndrome beim Hund dienen, werden beschrieben. Das Diabetes-insipidus-Syndrom wird definiert und seine Ursachen werden besprochen. Es wird vorgeschlagen, eine Störung in mehreren der für den Wasserhaushalt verantwortlichen Systeme in Fällen von Diabetes insipidus anzunehmen, einschließlich der Störung der Durstregulationsmechanismen.

Die für Polyurie in den Fällen des Cushing-Syndroms beim Hund verantwortlichen Faktoren werden besprochen und daraus gefolgert, dass sie zur Zeit unklar sind.
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