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RENAL FUNCTION IN DOGS WITH PYOMETRA

2. CONCENTRATING AND DILUTING ABILITY

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Pyometra (chronic purulent endometritis) occurs mainly in middle-aged and old bitches which have not whelped in recent years (*Thufvesson* 1953, *Dow* 1958). It is a fairly common disease which becomes manifest in the metoestrus phase of the sexual cycle and which is probably primarily caused by hormonal dysfunction (*Dow* 1959). Increased thirst is one of the most common clinical signs (*Dow* 1958). There is no satisfactory explanation for this polydipsia. It has been demonstrated in a previous report that there is so much antidiuretic hormone in the urine of dehydrated pyometra bitches that insufficient circulating ADH is unlikely to be the cause (*Åsheim* 1963).

The present report is concerned with studies to establish whether renal dysfunction can explain the polydipsia of bitches with pyometra. In this context the ability of the kidneys to form concentrated and dilute urine has received most attention. The concentrating ability of normal kidneys reflects the osmotic hypertonicity established in the medulla through a series of complicated physiological processes (*Wirz et al.* 1951). In the presence of antidiuretic hormone, water is resorbed from the contents of the collecting tubules and passes into the hypertonic medullary tissue until osmotic equilibrium is attained at both sites (*Wirz* 1957).

Since the ultimate concentration of the urine is the result of osmotic forces in the kidney it is more suitable to express urine concentration on the basis of the content of osmotically active particles, *i. e.* its osmolarity, instead of in terms of specific weight

as has been customary. Osmolarity, expressed in milliosmol per litre, indicates the number of osmotically active particles per unit volume and thus is independent of the molecular weight of the substances present in the urine. Substances with high molecular weights such as proteins and carbohydrates influence the specific weight to a much greater extent than they do the osmolarity. In renal disease the amount of such substances in the urine is often increased and this in turn increases the error resulting from the use of specific weight as a measurement of the concentrating ability of the kidneys. But even when the amounts of high-molecular substances are normal can the differences between specific weight and osmolarity be of sufficient magnitude to give a misleading impression of renal function (*Isaacson* 1959). This is especially the case when urinary osmolarity is of a magnitude corresponding to a specific weight from 1.005 to 1.020 (*Baldwin et al.* 1955, *Schoen* 1959).

MATERIAL AND METHODS

This study is based upon 15 control dogs, females 1—5 years old, which had shown no clinical signs of disease during an observation period of at least 4 weeks and 52 bitches with pyometra selected from a clinical material on the basis of clinical signs and for which the diagnosis was confirmed histologically after ovariohysterectomy. Only dogs with an anamnesis of polydipsia have been included in the clinical series. For practical reasons (introduction of catheters and collection of samples) the studies have been limited to animals of the medium-sized and large breeds. All examinations were made on unanaesthetised animals.

For the pyometra bitches the ability of the kidneys to form concentrated urine was studied after withdrawal of water for 18 to 21 hours. Sixteen hours after the beginning of this period the bladder was emptied through a catheter by application of prepubic pressure after insufflation of air. From this point onwards the bladder was emptied in the same manner at hourly intervals and the urine collected in graduated containers until the conclusion of the experiment after 21 hours. Most dogs received antidiuretic hormone (5 pressor units) i. m. as pitressin tannate in oil[1]) 18 hours after the beginning of the dehydration period.

[1]) Parke, Davis.

Results for the period with the highest osmotic urine/plasma ratio and the corresponding urine volume are included in the appropriate tables.

Plasma osmolarity was determined for blood samples taken from all animals after 18 hours. If pitressin had been injected another blood sample was taken after 20 or 21 hours.

The healthy dogs were deprived of water for 20 to 24 hours. Otherwise the experimental procedure corresponded to that applied to the pyometra animals.

At the conclusion of the experimental period the pyometra animals were given water and a subcutaneous injection of 5—10 ml./kg. isotonic saline solution. About one hour later ovariohysterectomy was carried out.

The dogs were again submitted to the same experimental procedure 9 to 14 days after the operation. Most of the pyometra animals left the clinic after the second examination. Ten of the bitches which did not have a normal concentrating ability at the time of this second examination were examined a third time after 35 to 114 days had elapsed.

Beginning on the day after operation, daily water consumption and urine excretion for 11 of the pyometra animals was measured by placing them for periods of 8 to 13 days in cages especially constructed for that purpose.

The ability to form dilute urine was studied before the concentration tests in 36 of the dogs. Each dog was given 40—50 ml./kg. water warmed to body temperature through a stomach tube. The water was divided into 2 doses given at an interval of 10 to 20 minutes to reduce the risk of emesis. Since these dogs were a clinical material and not trained for the tests the procedure of emptying the bladder through a catheter and the application of prepubic pressure would make them uneasy and presumably stimulate the neurosecretory system to result in an increased urine osmolarity (*O'Connor & Verney* 1942). For this reason catheterisation for emptying the bladder during the experiment was avoided and the dogs instead given the opportunity to urinate about an hour after the water was given. After a further 20 minutes a urine sample was taken, this time generally by catheterisation.

Urine and plasma osmolarity were determined by freezing-point depression. All values are given as the mean of double determinations. Coefficients of variation of 0.22 to 0.38 per cent

were obtained from 15 determinations on each of 4 standard solutions containing 100, 300, 500 and 750 mOsm/l. respectively. Body surface area was calculated according to the method described by *Cowgill & Drabkin* (1927).

Abbreviations

Uosm = urine osmolarity expressed in mOsm/l.
Posm = plasma osmolarity expressed in mOsm/l.
Osmotic U/P ratio = ratio between Uosm and Posm.
V = urine volume expressed in ml./min.

RESULTS

The concentrating ability of the normal dogs is listed in Table 1. The mean value obtained for osmotic U/P ratio was 5.4 ± 0.6.

Table 1. Uosm and osmotic U/P ratio in normal bitches after dehydration for 20 to 24 hours.

Dog	Max. Uosm mOsm/l.	Osmotic U/P ratio
F 0	1501	5.1
P 2	1830	6.4
P 9	1466	4.9
P 12	1530	5.2
P 17	1508	5.3
P 15	1404	4.9
P 5	1660	5.5
P 6	1371	4.8
F 7	1347	4.7
F 11	1500	5.1
F 10	1560	5.5
F 9	2092	6.9
F 12	1608	5.6
F 18	1604	5.4
F 16	1898	6.2
	1592	5.4
	±206	±0.6

The concentrating capacities of the pyometra animals are listed in Table 2. All the bitches investigated showed a depression of the concentrating ability although this depression differed in degree. The highest value obtained for osmotic U/P ratio was well below the normal values given in Table 1. In some dogs the

Table 2. Urine volume and concentrating ability in bitches with pyometra after dehydration for 18 to 21 hours. The right-hand column indicates the approximate degree of polydipsia at the time of admission to the clinic (N = normal water consumption, + = > N < 2N, ++ = > 2N < 5N, +++ = > 5N).

Dog no.	Body surface area m^2	Urine volume ml./min. per m^2	Max. Uosm mOsm/l.	Osmotic U/P ratio	Water consumption (according to anamnesis)
8	0.84	0.19	1176	3.9	+
9	0.83	0.26	1076	3.6	+
10	0.74	0.14	1050	3.6	+
11	1.31	0.18	1029	3.4	+
12	0.72	0.17	1024	3.6	++
13	1.04	0.19	1022	3.5	++
14	0.45	0.20	1008	3.4	+
15	1.18	0.21	982	3.3	+
16	0.51	0.18	963	3.1	+
17	0.59	0.27	919	2.9	+
18	0.93	0.15	909	3.0	+
19	0.56	0.36	901	3.0	+
20	1.07	0.14	886	3.0	+
21	0.44	0.20	873	3.0	+
22	0.65	0.26	868	3.0	+
23	0.39	0.31	866	2.7	++
24	1.01	0.13	863	2.7	+
25	0.32	0.16	806	2.7	+
26	0.93	0.29	801	2.7	+
27	0.79	0.18	757	2.4	+
28	1.13	0.21	740	2.5	+
29	0.54	0.22	719	2.6	+
30	0.63	0.32	715	2.3	++
31	1.34	0.31	713	2.4	+
32	0.67	0.42	708	2.3	++
33	0.63	0.21	692	2.3	+
34	0.56	0.36	662	2.2	++
35	0.74	0.31	652	2.2	++
36	0.92	0.47	647	2.1	+++
37	0.86	0.70	574	1.8	+++
38	0.89	0.42	571	1.8	++
39	0.47	0.32	563	1.9	++
40	0.90	0.49	551	1.9	+++
41	0.46	0.20	548	1.9	+
42	0.62	0.60	524	1.8	+++
43	0.95	0.39	518	1.6	++
44	0.64	0.38	434	1.4	+
45	0.96	0.63	423	1.4	+++
46	0.73	0.52	417	1.4	++
47	0.43	0.30	412	1.4	++

Table 2 (continued).

Dog no.	Body surface area $m.^2$	Urine volume ml./min. per $m.^2$	Max. Uosm mOsm/l.	Osmotic U/P ratio	Water consumption (according to anamnesis)
48	0.48	0.46	379	1.2	++
49	1.02	0.45	377	1.3	++
50	1.13	0.62	340	1.1	+++
51	0.76	0.86	311	1.1	+++
52	0.91	1.07	308	1.0	+++

concentrating ability was so severely depressed that the osmotic U/P ratio approached unity, i. e. Uosm was nearly the same as Posm.

Urine flow (V), measured simultaneously with determination of the maximum osmotic U/P ratio during dehydration, is also listed in Table 2. V was inversely correlated to osmotic U/P ratio as shown in Fig. 1.

Polydipsia is considered to be a "typical" sign of pyometra in the bitch. Table 2 demonstrates the relatively close agreement between the increase in urine flow, the reduction in concentrating capacity, and the degree of polydipsia mentioned in the anamneses.

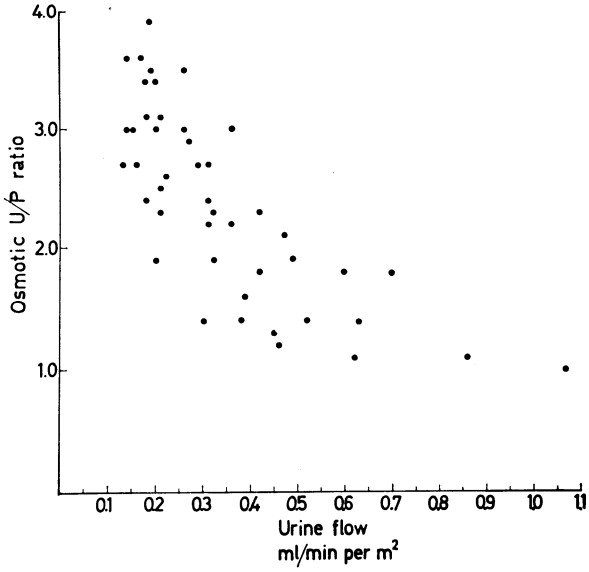

Fig. 1. Osmotic U/P ratio in relation to urine flow in bitches with pyometra after dehydration for 18—21 hours.

Nineteen dogs which after dehydration for 18 hours had a concentrating capacity of less than 650 mOsm/l. when first examined were divided into two groups. One group (11 animals) were given ADH i. m. as 5 U pitressin tannate in oil. For the other group (8 animals) dehydration was continued without any additional treatment. During dehydration from 18 to 21 hours both groups showed similar increases in Uosm (Table 3).

Table 3. Bitches with pyometra were dehydrated for 18 hours. The animals in Group I were then given 5 U pitressin tannate in oil i. m. and the dehydration period continued for both groups until 21 hours.

△ Uosm = difference in per cent between Uosm at 18 and 21 hours.

Group I				Group II			
Dog no.	Max. Uosm Dehydration 18 hours	Dehydration 21 hours + P.T.O.	△ Uosm 21-18 hours %	Dog no.	Max. Uosm Dehydration 18 hours	Dehydration 21 hours	△ Uosm 21-18 hours %
29	648	719	11.0	26	645	801	24.2
31	620	713	15.0	30	597	714	19.6
32	619	708	14.4	37	527	574	8.9
33	615	692	12.5	38	528	571	8.1
34	518	662	27.8	40	484	551	13.8
39	542	563	3.9	45	310	423	36.5
41	515	548	6.4	49	362	377	4.1
43	392	518	32.1	107	401	414	3.2
44	386	434	12.4			Mean:	14.8
46	405	417	3.0				
47	386	412	6.7				
		Mean:	13.2				

The maximum osmotic U/P ratio during dehydration was re-examined for 30 bitches between 9 and 14 days after operation. There was a distinct increase in the ratio for most animals (Figs. 2 and 3). A special effort was made to have the bitches not responding with a clear-cut increase in the U/P ratio at the first postoperative examination returned to the clinic for a second postoperative examination. The results for the ten animals available for a second postoperative examination 35 to 114 days after operation are given in Fig. 2. The osmotic U/P ratio had improved or become normal for 8 of the animals. The owners of these

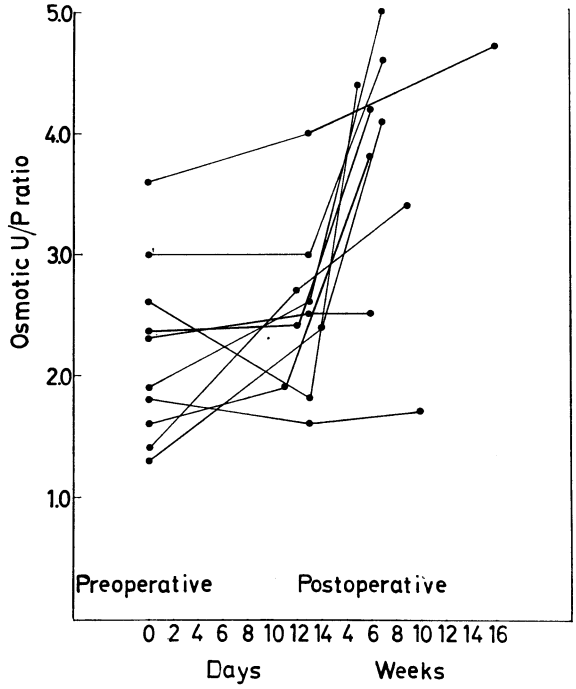

Fig. 2. Osmotic U/P ratios before and at different times after ovariohysterectomy of ten bitches with pyometra dehydrated for 18—21 hours.

bitches considered their animals to be fully healthy and to have normal thirst. Two animals still had decidedly abnormal values at this second postoperative examination 44 and 75 days respectively after operation. Unlike the other animals, these particular bitches had been reported by their owners to have had slightly increased thirst several months before the other clinical signs of pyometra became manifest. Thirst increased still more as the other signs became evident. One of these two dogs according to the owner still had a slightly increased thirst 8½ months after operation but otherwise was apparently healthy. The remaining animal was returned to the clinic 74 days after operation because of dullness, anorexia, and persistent polydipsia. This dog was killed, the kidneys showed histological signs of chronic pyelonephritis, the likely explanation for the persisting polydipsia.

The pre- and post-operative osmotic U/P ratios for the other

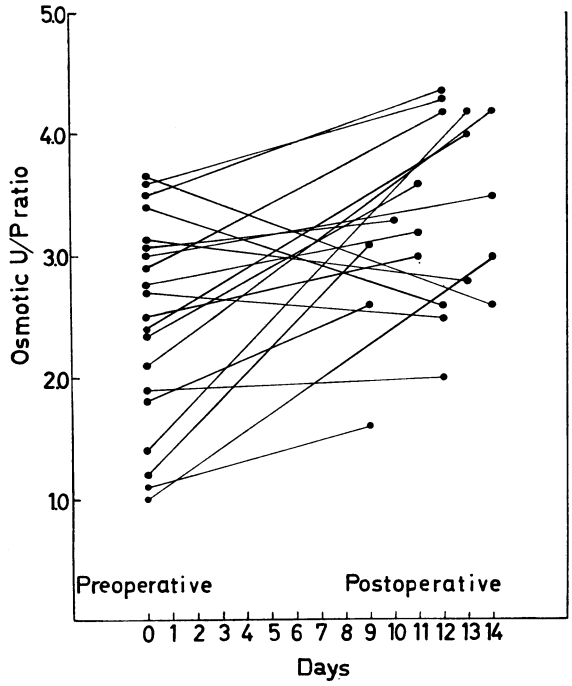

Fig. 3. Osmotic U/P ratios before and after ovariohysterectomy of twenty bitches with pyometra dehydrated for 18—21 hours.

twenty bitches which were not available for a second examination are given in Fig. 3. When the owners were questioned four to thirteen months after the first examination, eighteen reported (two could not be traced) that their animals had a normal thirst upon return from the clinic or by three to seven weeks after operation. These eighteen bitches included the four in Fig. 3 which had a deteriorated concentrating capacity when first examined after operation.

Ten of the 11 animals for which urine volume and water consumption was measured daily during the post-operative period showed a successive decrease in urine volume and water consumption and an increase in osmotic U/P ratio i. e. an improvement in the concentrating capacity of the kidneys after operation. A typical clinical pattern (dog no. 36) is illustrated in Table 4. For the remaining bitch (dog no. 38) there was no improvement in concentrating capacity and no decrease in the daily urine volume and water consumption (Table 4).

Table 4. Daily water consumption and urine volume for 2 bitches with pyometra before and after ovariohysterectomy.

Days post-op.	Dog 36				Dog 38			
	Water consumption ml./day	Urine volume ml./day	Dehydration for 18-21 hours		Water consumption ml./day	Urine volume ml./day	Dehydration for 18-21 hours	
			Max. Uosm	Osmotic U/P ratio			Max. Uosm	Osmotic U/P ratio
0			647	2.1			571	1.8
2	2190	1820			980	740		
3	1700	1280			1020	870		
4	1530	1210			1060	935		
5	1070	790			1070	965		
6	1210	940			975	830		
7	1290	1080			1030	960		
8	980	740			1010	880		
9	730	510			1040	890		
10	720	530					491	1.6
11			1307	4.2				

The capacity of the kidneys to form dilute urine was examined in 36 dogs. Since, for reasons mentioned previously, these animals were not catheterised urine volume could not be measured and on this account neither could free water clearance. Uosm must serve as the only criterion of diluting capacity. Uosm for the animals ranged from 34 to 526 mOsm/l. For 16 animals the lowest Uosm value obtained was less than 90 mOsm/l. These animals are listed separately in Table 5 and maximum values for Uosm and the osmotic U/P ratio obtained after dehydration for 18 to 21 hours are also included to permit comparison of the concentrating and diluting capacities.

Using Uosm as a basis for evaluation it appears from the table that diluting capacity is good even in animals with a greatly reduced concentration capacity.

DISCUSSION

From these studies of renal function it appears that the polydipsia often seen in bitches with pyometra is secondary to the polyuria resulting from a reduction in the capacity of the kidneys to concentrate urine. The body attempts to compensate for the unphysiological loss of water caused by the renal dysfunction.

In a previous study it has been shown that bitches with polydipsia associated with pyometra excrete normal amounts of ADH

Table 5. Ability to form dilute urine (min. Uosm) in bitches with pyometra. The corresponding maximum concentrations are listed.

Dog no.	Diluting ability Min. Uosm mOsm/l.	Concentrating ability Max. Uosm mOsm/l.	Concentrating ability Osmotic U/P ratio
10	81	1050	3.6
14	64	1008	3.4
102	74	992	3.3
103	65	955	3.2
104	34	904	3.1
19	56	901	3.0
26	49	801	2.7
32	74	708	2.3
34	45	662	2.2
105	81	659	2.2
35	52	652	2.2
36	85	647	2.1
40	41	551	1.9
43	70	518	1.6
106	68	327	1.2

in the urine and have normal amounts of Gomori-positive material in the hypothalamic-neurohypophyseal system (*Åsheim* 1963). These observations tally well with the demonstration in the present study that the administration of ADH in large doses does not markedly affect the concentrating capacity of the kidneys of polydipsic bitches with pyometra which had been denied access to water for 18 to 21 hours. It is, accordingly, unlikely that the polydipsia and polyuria often occurring in association with pyometra are the result of hypothalamic-hypophyseal insufficiency.

Polydipsic bitches with pyometra showed great differences in their ability to dilute the urine, presumably to some extent because of nervous influences stimulating release of ADH during the tests. A relatively large number of animals with a greatly reduced ability to concentrate urine had minimum Uosm values less than 90 mOsm/l., values of the same magnitude as the minimum Uosm values obtained in water tolerance tests on normal dogs (*Bricker et al.* 1959, *Levitin et al.* 1962). Chronic renal diseases of various types with a moderate reduction in the number of functioning nephrons are also first manifest as a reduction in concentrating capacity. At a later stage, as the number of functioning nephrons is reduced still further, a reduction in diluting

capacity becomes obvious (*de Wardener* 1958, *Bricker et al.* 1959, *Kleeman et al.* 1961). The condition ultimately results in isostenuria. Renal function in bitches with polydipsia associated with pyometra, however, differs from this characteristic course for chronic renal disease since animals with an osmotic U/P ratio as low as 1.2 after dehydration for 18 hours still have a normal capacity for forming dilute urine. If the renal dysfunction were simply the result of osmotic diuresis because of reduction in the number of functioning nephrons, animals with such a severe reduction in concentrating ability should also have dysfunction of their diluting ability (*Bricker et al.* 1960, *Kleeman et al.* 1960). The renal dysfunction in the polydipsic dogs studied here, then, cannot be explained solely as the result of reduction in the number of functioning nephrons. It seems more likely that the renal dysfunction implies an inability of functioning nephrons to form concentrated urine.

A notable feature is that the kidneys regain or improve their concentrating capacity rapidly — often within 14 days — after ovariohysterectomy. This fairly prompt restitution supports the assumption presented above that the renal dysfunction is more likely the result of a reduction in the concentrating ability of functioning nephrons than the result of a reduction in the number of functioning nephrons.

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SUMMARY

Renal function (concentration and dilution) has been examined in 52 bitches with polydipsia and polyuria associated with pyometra (chronic purulent endometritis).

All animals had a reduced capacity to form concentrated urine. The degree of polydipsia and polyuria was roughly proportional to the degree of reduction in concentrating ability.

The administration of ADH did not increase the concentrating ability.

The kidneys could retain a normal ability to form dilute urine even when the concentrating ability was greatly reduced.

The kidneys generally improved their capacity to concentrate urine after ovariohysterectomy. In only 2 animals could no improvement be detected (observation periods of 44 and 75 days).

ZUSAMMENFASSUNG

Die Nierenfunktion bei Hunden mit Pyometra. 2. Die Koncentrations- und Verdünnungsfähigkeit.

Bei 52 Hunden mit Polydipsie und Polyurie im Zusammenhang mit der Pyometra (Endometritis purulenta chronica), wurde die Konzentrations- und Verdünnungsfähigkeit untersucht.

Die Konzentrationsfähigkeit war in allen Fällen vermindert. Zwischen dem Grade der Polyurie bzw. Polydipsie einerseits, und dem Grade der Reduktion der Konzentrationsfähigkeit der Nieren andererseits, bestand eine klare Korrelation.

Die Konzentrationsfähigkeit der Nieren wurde durch Zufuhr von ADH nicht erhöht.

Die Verdünnungsfähigkeit der Nieren kann normal sein auch im Falle wenn die Konzentrationsfähigkeit stark vermindert ist.

Nach der Ovario-Hysterektomie erhöhte sich in meisten Fällen die Konzentrationsfähigkeit der Nieren. Nur in zwei Fällen erfolgte keine Besserung der Nierenfunktion (Beobachtungszeit 44 bzw. 75 Tage).

SAMMANFATTNING

Njurfunktionen hos hundar med pyometra. 2. Koncentrations- och utspädningsförmågan.

Hos 52 hundar med polydipsi och polyuri i samband med pyometra (kronisk purulent endometrit) har njurarnas koncentrations- och utspädningsförmåga undersökts.

Koncentrationsförmågan var i samtliga fall nedsatt. Graden av polyuri resp. polydipsi visade en god korrelation till graden av reduktion av njurarnas koncentrationsförmåga.

Tillförsel av ADH ökar inte njurarnas koncentrationsförmåga.

Njurarnas utspädningsförmåga kan vara normal även i fall med starkt reducerad koncentrationsförmåga.

Efter ovario-hysterektomi ökar i flertalet fall njurarnas koncentrationsförmåga. Endast i 2 fall inträdde ingen förbättring av njurfunktionen (observationstid 44 resp. 75 dagar).

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