THE CONTROL OF THE RENAL EXCRETION OF WATER*

II. The Rate of Liberation of the Posterior Pituitary Antidiuretic Hormone in the Dog

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These experiments were performed for two purposes. The first was to define the normal rate of liberation of the antidiuretic hormone. The action of the hormone on the renal tubular reabsorption of water is fairly clear, at least in its qualitative aspects. Its normal participation, with the suprarenal cortical hormone, in control of the renal tubular reabsorption of sodium (1–3) is less certain because of the excessive amounts of antidiuretic hormone commonly used to demonstrate such an action. A decision on the function of the antidiuretic hormone and its relation to other variables in the two systems cannot be arrived at until its normal rate of liberation is defined.

The second purpose was the clarification of those relationships within the nephron which appear to be important in determining the volume as well as the composition of the final urine. There is normally a rather precise balance between the glomerular filtration rate and tubular reabsorptive capacity (proximal) in the individual nephra which permits the kidney to function as if the operations of filtration and reabsorption were taking place in a single nephron (4, 5). This balance is particularly important in the case of electrolyte if, as seems likely, the reabsorption of osmotically active material in the proximal portions of the nephron (6) indirectly provides the force for the reabsorption of a large portion of the filtered water (5, 7). A disturbance of the normal relationship, such as an increase in glomerular filtration without a comparable increase in the reabsorptive capacity of the tubules, establishes conditions which favor an increase in the rate of urine flow. The converse is also to be expected (8).

EXPERIMENTAL

Material.—Seven female dogs were used. Four dogs had permanent diabetes insipidus and their state has been previously described (8); the remainder were normal. The following data (May 6 to 13, 1940) on the weight and urine flow of the diabetes

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insipidus dogs are typical of the period covered by these experiments. Dog A, 11.65 kilos, 3.45 liters per day; dog B, 7.25 kilos, 4.15 liters per day; dog D, 8.8 kilos, 4.21 liters per day; dog C, 11.3 kilos, 3.34 liters per day. The slight reduction of the polyuria, as compared to that of the initial observations may be attributed, if significant, to quantitative changes in the diet (9, 10) rather than to an essential change in the fundamental deficiency in the animals. The normal dogs weighed between 12 and 15 kilos.

Methods.—The method of administration of a hormone is of particular importance if the collected data are to be used to define its normal rate of liberation. The procedure must mimic the normal process as far as is experimentally possible. Administration of the hormone in our experiments was by a slow infusion into the marginal ear vein of the dogs at a rate of 5.0 or 10.0 ml. of fluid per hour. The infusion arrangements were as follows: The shaft of a 20 gauge, short beveled needle was used as a cannula and was connected to an infusion pump by small caliber, light weight rubber tubing. The tubing was clipped to the dog's head and the cannula was attached to the ear by a paper clip, with the edge of the ear supported by a small piece of celluloid. Both ears were then folded and taped together for added stability. Such arrangements allow the animals considerable freedom and permit prolonged observations without requiring the use of restraints. The shortest time which elapsed between the beginning of a hormone infusion and the beginning of an experimental observation was 25 minutes; frequently a longer preliminary adjustment period was permitted, particularly at the low rates of hormone administration.

Three general types of experiments were performed; some were less extensive than those shown in Tables I to III in that fewer variables were examined serially. The preparation of the animals was the same for all experiments unless stated to the contrary. They were permitted water up to an hour before the beginning of the experiment, which was performed 16 to 20 hours after the last meal. Creatinine for the measurement of glomerular filtration rate was injected subcutaneously or included in the infusion fluid. The general experimental routine, the preparation of samples for analysis, and the chemical methods were the same as those previously used by us (8). A single preparation of pituitary liquid (U.S.P., Armour) was used throughout. Bioassay, at the beginning and termination of the study, showed it to contain 10 pressor units per ml. of solution.[1] The hormone infusions were prepared by dilution with physiological saline solution acidified with hydrochloric acid to a pH of 5.5–6.0. Such solutions of hormone are quite stable. However, fresh dilutions of hormone were made each 60 to 90 minutes.

RESULTS

Antidiuresis.—The following observations on dogs with diabetes insipidus relate to the antidiuresis produced by the constant intravenous infusion of the antidiuretic hormone. Some of the salient features of this portion of the data are summarized in Fig. 1. The experiments were similar in design to that of Table I and the early portion of the experiment of Table II.

[1] We wish to thank Dr. E. M. K. Geiling for the bioassays at the termination of the study.

1. Administration of the antidiuretic hormone was not accompanied by a change in the rate of glomerular filtration in the range of hormone administration used (1.0 to 350 milliunits per hour). All changes in urine flow were therefore the result of changes in the reabsorption of water.

2. There was considerable variation in the degree of antidiuresis produced by a given level of hormone administration in the different animals and in each animal at different times. This was true however the antidiuresis is evaluated;

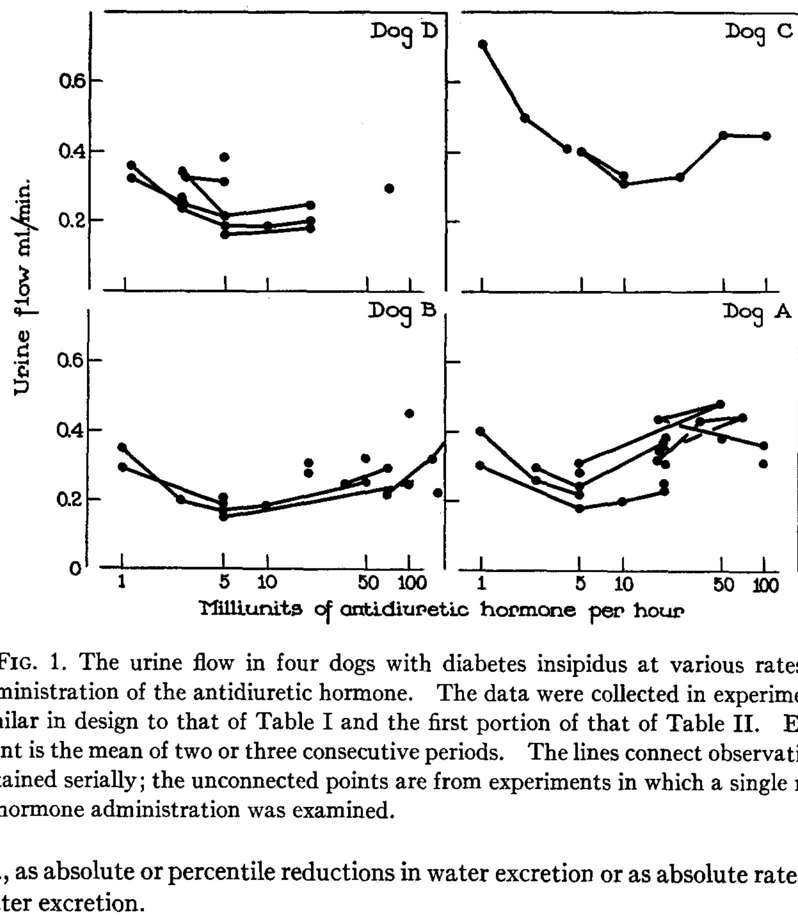

FIG. 1. The urine flow in four dogs with diabetes insipidus at various rates of administration of the antidiuretic hormone. The data were collected in experiments similar in design to that of Table I and the first portion of that of Table II. Each point is the mean of two or three consecutive periods. The lines connect observations obtained serially; the unconnected points are from experiments in which a single rate of hormone administration was examined.

i.e., as absolute or percentile reductions in water excretion or as absolute rates of water excretion.

3. Graded antidiuresis with graded hormone administration was consistently observed only in the range of 1.0 to 5.0 milliunits per hour.

4. When a single experiment included a series of progressively increasing rates of hormone administration maximal antidiuresis was usually reached at 5.0 milliunits of hormone per hour. There was never a further increase in the antidiuresis when the hormone was raised from 20 milliunits to some higher

value. Under the latter condition the urine flow remained the same or increased with the increase in the rate of hormone administration.

5. The minimal urine flows during hormone antidiuresis were frequently higher than those sometimes observed in the same animals after simple dehydration for 18 to 24 hours. However, in hormone antidiuresis the urine was consistently more hypertonic than in the oliguria of simple dehydration. (Compare Fig. 1 with Table II, in the preceding paper.)

TABLE I

An Experiment on a Dog with Diabetes Insipidus Which Examines into Some Effects of the Administration of the Antidiuretic Hormone by Constant Intravenous Infusion

This experiment is typical in that it shows no significant change in glomerular filtration rate, graded antidiuresis in the lower range of hormone administration, and an increase in electrolyte excretion which is related to the hormone administration.

Dog D, weight 8.8 kilos. Creatinine was incorporated in the influsion fluids; its plasma concentration varied from 5.31 to 5.67 mg. per cent; the serum sodium was 149.0, the chloride 114.2 mM per liter.

Period	Concurrent time	Urine flow	Creatinine U/P ratio	Creatinine clearance	Urine Na	Urine Cl	Na excretion	Cl excretion
	min.	*ml./min.*		*ml./min.*	*mM/liter*	*mM/liter*	*mM/min.*	*mM/min.*
1	0–21	2.10	16.3	34.2	6	8	0.013	0.017
2	–40	2.42	14.7	35.6	7	8	0.017	0.019
	43	Pituitrin infusion 0.001 unit per hr.						
3	75–91	0.33	106	35.0	63	60	0.021	0.020
4	–110	0.32	104	33.2	68	62	0.022	0.020
	112	Pituitrin infusion 0.0025 unit per hr.						
5	141–161	0.24	141	33.8	112	104	0.027	0.025
6	–180	0.25	140	35.0	118	107	0.030	0.027
	183	Pituitrin infusion 0.005 unit per hr.						
7	210–230	0.21	165	34.7	161	147	0.034	0.031
8	–249	0.21	172	36.1	157	145	0.033	0.030
	254	Pituitrin infusion 0.020 unit per hr.						
9	281–303	0.26	137	35.6	169	152	0.044	0.040
10	–325	0.25	137	34.5	172	154	0.043	0.039

6. Urine flows at true oliguric levels (*i.e.*, 0.1 ml. per minute or less in a 10.0 kilo dog) were only obtained by the combination of moderate to severe dehydration and hormone administration. This régime produced creatinine U/P ratios comparable to those commonly observed with severe dehydration in the normal dog (11).

7. The administration of 40 to 50 ml. of water per kilo elevated the range of hormone administration which produced graded antidiuresis and diminished the degree of antidiuresis at a constant rate of hormone administration.

These observations define the quantitative relationship between hormone administration and antidiuresis in the dog with diabetes insipidus, in so far as a definition can be made in terms of the overall effect; *i.e.*, rate of urine flow. Of equal importance is the support which they give to the viewpoint that the antidiuretic hormone is only one of a series of variables which are concerned in the production of variations in the rate of urine formation.

Sodium and Chloride Excretion.—Observations on the influence of the antidiuretic hormone on the excretion of electrolyte were limited to sodium and chloride. The experiments were similar in design to the one shown in Table I and the first portion of that in Table II and were, for the most part, the experiments from which Fig. 1 was constructed. There were some additional experiments on dogs B and C which differ somewhat from the remainder in that minor variations in the water balance of the animals were induced. Both ions were studied in the majority of cases but in some only chloride was observed. Variations in the excretion of sodium in these experiments were accompanied by equivalent variations in the excretion of chloride. For this reason and because the chloride data are more extensive we have chosen them for presentation (Fig. 2).

An outstanding characteristic of these data is the great variability in the effect of the hormone on electrolyte excretion. There was a significant increase in the excretion of sodium and chloride at low rates of hormone administration (*i.e.*, 20 milliunits per hour or less) in three dogs while in the fourth (dog D) no systematic and reproducible effect, which could be attributed to the action of the hormone, was observed. The higher ranges of hormone administration were not examined in the latter animal. The increase in excretion observed in the other three animals represents an equivalent depression in renal tubular reabsorption since glomerular filtration rate is not affected in this range of hormone administration. It should be noted that small percentile depressions in the reabsorptive process will result in large percentile and large absolute increases in the excretion rate of sodium and chloride because of the relationship that normally exists between their filtration, reabsorption, and excretion. The variability in the excretion data may result in part from this circumstance.

The effect of the hormone on sodium and chloride excretion is great in dogs A and C when considered in terms of the daily sodium and chloride balance. An increase of 0.01 mM per minute in the excretion of chloride in these animals would result in an additional loss of 14.4 mM in a 24 hour period or about 5 per cent of their total chloride content. However, this rate of hormone administration did not affect sodium or chloride excretion as greatly when the animals were moderately dehydrated and this was also the case for normal animals under similar conditions. The latter finding is perhaps correlated with the lowered rate of glomerular filtration (and hence filtration of electrolyte) commonly observed under these conditions (8).

The depression of electrolyte reabsorption frequently produces a higher electrolyte concentration in the urine during hormone antidiuresis in the diabetes insipidus animal than is usually observed during oliguria at a comparable urine flow in normal dogs and may operate to limit the degree of antidiuresis which the hormone can produce in a normally hydrated animal with diabetes insipidus (8). The increase in the excretion of electrolyte which may result from an increase in hormone administration is frequently accompanied by an increase in

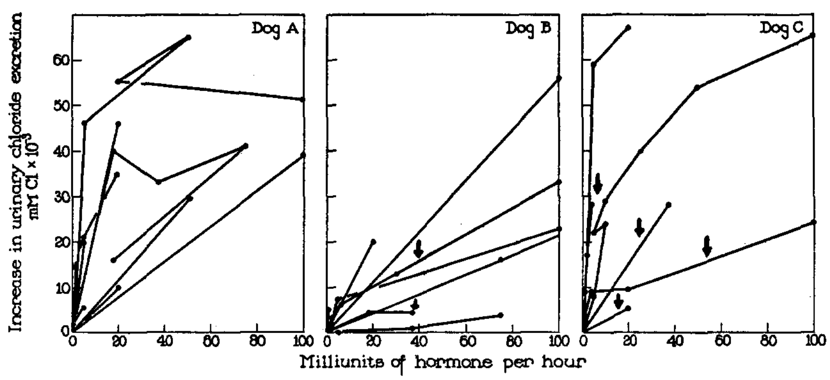

FIG. 2. The increase in chloride excretion in dogs with diabetes insipidus at different rates of antidiuretic hormone administration. The data were collected in experiments similar in design to that of Table I and of the first portion of Table II. Each point is the mean of two or three consecutive periods; the lines connect observations obtained serially. Since all experiments have an initial control period the line to the initial observation must of necessity start at the intersection of the coordinates. The data from dog A are from the same experiments that were used in the construction of Fig. 1; and in the case of dogs B and C additional experiments have been included. In two experiments on dog B water had been withdrawn for a period of 4 hours (arrows); in four experiments on dog C 40 ml. per kilo of water had been administered 3 hours prior to beginning (arrows). Neither of these procedures was expected to influence the data nor do they appear to have done so. Electrolyte excretion was measured in six experiments performed on dog D, and there was no systematic effect on chloride excretion (see text, page 391).

the rate of urine formation. The increase in the urine flow appears to be causally related to the electrolyte effect since it occurs only when there is a significant increase in the excretion of electrolyte at the higher rate of hormone administration.

The Effect of Water Administration.—The effect of water administration on hormone antidiuresis was studied in a series of experiments similar in design to that of Table II. There was an invariable increase in urine flow during the 1st hour after the administration of water, which at times reached values above 1.0 ml. per minute (Fig. 3). The experimental periods were too long to reveal the true rate of increase in the urine flow after the water but, in general, it appears to follow the same time course as water diuresis in the normal animal (12). When observed during the 2nd hour the urine flow was usually at a lower value but was above the control rate. There was no close correlation between the extent of the change in urine flow and the rate of hormone administration.

TABLE II

An Experiment on a Dog with Diabetes Insipidus Which Examines into the Effect of the Administration of Water during a Continuous Infusion of the Antidiuretic Hormone

The terminal portion of the experiment demonstrates the rapid lessening in antidiuresis when the hormone infusion is stopped.

Dog A, weight 11.6 kilos. Plasma creatinine varied from 9.78 to 13.86 mg. per cent; the initial serum total base was 159.3 mM, the chloride 110.7 mM per liter.

Period	Total concurrent time	Urine flow	Creatinine clearance	Urine Na	Urine Cl	Urine −Δ
	min.	*ml./min.*	*ml./min.*	*mM/liter*	*mM/liter*	*°C.*
1	0–15	1.86	26.3	11	13	0.18
2	–34	1.84	25.6	12	14	0.18
	45	Pituitrin infusion started 0.020 unit per hr.				
3	77–94	0.27	24.6	178	173	1.34
4	–114	0.30	26.3	162	161	1.42
	115	50 ml. per kg. of water by stomach tube				
5*	114–130	0.59	—	—	—	—
6*	–150	0.83	—	—	—	—
7	–165	1.07	35.0	150	119	0.78
8	–181	1.13	38.0	141	113	0.79
9	–202	0.86	37.6	138	106	0.81
10	–222	0.52	35.0	142	111	1.07
11	–241	0.43	38.7	138	99	1.03
12	–262	0.51	35.0	144	110	0.91
13	–284	0.43	38.8	141	100	0.99
	Pituitrin infusion stopped					
14*	284–300	0.42	—	—	—	—
15*	–316	1.61	—	—	—	—
16	–334	2.38	—	—	3	—
17	–345	2.15	—	—	2	0.07

* Significant dead space error due to increase in urine flow during periods.

The data indicate, as shown in Table II, that there was an increase in glomerular filtration rate during the 1st hour which was sustained throughout the 2nd except in one experiment on dog A (indicated by an arrow in Fig. 3). Electrolyte excretion also increased consistently after the water, presumably due to the increase in glomerular filtration. However, the concentrations of sodium and chloride and the freezing point depressions of the urines were not regularly sufficient for either to be the immediate cause of the increase in water excretion, it being unusual for urinary sodium to be in excess of 200 mM per liter and freezing point depressions to be in excess of 1.2°C.

The increase in the glomerular filtration rate which commonly follows the administration of a large amount of water is undoubtedly an important factor in producing the increase in urine flow. This effect may be expected to be an exaggeration of that which occurs in the normal animal since, owing to the hormone administration, a major portion of the absorbed water is retained. The mechanism by which such a factor may be expected to operate has been discussed at length in the accompanying paper (8). However, the absence of an increase in filtration rate in one experiment and the absence of a close correlation between the increase in filtration and increase in urine flow indicate that other factors are concerned in the phenomenon. It does not seem likely that a change in the dynamics of renal interstitial fluid movement resulting from an expansion in plasma volume or a dilution of the plasma is important since these changes would be expected to be small (5, 13). Nor does the increase in urine flow appear to be conditioned to any extent by a decrease in the reactiveness of the distal tubule cells to the antidiuretic hormone since the response is still apparent at high rates of hormone administration (Fig. 3). It is necessary to suppose that the phenomenon is due to a combination of factors which defy exposition at the moment.

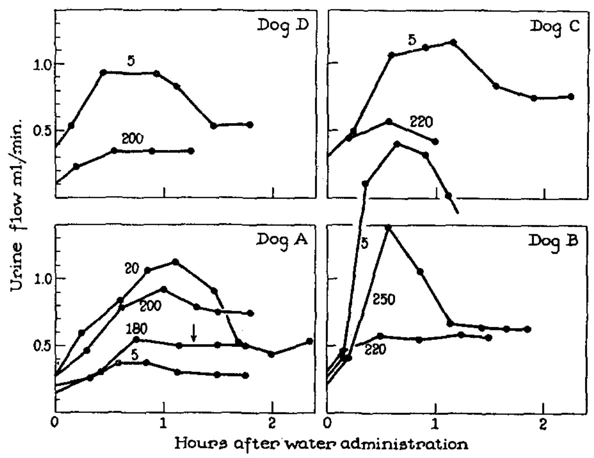

FIG. 3. The influence of the administration of water on the urine flow of dogs with diabetes insipidus during a constant intravenous infusion of the antidiuretic hormone. These experiments are similar in design to that of Table II. The rate of hormone administration in milliunits per hour is given by the number above each curve. The points are placed at the midperiod of the urine collection periods.

Whatever its mechanism, the demonstration of the phenomenon is important.

It has been frequently stated that the dog with diabetes insipidus is particularly sensitive to the antidiuretic hormone as compared to the normal animal. Our results suggest that the difference between the two may be due simply to the method of examination and that the apparent insensitivity of the normal animal to the hormone results from the water which must be administered before making the antiduretic test.

TABLE III

An Experiment on a Normal Dog Demonstrating the Effect of the Antidiuretic Hormone during Water Diuresis

Dog E, weight 14.1 kilos. Creatinine concentration in the plasma varied from 3.5 to 6.3 mg. per cent.

Period	Time	Urine flow	Creatinine clearance	Urine Cl	Urine $-\Delta$
	hrs.:min.	*ml./min.*	*ml./min.*	*mM/liter*	*°C.*
	0 50 ml. water per kg. by stomach tube				
1	1:07–1:17	10.00	86.4	13	0.26
2	–1:29	9.61	86.8	13	0.27
	1:43 Pituitrin infusion 0.005 unit per hr., excreted water replaced				
3	2:20–2:30	1.52	86.3	129	1.64
4	–2:40	1.25	80.0	129	1.86
	2:45 Pituitrin infusion 0.020 unit per hr.				
5	3:15–3:30	0.53	78.3	185	3.27
6	–3:45	0.58	76.0	185	3.17
	3:47 Pituitrin infusion off				
7	3:45–4:03	0.71	—	179	2.82
8	–4:16	1.84	—	86	1.17
9	–4:31	4.86	77.3	11	0.36
10	–4:47	7.07	78.4	6	0.23
11	–5:02	6.45	76.3	7	0.22
12	–5:34	3.97	—	16	0.37
13	–5:51	0.96	—	70	1.28
14	–6:08	0.65	73.6	108	1.77
15	–6:26	0.40	61.2	116	2.24
16	–6:58	0.37	62.8	110	2.51
17	–7:27	0.37	62.0	105	2.53

Supporting evidence for this view was obtained in experiments performed on normal dogs. Water was administered (40 or 50 ml. per kilo) and a series of pituitrin infusions given at the height of water diuresis. Diuresis was then permitted to resume and continuous observations were made until the urine flow returned to the oliguric level. The water turnover in such experiments is large and it is difficult to reproduce conditions closely. However, the experiment of Table III may be taken as fairly typical except that the freezing point depressions at all urine flows in this experiment are somewhat higher than usually obtain. Antidiuresis with 1.0 to 5.0 milliunits of hormone per hour was usually moderate and the urines had higher electrolyte concentrations and greater freezing point depressions than the urines at comparable flows in the absence of exogenous hormone. At a higher rate, 20 milliunits of hormone per hour, abnormally large freezing point depressions were commonly observed and truly oliguric levels of urine flow never obtained. Subsequent to the return of diuresis, the urine flow reapproached the oliguric level only when the glomerular filtration rate had become depressed. These experiments demonstrate directly that the antidiuretic hormone has a prounounced physiological effect in the normal animal at low rates of administration (*i.e.*, 1.0 to 5.0 milliunits per hour),

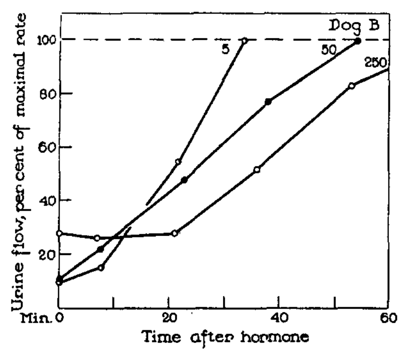

FIG. 4. The falling off of antidiuretic activity in a dog with diabetes insipidus, following the cessation of a constant intravenous infusion of the antidiuretic hormone. The rate of hormone administration, in milliunits per hour, is given by the number above each curve. The time of attaining the maximal urine flow after the cessation of the hormone infusion has been taken as the time which must elapse for the complete dissipation of the antidiuretic hormone in the body. The urine flows have been expressed as the percentages of the maximal flow in each experiment and are plotted at the midpoint of the collection periods.

and offer an explanation for the apparent insensitivity of the normal animal to this hormone.

The effect of a low rate of hormone administration (5 milliunits per hour) was examined during spontaneous antidiuresis in the normal dog. There was an invariable reduction in the rate of urine flow unless the animals had been previously dehydrated. It can be concluded that normal antidiuresis in the dog does not result from a rate of hormone liberation which is in excess of the amount which produces graded antidiuresis.

Falling Off in Antidiuretic Activity.—The return to a high urine flow is quite rapid in the dogs with diabetes insipidus when a constant intravenous infusion of the antidiuretic hormone is stopped. The lessening in activity has been examined in experiments specifically designed for such a study, and in others by making use of the terminal portions of an experiment as in Table II. Water had been administered in some experiments but not in the majority. In all, the hormone was administered for a period of at least 1 hour. A series of typical recovery curves is given in Fig. 4. The data of other experiments on dog B and on the other animals are in keeping with the salient features of this figure. Return of the polyuria, or the lessening in antidiuretic activity, is quite rapid in the lower range of hormone administration (*i.e.*, 1.0 to 5.0 milliunits per hour) being complete in less than 30 minutes. The time required for complete recovery increases progressively as the rate of hormone administration is increased.

The peak of water diuresis in a normal dog is reached about 50 minutes after the administration of water (13). The interval must include the time required for the passage of water into the intestine; for some of its absorption or for the entrance of electrolyte in the gastrointestinal tract; for the depression in posterior pituitary activity; and for the falling off in the activity of the peripherally placed antidiuretic principle. The time of this last at rates of hormone administration of 5 milliunits of hormone per hour is sufficiently short to be contained within the 50 minute period.

DISCUSSION

The normal rate of liberation of the antiduretic hormone in a 10 to 15 kilo dog appears to be in the order of magnitude of 1.0 to 5.0 milliunits per hour. It is only in this range that graded antidiuresis is consistently obtained when the hormone is infused intravenously into a normally hydrated dog with diabetes insipidus, and minimal urine flows were usually obtained at its upper limit. The applicability of these data to the normal animal seems justified by the following considerations. The administration of water to an animal with diabetes insipidus reduces the antidiuresis at all levels of hormone administration so that the animal reacts to the hormone in much the same manner as do normal animals during water diuresis. Experiments on the normal dog directly demonstrate that the above range of hormone administration is physiologically effective and that antidiuresis is normally accompanied by the endogenous liberation of hormone at a rate below that which will produce maximal hormone antidiuresis.

The lack of peripheral storage of the antidiuretic hormone and its prompt destruction are of physiological importance. Otherwise, the onset of water diuresis would be delayed and the administration of water would represent a serious physiological hazard. Actually, the rate of destruction is too rapid at physiological rates of administration (*i.e.*, 5.0 milliunits or less) for the lessening of antidiuretic activity to dominate the normal curve of water diuresis. The presence of other determining factors is emphasized by the experiments in which water administered during a constant intravenous infusion of the hormone produced a prompt increase in the urine flow of dogs with diabetes insipidus. It is safe to conclude that the curve of water diuresis in the normal animal, and perhaps the magnitude of the resulting polyuria, are due to the combination of the latter factors (Fig. 3) as well as to the peripheral lessening in antidiuretic activity (Fig. 4).

The demonstration of a significant depression in the reabsorption of sodium and chloride at physiological rates of hormone administration is also important even though this effect is not invariable. Excessive, unphysiological amounts of the hormone were used in previous demonstrations (1–3) and hence the results of these are of questionable significance. Since the antidiuretic hormone may depress, and the suprarenal cortical hormone may enhance, the renal tubular reabsorption of sodium, both hormones are involved in the control of sodium balance. However, the action of the two does not appear to be integrated in the ordinary sense of the word. Relief of physiological oliguria by moderate amounts of water is usually accompanied by an increase in glomerular filtration rate (11) which involves an equivalent increase in the filtration of sodium. A deficiency of the antidiuretic hormone during such diuresis may be expected to enhance the reabsorptive capacity of the proximal tubule for sodium and thus permit water to be discarded and sodium to be retained (*cf.* electrolyte excretion Table II). In this view, the hormone is important in the regulation of water balance *per se* and only incidentally of sodium. It is difficult to see how the acute changes which are involved in such responses can be closely integrated with the more stable influence of the suprarenal cortical hormone in the control of sodium reabsorption and excretion.

These experiments again emphasize the balance that normally obtains between glomerular and proximal tubular function and the consequences of a variation in one or another in the ultimate determination of the quality and quantity of urine formed (4, 5, 8). A direct demonstration of the relationships has not been achieved nor does it seem possible until more is known about the renal tubular reabsorption of sodium. However, the experimental data presented here and in the accompanying paper (8) lend strong support to the concept. Similarly, the loci of action of the antidiuretic hormone cannot be simply defined. However, to place its sodium effect in the proximal segment and its direct water reabsorptive action, *i.e.* the active process, in the distal, is in keeping with other evidence (6) and with our own experimental data.

SUMMARY

1. The administration of the posterior pituitary antidiuretic hormone by constant intravenous infusion has been used to examine the two characteristic actions of the hormone; namely, the facilitation of the active renal tubular reabsorption of water distally in the nephron and the inhibition of the renal tubular reabsorption of sodium proximally.

2. Experimental evidence was obtained which indicates that variations in the excretion of water and electrolyte involve the integration of these two actions with obscure variables which are discernible in the experimental data but are not subject to definition at this time.

3. Graded antidiuresis in the animal with diabetes insipidus, when normally hydrated, was only obtained in the range of 0.001 to 0.005 unit (pressor) per hour. This range of hormone administration was also found to be physiologically active in the normal animals. These observations together with others permit the placing of the normal rate of liberation of the antidiuretic hormone in a10 to 15 kilo dog in the range of 0.001 to 0.005 unit per hour.

BIBLIOGRAPHY

1. Silvette, H., and Britton, S. W., *Science*, 1938, **88,** 150.
2. Silvette, H., *Am. J. Physiol.*, 1940, **128,** 747.
3. Corey, E. L., and Britton, S. W., *Am. J. Physiol.*, 1941, **133,** 511.
4. Shannon, J. A., Farber, S., and Troast, L., *Am. J. Physiol.*, 1941, **133,** 752.
5. Shannon, J. A., Annual review of physiology, (J. M. Luck, editor), Stanford University, American Physiological Society and Annual Reviews, Inc., 1942, **4,** 297.
6. Walker, A. M., Bott, P., Oliver, J., and MacDowell, M. C., *Am. J. Physiol.*, 1941, **134,** 580.
7. Smith, H. W., The physiology of the kidney, New York, Oxford University Press, 1937.
8. Shannon, J. A., *J. Exp. Med.*, 1942, **76,** 371.
9. Winter, C. A., Sattler, D. G., and Ingram, W. R., *Am. J. Physiol.*, 1940, **131,** 363.
10. Winter, C. A., and Ingram, W. R., *Am. J. Physiol.*, 1941, **133,** 495.
11. Shannon, J. A., *Am. J. Physiol.*, 1936, **117,** 206.
12. Klisiecki, A., Pickford, M., Rothschild, P., and Verney, E. B., *Proc. Roy. Soc. London, Series B*, 1933, **112,** 496.
13. Eggleton, M. G., Pappenheimer, J. R., and Winton, F. R., *J. Physiol.*, 1940, **98,** 336.