612.463.1[612.014.461:615–032:611.14

THE EFFECT OF THE INTRAVENOUS ADMINISTRATION OF WATER UPON THE RATE OF URINE FORMATION.

By W. H. NEWTON and F. H. SMIRK (*Beit Memorial Fellow*).

(*From the Department of Physiology, University College, and the Medical Unit, University College Hospital Medical School, London.*)

It is of importance to know whether absorption through the alimentary mucous membrane is an essential preliminary to water diuresis, for some workers have reported that no diuresis occurs when water is injected intravenously. Cow [1914] suggested the presence of a diuretic hormone in the intestinal mucosa, and other workers have thought that such a hormone might be present in the liver.

When water is given orally diuresis begins after about 20–60 min., and it is of interest to know how much of this delay is of enteral origin.

Experimental evidence.

A. *Rabbits.*

About 1 p.c. of the body weight of tap water at 37° C. was injected into the marginal vein of an ear, locally anæsthetized with 2 p.c. novocaine. No general anæsthetic was given at this stage in any of the experiments. Female animals were used, and the bladder emptied periodically by expression. The rabbits sat quietly in a box during the injection and were free for the rest of the experiment. In all experiments the rabbits had been kept for 24 hours on a diet rich in cabbage which, as is well known, increases their susceptibility to water diuresis. Animals fed on oats, even with unlimited water, have much smaller urinary outputs.

(1) *Hæmoglobinuria.*

Hæmoglobinuria was usually observed. It was very variable in degree, usually of short duration and bore no apparent relation to the delay in onset, the degree or duration of diuresis. The delay in onset was certainly present in a few animals where there was only a trace of hæmoglobin present in the first urine sample obtained after injection (see also the findings in cats).

When about 2 c.c. of a hæmoglobin solution, prepared by alternate freezing and thawing of the animals' own blood, were reinjected intravenously, no change in the rate of urine formation was observed in three out of three cases in spite of the occurrence of hæmoglobinuria. The urine was collected for 2·5 hours after the injection.

It appears from these observations that the presence of free hæmoglobin in the blood does not of itself cause diuresis.

(2) *The effect of intravenous water on the rate of urine formation.*

In eighteen out of twenty-two rabbits a copious diuresis followed the intravenous injection of water. In six cases the diuresis was allowed to proceed without interruption. Five of these animals excreted 140–250 p.c. of the volume of water injected and one excreted 110 p.c. At the peak of diuresis the rate of excretion was from ten to fifteen times the original rate, the urine was paler in colour and the urea percentage had fallen considerably in all cases where it was estimated.

(3) *Comparison between the time relations in diuresis, from water given intravenously and enterally.*

In animals receiving injections of water intravenously, diuresis started after an average interval of 60 min.; 15 min. was the least interval (exceptional), and 105 min. the longest.

When 4 p.c. of the body weight of water is given by stomach tube to rabbits, the diuresis also starts about an hour after giving water. When small doses of water (say 1 p.c. of the body weight) such as were injected intravenously are given by stomach tube, very variable results are obtained owing no doubt to the large amount of food residue contained in the stomach and intestines.

Nevertheless, it seems probable that the delays in onset are not very different because in man and in rats (unpublished observations) the delay after drinking water is not greatly altered by increasing the dose of water administered.

(4) *Factors inhibiting the diuresis produced by intravenous water administration.*

(*a*) *Anæsthetics.* In four experiments the animals were lightly anæsthetized with ether and in five experiments with chloroform. In most cases the anæsthetic was given as soon as the urinary output had increased threefold or more. It will be seen from section (2) that in general a still greater rate of urine formation was to have been expected, on measurement of the next urine sample, had no anæsthetic been given. In all of these experiments the anæsthetic caused a marked inhibition of urine formation (Fig. 1).

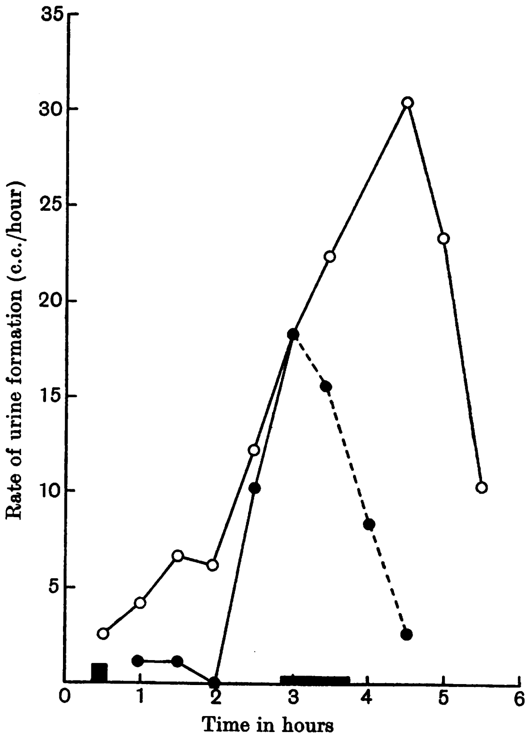

Fig. 1. The effect of ether on the diuresis after intravenous water. ○ Diuresis uninterrupted. ● - - - ● Diuresis interrupted by ether. ■ 25 c.c. water given intravenously. ▬ Ether administration. The same rabbit was used for both experiments.

In all of three experiments where the rate of urine formation was followed for some time after recovery from the anæsthetic (Fig. 2) a renewal of the diuresis was observed, which took place when the animals had excreted all of, or more than, the additional water given. In one case the second diuresis was large and the amount of urine much greater (170 p.c.) than the amount of water given. It seems that the mechanism causing diuresis is not directly controlled by the excess of water then present in the body as a whole, since the diuresis is renewed at a time when there is no excess of water. This is consistent with the experiments of Heller and Smirk [1932 *a*, *b*], where diuresis was obtained in rabbits and rats, previously depleted of as much water as was subsequently given.

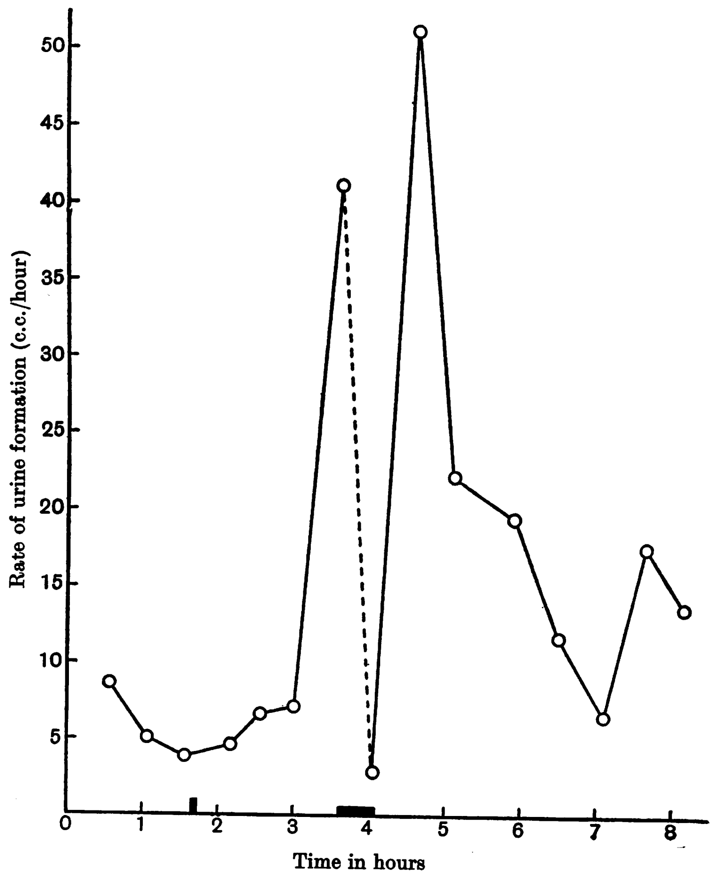

Fig. 2. The effect of chloroform on the diuresis after intravenous water. O---O Diuresis interrupted by chloroform. ▮ 25 c.c. water given intravenously. ▬ Chloroform administration.

(*b*) *Struggling.* It is well known that violent exercise inhibits water diuresis. On this account a few experiments were performed to see if the results described in the previous section might be partly or wholly explained by a struggling of the animals during the induction of anæsthesia.

The rabbits were, therefore, held with their noses in the anæsthetic mask and struggling induced by filling the mask with tobacco smoke. In two of our three experiments the rate of urine formation fell temporarily below the previous rate. This represents a greater inhibition than the actual measurements suggest owing to the fact that the urine output was on the increase. The degree of inhibition is much less, however, than that observed with anæsthetics which reduce the output to the basal rate or even below.

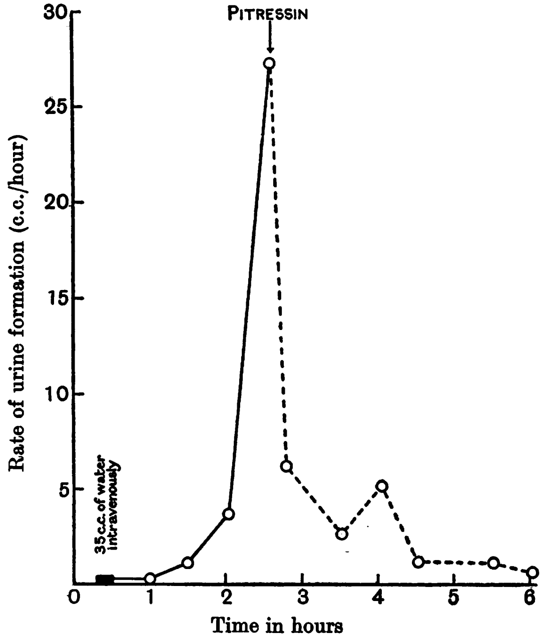

Fig. 3. The effect of pitressin on the diuresis after intravenous water. This experiment was performed on the same rabbit as those illustrated in Fig. 1.

(c) *Pituitary hormone* (*pitressin*). In all of five experiments the diuresis after intravenous water was inhibited by the injection of 0·05–0·1 c.c. of pitressin, administered either intravenously or subcutaneously (Fig. 3).

B. *Cats.*

Three groups of experiments were performed on cats. In each case the animal was anæsthetized with chloroform, and a cannula inserted into the saphenous vein. The chloroform was discontinued, and immediately 0·05 g. per kg. (except where otherwise stated) of body weight of chloralose, in 2 p.c. solution of normal saline, was run into the vein. Through a suprapubic incision, a cannula was inserted into the urethra so that it just entered the bladder. Finally, both the wounds were well swabbed with percain (1/1000), and the suprapubic incision sewn up. Under these conditions the animal remained quiet for about 6 hours, at the end of which time it was killed with chloroform. For 2 or 3 hours after the urethral cannula was put in, the rate of urinary secretion was observed by quarter- or half-hourly readings of the urine volume. About 1 p.c. of the animal's body weight of glass-distilled water at 37° C. was then allowed to run into the saphenous vein. (There appeared to be no difference in the actions of distilled and tap water.) The rate of the injection varied, but averaged about 4 c.c. per minute. In the last few experiments made it was observed that if the tubing and cannula (capacity 2 c.c.) connecting the water burette to the vein were filled with normal saline, the incidence of hæmoglobinuria was much reduced.

(1) *The effect of intravenous water on the rate of urine formation.*

The results are summarized in Table I; in nine out of the twelve cats a diuresis followed a single injection of water. In two of the remaining

TABLE I. The effect of intravenous water on the secretion of urine in cats anæsthetized with 0·05 g. of chloralose per kilogram of body weight.

Hæmoglobinuria: "Slight" ≡ urine clear within 1 hour
+ ≡ urine clear in 2 hours
+ + / + + + ≡ urine coloured after 2 hours

Cat	Interval between injection and diuresis min.	Duration of diuresis hours	Max./initial rate of urine formation	Increase in output of urine, expressed as p.c. of H_2O given	Hæmoglobinuria	Remarks
10	15	1½	14	90	Slight	—
11 1st water injection	—	—	(2·5)	—	+	Slight increase in urine output
11 2nd water injection	15	2	11·5	87	+	—
12	55	2½	14	115	Slight	—
13	15	4	9·5	112	+	—
14	55	3½	27	56	+ + +	Continuous infusion of 85 c.c. in 2¼ hours
15	40	1¼	3	45	+	—
16	0	3	5	107	Slight	—
17	—	—	—	—	Nil	—
18	70	5 +	9	140 +	+ +	Diuresis still in progress when killed
19	25	3	4·5	80	+	—
20	20	3	15	155	Slight	—
21 1st water injection	—	—	—	—	Nil	—
21 2nd water injection	15	2½ +	6	83 +	Nil	Diuresis in progress when killed
Average	30	3	11	97		

three animals a second dose of water was given after a suitable interval, and in both cases a diuresis was then obtained. The extra amount of urine secreted during the diuresis varied, but the average of the experiments gave 97 p.c. of the amount of water given. The rate of secretion at the peak of diuresis was often increased from ten to fifteen times the normal rate. Delay between the administration of water and the onset of diuresis averaged about half an hour, being shorter than the corresponding average delay in rabbits.

It was thought unnecessary to control the hæmoglobinuria as a possible factor in causing the diureses, for it was completely absent in four cases. In others it was very slight and transient, and in no case did its severity appear to bear any relation to the time of onset, the amount, or the duration of the diuresis.

(2) *The effect of larger doses of chloralose.*

The results obtained are summarized in Table II. The animals in this group were given 0·075–0·1 p.c. of body weight of chloralose intravenously instead of the routine dose of 0·05 p.c. of body weight which was finally adopted. Only one of the five animals in this group gave a diuresis after a single injection of water. Two of the remainder were tried with a second dose, and one gave a moderate diuresis.

TABLE II. The effect of intravenous water on the secretion of urine in cats anæsthetized with 0·075 g. or more of chloralose per kilogram of body weight.

Cat		Interval between injection and diuresis min.	Duration of diuresis hours	Max./initial rate of urine formation	Increase in output of urine, expressed as p.c. of H_2O given	Hæmoglobinuria	Dose of chloralose per kilogram of body weight g.
2		15	4	13	200	+ +	0·075
3	1st water injection	—	—	—	—	Slight	0·1
	2nd water injection	—	—	—	—	+	
4	1st water injection	—	—	—	—	Nil	0·075
	2nd water injection	40	1¼	11·5	56	Slight	
5		—	—	—	—	Slight	0·075
6		—	—	—	—	+	0·075

This comparative failure to obtain diuresis where more chloralose was given suggested a parallel to the action of ether or chloroform on the rabbit diuresis.

(3) *The effect of evisceration on cats.*

The same procedure was followed as in section B (1), except that the animals were eviscerated. This was done after cutting between ligatures and in the following order, the inferior mesenteric artery, the superior mesenteric artery, the cœliac axis, the portal vein, and finally the rectum and œsophagus. The abdominal wound was swabbed with percain and sewn up.

Out of seventeen experiments on eviscerated animals, a diuresis was only observed in five cases, but these seem worth recording as being definitely positive results (Table III). The diureses were similar in character to those obtained from the intact animals, except that the maximum rate of secretion never rose so high, and the amount of urine output was less. Nevertheless, they prove that a diuresis may result from the intravenous administration of water and that the presence of the alimentary canal is not essential for establishing such a diuresis. This finally disposes of the theory that the alimentary route of absorption is necessary for the production of a diuresis after giving water.

TABLE III. The effect of intravenous water on the secretion of urine in eviscerated cats anæsthetized with 0·05 g. of chloralose per kilogram of body weight.

Cat	Interval between injection and diuresis min.	Duration of diuresis hours	Max./initial rate of urine formation	Increase in output of urine, expressed as p.c. of H_2O given	Hæmoglobinuria
A	40	2½	3	90	Nil
B	25	2½	5	50	+
C	25	1½	4	35	Nil
D	25	3	15·5	90	Nil
E	55	2	5	100	?

In one case only the liver was in the circulation, the cœliac axis having been ligatured distal to the origin of the hepatic artery. In the remaining four cases the liver was out of the circulation as was shown by the intravenous injection of dyes before death, which were seen to colour all tissues except the liver. It seems very probable that the presence of the liver is also unnecessary for the production of a water diuresis.

DISCUSSION.

It has been shown that in unanæsthetized rabbits the intravenous injection of water in sufficient amount causes diuresis. It is necessary to decide, however, if there is justification for calling this a water diuresis.

The characteristics of a water diuresis are that there is a definite delay before diuresis begins; that the rate of secretion rises rapidly to a peak, where it may be 10 to 20 times the normal rate; that it is of short duration (in hours); that the amount of urine secreted during the diuresis is of the same order as the amount of water given; and that it is cut short by pituitary hormone and inhibited also by certain anæsthetics such as ether and chloroform. Our results show that these criteria were fulfilled in the rabbits, and, so far as tested, in the cats, with the possible exception of the amount of water put out. Although this is irregular in the cats it is of the order of the amount of water given, but in the rabbits it is in excess of that given.

Our results also show that diuresis is not evoked by the intravenous injection of laked blood in amounts sufficient to cause hæmoglobinuria, and the water diuresis did not appear to be influenced, either in respect of delay before the onset or of the amount of urine formed, by the moderate degrees of hæmoglobinuria which usually followed intravenous injection of water; although gross hæmoglobinuria appeared to prevent or reduce the diuresis.

We, therefore, find ourselves in agreement with Frey [1907] and differ from Ginsberg [1912] and Cow [1912, 1914]. The proof that a diuresis of the water diuresis type results from the intravenous injection of water removes the need for assuming absorption of a diuretic hormone from the intestinal mucosa.

The inhibition of the diuresis in rabbits by ether, chloroform and pituitrin indicates that these substances have a parenteral action and that the reduction in diuresis which they cause is not due merely to prevention of alimentary absorption. This confirms the experiments of Heller and Smirk [1932 *b*].

In cats the use of the standard dose of chloralose as an anæsthetic did not seem to interfere with diuresis, but it may be significant that in those cats which received more than the standard dose there was little success in the attempts to procure a diuresis (see Table II).

Our experiments have a further bearing on some previous work by Heller and Smirk in which rats, previously depleted of water, were given a dose of water by mouth insufficient, or just sufficient, to restore their normal water content. These animals had a diuresis, in which the amount of excess urine secreted was not much less than that secreted by controls, in which all the water given constituted an excess over their normal body content. Our present experiments discount the possibility that this diuresis might have been due to the stimulus of a temporary excess of water in the gut, or to preferential storage of water in the liver.

The experiments on eviscerated cats were designed to see if a diuresis of the water diuresis type could be produced after complete removal of the stomach and intestines and when the liver was out of the circulation. The conditions of the experiments were extremely unfavourable, as it has been shown that even simple laparotomy may be sufficient to inhibit water diuresis [Heller and Smirk, 1933]. In addition the longer and deeper chloroform anæsthesia necessary for evisceration no doubt played a part in preventing frequent success in this experiment. Again, in the simple diuresis experiments the diuresis was only obtained at the first water injection in nine out of twelve cats, and in eviscerated cats the general condition is not maintained long enough to permit of two trials. Five experiments, however, yielded a definite diuresis after water injection. This could not be accounted for by the picking up of some diuretic substance from the alimentary canal, which was absent; nor from the liver, which was completely out of the circulation in four experiments as proved by the intravenous injection of dyes.

A further point of interest is the latent period between water administration and diuresis. This is always seen when the alimentary route of absorption is used, and is also apparent in our experiments (though not demonstrable in cats 11 and 16). This confirms the work of Heller and Smirk [1932 *a*], Klisiecki, Pickford, Rothschild and Verney [1933] and Smirk [1933] who found that alimentary absorption is in advance of diuresis. In rabbits the delay in the onset of diuresis is about the same whether they receive water intravenously or by the alimentary tract; but individual variations in both cases preclude an accurate statement of the relative time intervals.

It is evident, however, that the delay when water is taken in the normal way is due only in part to the time spent in alimentary absorption. Other time-consuming processes must intervene between the initial dilution of the blood and the final excretion by the kidney.

Summary.

1. Unanæsthetized rabbits and chloralosed (0·05 g. per kg.) cats have a typical water diuresis after intravenous injection of water. The urine formed is pale and hypotonic; the extra amount secreted varies, but in cats is of the same order as the amount of water given, and in rabbits more.

2. Intravenous water may cause hæmoglobinuria, but reasons are advanced for excluding this as a factor in causing the diuresis.

3. In rabbits the diuresis after intravenous water is inhibited by pituitrin, ether and chloroform. It follows that the antidiuretic action of pituitrin, ether and chloroform is obtained parenterally.

4. A diuresis after intravenous water has been obtained in cats from which the alimentary canal has been removed and where the liver has been excluded from the circulation. The portal route of absorption is not essential, therefore, for the production of a water diuresis.

5. There is a considerable delay in the onset of diuresis even when the water is given intravenously. This suggests that the time expended in alimentary absorption is not alone responsible for the latent period when water is given orally.

The expenses of this work were defrayed in part by a grant to one of us (W.H.N.) from the Medical Research Council.

REFERENCES.

Cow, D. (1912). *Arch. exp. Path. Pharmak.* **69**, 393.
Cow, D. (1914). *J. Physiol.* **48**, 1.
Frey, E. (1907). *Pflügers Arch.* **120**, 93.
Ginsberg, W. (1912). *Arch. exp. Path. Pharmak.* **69**, 381.
Heller, H. and Smirk, F. H. (1932 *a*). *J. Physiol.* **76**, 1.
Heller, H. and Smirk, F. H. (1932 *b*). *Ibid.* **76**, 283.
Heller, H. and Smirk, F. H. (1933). *Arch. exp. Path. Pharmak.* **169**, 298.
Klisiecki, A., Pickford, M., Rothschild, P. and Verney, E. B. (1933). *Proc. Roy. Soc.* B, **112**, 496.
Smirk, F. H. (1933). *J. Physiol.* **78**, 113.