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STUDIES CONCERNING THE ALIMENTARY ABSORPTION OF WATER AND TISSUE HYDRATION IN RELATION TO DIURESIS.

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Part III. The influence of posterior pituitary hormone on the absorption and distribution of water.

Introduction.

It is known that the diuresis which normally follows a large dose of water is inhibited by pituitrin and likewise the polyuria of diabetes insipidus is usually reduced. It was shown by Verney [1926] that the abundant hypotonic urine formed by isolated kidneys when perfused by a simple heart-lung preparation is both reduced in amount and increased in concentration by pituitrin or by the inclusion in the blood circuit of a head, provided the pituitary gland of that head remains intact. Although the polyuria of isolated kidneys is not a water diuresis, since no additional water has been given, the inhibition of their activity by pituitrin is an indication that the hormone of the pituitary body has a direct renal action and suggests [Verney, 1929] that this inhibition of water diuresis is primarily of renal origin. This is further supported by the observation of the same author that in unanæsthetized dogs with denervation of one kidney the urine flow from the ureters is normally equal and the kidneys respond equally to water diuresis and are equally inhibited by pituitrin. On the other hand, except by some extrarenal action, it is difficult to explain the results of Miura [1925], and Buschke [1928], who observe increases in the blood chlorides when pituitrin is given to nephrectomized rabbits.

Our object is to examine the effect of this hormone upon the absorption and distribution of water administered by stomach tube to intact unanæsthetized animals.

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Firstly, we have administered water to rats and compared the normal absorption curve with the absorption curve after pituitary extracts by killing sets of rats at varying times after water was given and determining the amounts of water remaining in the alimentary canals. Secondly, in rabbits we have obtained for analysis samples of muscle, skin and blood during the course of the experiments by the procedures which have been shown in the first paper of this series to leave the diuresis uninfluenced and afterwards we have made post-mortem examinations.

A. The absorption of water from the alimentary canal of rats under the influence of pituitary hormone.

Experimental procedure.

The rates of water absorption of rats which have received about 1 unit of pitressin per 100 g. rat subcutaneously 30 min. before the administration of 5 p.c. of their body weight of warm water have been compared with the absorption rates of rats receiving only the dose of water. The method of study is precisely as described in the first paper of this series, Part I, Section B.

Results.

Table I gives the weight of gut and contents at varying times after administering 5 p.c. of the body weight of water. The left-hand columns are control experiments, the right-hand columns give the results on animals under the influence of pituitrin. It will be evident from Table I and Fig. 1 that the pituitary hormone has no significant influence on the water absorption rate in rats.

Table I.

Time after giving water (min.)	Rats without pitressin			Rats with pitressin		
	No. of rats	Weight of gut as p.c. of body weight	Average	No. of rats	Weight of gut as p.c. of body weight	Average
15	3	8·9, 8·5, 9·2	8·9	4	10·4, 8·3, 7·1, 8·9	8·7
30	4	9·6, 6·5, 4·8, 6·9	7·0	4	7·2, 6·7, 6·4, 6·8	6·8
45	6	6·9, 6·2, 6·4, 6·1, 6·2, 5·7	6·2	6	5·2, 7·1, 6·2, 7·6, 6·6, 6·4	6·7
75	7	4·6, 10·3, 6·4, 7·9, 5·9, 5·5, 4·9	6·5	7	4·8, 8·4, 6·6, 8·9, 10·9, 4·7, 5·8	6·9
120	6	6·8, 6·2, 7·4, 7·6, 5·9, 4·8	6·5	6	5·2, 6·8, 6·8, 6·3, 5·9, 6·6	6·3
Controls, no water	5	6·6, 6·2, 8·6, 5·6, 5·4	6·5			

Discussion.

In rats water given per os is absorbed as usual under the influence of pitressin, but is only excreted at a greatly diminished rate by the kidney. This water, which forms 5 p.c. of the body weight of the animal, in a period of about $\frac{1}{2}$ hour is absorbed and either stored in the blood and

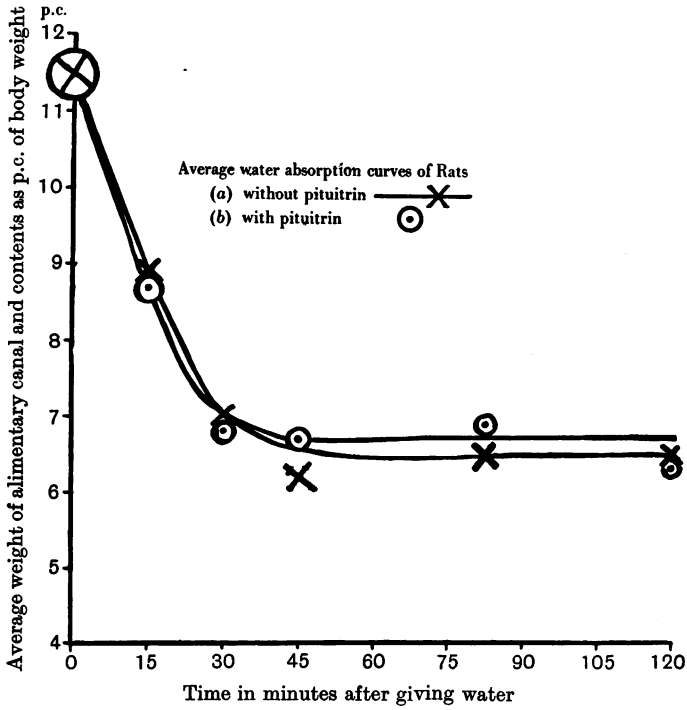

Fig. 1.

tissues of the animal or excreted by some channel other than the kidney. The only channel not under direct observation is the respiratory tract. As a precaution, therefore, a number of animals were weighed some hours after giving the water to make sure that such water as had not been excreted by the kidneys was still present in the body. There was indeed a loss of weight, but this did not account for the greater part of the water which was evidently stored in the blood and tissues of the animal.

Since it is difficult to take tissue and blood samples from a small animal such as the rat it was decided to continue our investigations on water distribution in another animal, the rabbit.

B. The storage of water in the muscle, skin, blood and serous cavities of rabbits during the inhibition of a water diuresis by pituitary hormone.

Experimental procedure.

0·2–0·4 c.c. of pitressin was given 30–45 min. before water administration. The animals then received 4 p.c. of their body weight of water by stomach tube and samples of muscle and blood were taken by the procedure outlined in the first paper of this series [Heller and Smirk, 1932]. At the conclusion of the experiment the fluid contained in the serous cavities was collected and measured.

Results.

When diuresis was inhibited by pituitrin the water content of the blood was increased to a much greater degree than it was in cases where the inhibition was produced by anæsthesia (see Part IV) or laparotomy (unpublished observation). Also the water uptake of muscle was greater where diuresis was inhibited by pituitrin than where diuresis was allowed to proceed normally. These results are summarized in Table II.

In two very nervous rabbits, Nos. 6 and 7, this increase in water content of muscle was slight, which suggested that perhaps there was an inhibition of alimentary absorption as well as of renal activity.

In post-mortem examinations made at the end of the experiments, but unfortunately only on the last six animals, quite large quantities of fluid were obtained from the peritoneal cavities: 15, 20, 20, 10, 4 and 14 c.c. respectively. Not only was there more fluid in the peritoneum but also there was more in the pleural and pericardial cavities than had been found in six of the rabbits where no pituitrin had been given and an examination of these cavities made at the conclusion of the experiment. In these latter animals there had been no inhibition of diuresis.

It is clear then when water is absorbed from the alimentary tract and fails to be excreted by the kidneys there is a greater increase in the water content of muscle and of serous cavities. Our methods, therefore, detect this water when it is absorbed, and our previous and subsequent observations concerning the absence of an appreciable increase in the water content of muscle must be regarded as strong evidence that when diuresis has been inhibited without an appreciable increase in the water

TABLE II.

Animal No.	3-hour output of urine: Normal c.c.	3-hour output of urine: Under pituitrin c.c.	Increase in p.c. water of muscle	Degree of blood dilution (as a percentage of the initial concentration)	Post-mortem examination after 3 hours	Notes
1	57	1	+3·0	—	None made	Previous diet of oats, 0·2 c.c. pitressin
2	42	11	+3·2	—		
3	48	10	+4·4	—		
4	84	18	+2·7	—		
5	76	57	+2·5	—		
6	—	10	+0·5	93·5		Previous diet of cabbage, 0·3 c.c. infundin
7	—	30	+0·4	94		
8	89	11	+1·2	91	15 c.c. of fluid in serous cavities	Cabbage diet, 0·5 c.c. infundin
9	98	22	+1·8	88	20 c.c. of fluid in serous cavities	—
10	92	10	+2·0	95	20 c.c. of fluid in serous cavities	Cabbage diet, 0·2 c.c. pitressin
11	66	9	+1·9	92	10 c.c. of fluid in serous cavities	Cabbage diet, 0·2 c.c. pitressin P.D.
12	49*	4	−0·2	94	4 c.c. of fluid in serous cavities	Cabbage diet, 0·4 c.c. pitressin P.D.
13	67*	11	+1·3	88	14 c.c. of fluid in serous cavities	Cabbage diet, 0·4 c.c. pitressin P.D.

* These two animals passed copious fluid stools shortly after receiving their doses of water.

content of muscle there has been a reduction in the alimentary absorption of water (see Parts I and IV).

It is clear from Table II that an increase is obtained in the water content of longissimus dorsi muscle, but the degree of increase varies. The water uptake of a second muscle—the vastus externus—was next studied (Table III), to obtain an idea of how far the changes in the water content of one muscle were an index of changes in the musculature as a whole.

TABLE III. The uptake of water by two different muscles under the influence of pitressin.

Exp. No.	Increase in p.c. water of two muscles 90 min. after giving water: Longissimus dorsi	Vastus externus
1	+2·9	+1·9
2	+2·0	+1·6
3	+1·4	+1·4
4	+1·3	+1·6
5	+3·1	+2·0
Average	+2·1	+1·7

As a control observation the influence of pitressin alone on the water content of muscle was investigated in five animals. Beyond the fact that no additional water was given the experimental conditions were unaltered.

The changes in the water content of muscle were + 0·6, + 1·4, + 0·3, − 0·8, − 0·2, averaging + 0·3 p.c.

The corresponding control in which water but no pituitrin was given has been described in the first paper of this series.

Because the removal of as little as 2 c.c. of blood may be associated with a blood dilution in the subsequent sample [Smirk, 1932] and also because the loss of blood from muscle sampling though slight is indefinite, it has been thought desirable to make a few separate experiments on the blood dilution in animals where no muscle samples were taken.

The results are divided into two groups (Tables IV and V) which differ in the lengths of the time periods between giving pitressin and water and between giving water and taking the second blood sample. To the first group (Table IV), in which a considerable blood dilution is

TABLE IV. Animals received 0·2 c.c. pitressin ½–¾ hour before giving water and the second blood sample was taken 1½ hours after giving 4 p.c. body weight of water.

Exp. No.	Degree of blood dilution expressed as a percentage of the initial concentration		Urinary output in 1½ hours after water
	By hæmatocrit	By hæmoglobin	c.c.
1	93	86	0·0
2	—	96·5	1·0
3	98·5	96·6	5·0
4	92·2	87·8	4·5

TABLE V. Animals received 0·2 c.c. pitressin at least 2 hours before giving water and the second blood sample was taken 2 hours after giving 4 p.c. body weight of water.

Exp. No.	Degree of blood dilution expressed as a percentage of the initial concentration		Urinary output in 2 hours after water
	By hæmatocrit	By hæmoglobin	c.c.
1	98·8	101	0·0
2	101·4	105·4	4·0
3	100	99·0	0·0
4	107·3	100·4	5·5
5	110	104·8	6·0

the rule, may be added the results of eight experiments from Table II, in which the experimental conditions were similar. In the second group, of five experiments in all, there is no regular diminution in either the hæmatocrit reading or the hæmoglobin percentage. The only essential difference appeared to be that pitressin was given a longer time before the water in the experiments where there was no regular blood dilution.

For the present we do not intend to investigate this time difference in the action of pitressin or to confirm whether it is indeed a regular phenomenon. It may indicate some mechanism by which the partition of water between blood and tissues can be altered. There did not appear to be any defect in alimentary absorption.

Magnus and his school have investigated the part played by the skin in the storage of water and salt. Since water is normally stored in skin [see also Heller and Smirk, 1932] we decided to investigate the changes in water content after giving pituitrin and water.

A small piece of skin was excised from the back with the aid of local subcutaneous anæsthesia. The five animals were given 0·2 c.c. of pituitrin and then 4 p.c. body weight of water by stomach tube. After 90 min. a second skin sample was removed in the same way and the animals were killed. This procedure was repeated in a series of another five animals in which water but no pituitrin was given. At 105 min. after giving pituitrin and 90 min. after giving water the changes in the water content of muscle were: − 2·5, − 1·0, − 0·8, − 0·3, − 1·2, average − 1·2 p.c. In the control animals which received water only the changes were: + 3·5, + 1·1, − 1·6, + 0·6, + 5·5, average + 1·8 p.c. It appears that the water content of skin is diminished in the animals which received pituitrin injections despite the administration of additional water.

The influence of pituitrin upon the extrarenal water loss. In view of the marked variations in the extrarenal loss of water which followed changes in the temperature of the surrounding air (Part II) we considered it worth while to determine whether there was any appreciable change in the extrarenal water elimination when a water diuresis is inhibited by pituitrin.

In five rabbits the non-fæcal extrarenal loss of water was determined by weighing the animals before and 4 hours after a dose of water, and then again before and 4 hours after a dose of water together with 1 unit of pituitrin subcutaneously. The room temperature was $17 \pm 1°$ C. on both occasions.

The losses of water were 13·5, 16, 10, 8 and 10·5 g. in 4 hours, average 11·6, when the animals received water only, and 27·5, 16, 15, 31·5, and 30·5 g. in 4 hours, average 24·1, when the diuresis was inhibited by pituitrin.

Presumably, since rabbits do not sweat, this increased loss of water takes place through the lungs. The increased loss may be caused either by an increase in the moistness of the respiratory passages or by an increase in the pulmonary ventilation.

It is clear, however, that although the extrarenal water elimination appears to be greater after pituitrin yet the difference in the quantities of water lost is in no case sufficient to account for the inhibition of renal activity. More detailed confirmation of this point would not, however, be relevant to our present work.

Discussion.

It will be seen from the results obtained in rabbits (see Tables II and IV) that when pituitrin is injected subcutaneously ½ hour before the administration of a large dose of water so that the diuresis which normally results is prevented, there is usually a definite hydræmia. The water content of the muscles is also increased (Tables II and III), and the degree of this is much greater than that met when diuresis is allowed to proceed normally. In addition in all those cases where an examination has been made there was an increase in the fluid content of the serous cavities, so that whereas normally it is difficult to collect more than 1 or 2 c.c. of fluid, one is now able to obtain as much as 15 c.c. or 20 c.c. As a parallel observation one of us [Heller, 1930] has previously reported the distension of the lymph spaces in frogs. It was suggested by Rees [1920] and by Koref and Mauntner [1926] that failure of alimentary absorption might account for a part of the inhibitory action of pituitrin. In the rabbit it is clear, however, that there is a definite excess of water present in both musculature and blood. We suggest that, since inhibition is present when there is an excess of absorbed water to be disposed of, it is not likely that changes in the water absorption rate play any considerable part in the pituitrin inhibition.

It has been argued that the excess of water which has been shown to be present in the blood may not be free but in some physico-chemical way "bound." This, however, is unlikely, since there is regularly an increased fluid content of the serous cavities which would appear to result from the increased transudation following a dilution of blood colloids.

An increased "avidity" of plasma for water would hardly be associated with increased transudation from the capillaries into the body cavities, and any increased "avidity" of tissues would surely need to prevent blood dilution before it could be cited as a direct cause of diminished renal activity. Heller's work on frogs [1930] yielded no evidence of a direct action of pituitrin on the water metabolism of living muscle, or upon the physico-chemical properties of tissue proteins. Heller was able to show that the increase of weight in frogs under the influence of pituitrin is not decreased by a rise in body temperature.

It appears likely therefore that the mechanism of the inhibition of water diuresis by pituitary hormone is renal and not extrarenal. There remain facts which would be difficult to explain if it were assumed that all the changes in water metabolism after pituitrin were the result of the inhibition of renal activity.

From Table III it is clear that the water distribution and storage is not uniform throughout the musculature, and similar differences in the water uptake of different muscles have been reported by Baer [1926] and Tashiro [1926]. The results obtained on skin—in which the water content was actually reduced after pituitrin and water administration—make it clear that a complete picture of the water distribution could only be obtained by the analysis of several samples of every tissue and by the elimination of errors due to changing vascularity.

The fall in the water content of skin may very well be due to its lessened blood content, the percentage water content of blood being greater than that of muscle. If corrections could be introduced which eliminated this factor, it is possible that the water content of the actual skin substance would be increased. The actual amounts of water involved are in any case small since the skin forms only 12 p.c. of the body weight.

Poulsson [1930] concludes that the reduced output of water after pituitrin is due to an increased reabsorption of water in the tubules, since the action of pituitrin in inhibiting diuresis is not accompanied by any appreciable change in the calculated amount of glomerular filtrate.

His calculations of the amounts of glomerular filtrate require, however, the assumption that all the creatinine and sulphate excreted in the urine is filtered by the glomeruli and reaches its urinary concentration by water absorption in the tubules.

The internal localization of function in the kidney is a subject of great difficulty, and the work of Starling and Verney [1925] is not in agreement with the assumption which Poulsson and others have used to calculate the amount of glomerular filtrate.

Summary.

1. In rats the alimentary absorption rate for a 5 p.c. body weight dose of water is uninfluenced by giving 1 unit of pitressin per 100 g. rat subcutaneously. This dose of pitressin considerably reduces the formation of urine.

2. In rabbits receiving 0·2–0·4 c.c. of pitressin and 4 p.c. body weight of water, there is reduced urine formation and increased water storage in the blood, muscle and serous cavities.

3. The nature of the anti-diuretic action of pituitary hormone is discussed in the light of these observations.

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Part IV. The influence of anæsthetics and hypnotics on the absorption and excretion of water.

Introduction.

It has been demonstrated by many workers, Schroeder [1888], Frey [1907], Molitor and Pick [1925, 1926, 1927], Smith and McClosky [1925], Stehle and Bourne [1928], Buschke [1928], Fee [1928], Kugel [1929], Bonsmann [1930], that the excretion by the kidneys of a large dose of water administered by stomach tube is rarely normal in an anæsthetized animal. The effect of anæsthesia appears to depend upon the nature of the anæsthetic, upon the depth of anæsthesia and also upon

the animal used. With most anæsthetics the urinary output is diminished, with a few it is increased. The school of Pick conclude that in general the influence of anæsthetics results from their action upon the central nervous system. Narcotics which depress first the higher centres such as paraldehyde, chloralose, avertin, and alcohol tend to increase the outflow of urine; those which first depress the mid-brain areas tend to diminish the activity of the kidney (luminal, chloretone). It is supposed by them that the normal control of diuresis is through a diuretic centre in the mid-brain: the depression of its activity diminishes renal activity; the depression of higher control centres with release of its activity is said to increase urinary outflow.

Though opinions may differ as to the precise way in which anæsthesia influences the output of urine there is little doubt that a number of substances of differing chemical structures but having in common the property of producing narcosis have also in common the property of reducing the urinary outflow. The object of this paper is to determine whether some alteration in the kidney or tissues is responsible for this anti-diuretic action or if alterations in alimentary absorption play a part.

In a few experiments performed by us on rabbits anæsthetized with ether it was observed that a dose of about 4 p.c. of the animal's body weight of water produced little or no increase in the output of urine. But samples of muscle in these animals showed only slight increases in their water content. Now in rabbits where renal activity was prevented by pituitrin but where there was every evidence of water absorption the extra water given was readily detected in muscle samples (see Part III). Therefore, the absence of any considerable increase in the water content of muscle in these anæsthetized rabbits suggested to us that a part at least of this apparent inhibition of renal activity might be of alimentary origin and due to the non-absorption of the water given.

For this reason we decided to investigate the matter more accurately, using the statistical method of studying alimentary absorption in rats already described in Part I of this series [Heller and Smirk, 1932]. The rat is particularly suitable for this investigation since we have shown that water absorption is practically complete before the onset of diuresis. It is, therefore, possible to investigate also the effect of anæsthesia on diuresis as distinct from absorption by administering the anæsthetic at a time when water absorption is almost complete and diuresis is only just beginning.

Experimental procedure.

Rabbits weighing about 2·kg. were used and a uniform dose of 75 c.c. of water was given. The methods employed were light ether anæsthesia, deep chloretone anæsthesia and light chloretone anæsthesia. The water and chloretone were given by stomach tube, the ether by inhalation.

The procedure for rats has been exactly as described in Part I, chloroform and ether were given by inhalation; paraldehyde, luminal, urethane and chloralose were given subcutaneously. The doses and previous diet are stated with the protocols. Body temperatures were measured per rectum.

Results.

Preliminary experiments on rabbits. Four animals received ether. Under ether their urinary outputs for periods of 4, 4, 3 and 4 hours were 2, 19, 5 and 0·5 c.c. as compared with their normal outputs of 29, 35, 36 and 52 c.c. for corresponding time periods. The increases observed in the percentage water content of muscle 1½ hours after giving water were only + 0·8, + 0·9, 0·0, + 0·8, averaging + 0·6 as against an average increase of + 2·0 p.c. where diuresis is inhibited to a corresponding degree by pituitrin (see Part III).

Four experiments, two with light chloretone anæsthesia and two with deep chloretone anæsthesia, gave a similar absence of appreciable change in the water content of muscle and no increase in the water content of liver (determinations made on 16 samples of muscle and 18 samples of liver). The technique of removing liver samples and the influence of the procedure of laparotomy upon absorption and diuresis will be described in a subsequent paper. The urinary output was also inappreciable.

Although the chloretone experiments are complicated by the intestinal method of administration as well as by laparotomy, the absence of expected increases in the water content of the tissues examined appears to be a justification for further work.

I. *The influence of anæsthetics on water absorption in rats.* It will be clear from the following results that the rate of absorption of water from the alimentary canal of rats is greatly diminished by ether (Table I)

TABLE I. Ether. Light ether anæsthesia with usually a positive corneal reflex. Deprived of water overnight.

Time after giving 5 p.c. body weight of water	No. of rats used	Weight of the alimentary canal and contents expressed as a percentage of body weight	Average
60 min.	5	9·0, 10·2, 9·5, 7·3, 8·7	9·0
Controls, no extra water	5	5·3, 5·8, 6·7, 6·8, 7·0	6·3

and chloroform (Table II); slightly diminished by luminal (Table III), paraldehyde (Table IV) and urethane (Table V), and hardly diminished by chloralose (Table VI). The inhibition of absorption produced by ether is unaltered by physostigmine (Table VII).

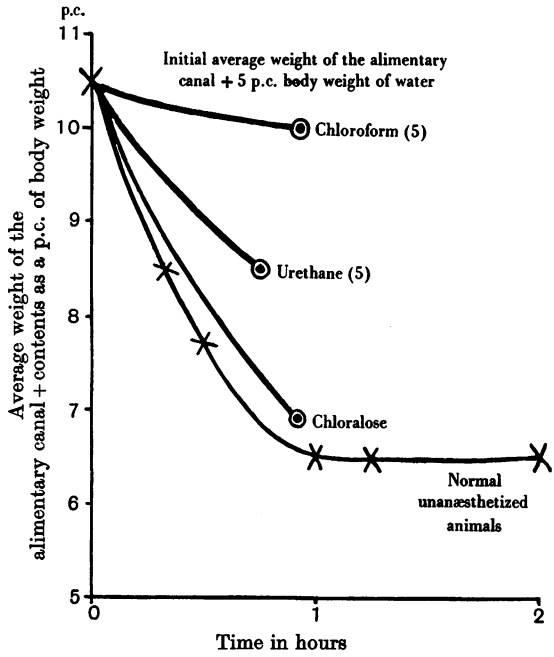

Fig. 2. The influence of chloroform, urethane and chloralose upon the alimentary absorption of water. (The animals were allowed access to water overnight.)

TABLE II. Chloroform. Light chloroform anæsthesia with usually a positive corneal reflex. Allowed water up to the time of the experiment.

Time after giving 5 p.c. body weight of water	No. of rats used	Weight of the alimentary canal and contents expressed as a percentage of body weight	Average
55 min.	5	10·2, 8·3, 10·7, 10·4, 10·4	10·0

TABLE III. Luminal. (0·015 g. of sodium luminal per 100 g. rat deprived of water overnight.)

Time after giving 5 p.c. body weight of water	No. of rats used	Weight of the alimentary canal and contents expressed as a percentage of body weight	Average
30 min.	5	8·5, 8·8, 8·3, 11·5, 9·9	9·4
45 „	5	7·2, 7·7, 5·2, 9·5, 9·6	7·8
90 „	6	5·0, 5·8, 5·9, 7·6, 8·4, 6·8	6·6
Controls, no extra water	5	5·3, 5·8, 6·7, 6·8, 7·0	6·3

TABLE IV. Paraldehyde. (0·2 g. of paraldehyde subcutaneously per 100 g. rat. Deprived of water overnight.)

Time after giving 5 p.c. body weight of water	No. of rats used	Weight of the alimentary canal and contents expressed as a percentage of body weight	Average
30 min.	4	8·4, 6·4, 7·2, 7·5	7·4
45 ,,	5	8·9, 7·5, 7·3, 7·4, 7·0	—
		5·2 (very lightly narcotized)	7·6
Controls, no extra water	3	6·3, 5·0, 5·1	—

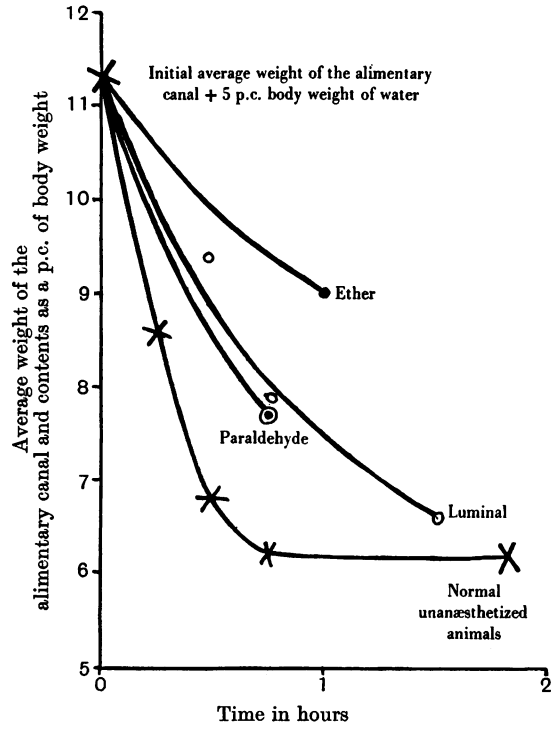

Fig. 3. The influence of ether, paraldehyde and luminal upon the alimentary absorption of water. (The animals were previously deprived of water overnight.)

TABLE V. Urethane. 0·12 g. of urethane per 100 g. rat. Water allowed up to the time of the experiment.

Time after giving 5 p.c. body weight of water	No. of rats used	Weight of the alimentary canal and contents expressed as a percentage of body weight	Average
45 min.	5	8·2, 7·4, 7·1, 8·9, 10·8	8·5
Controls, no extra water	7	6·3, 5·0, 5·1, 5·5, 6·8, 6·6, 5·5	5·7

TABLE VI. Chloralose. Two animals had 0·01 and one animal 0·008 g. chloralose per 100 g. rat. Water allowed up to the time of the experiment. Because of the relative insolubility of chloralose larger quantities of fluid had to be injected. The controls were given the same amount of 0·2 p.c. NaCl (2 c.c.) subcutaneously.

Time after giving 5 p.c. body weight of water	No. of rats used	Weight of the alimentary canal and contents expressed as a percentage of body weight	Average
55 min.	5	6·0, 6·8, 8·9, 6·5, 7·0	6·9
Controls, no extra water	7	6·3, 5·0, 5·1, 5·5, 6·8, 6·0, 5·5	5·7

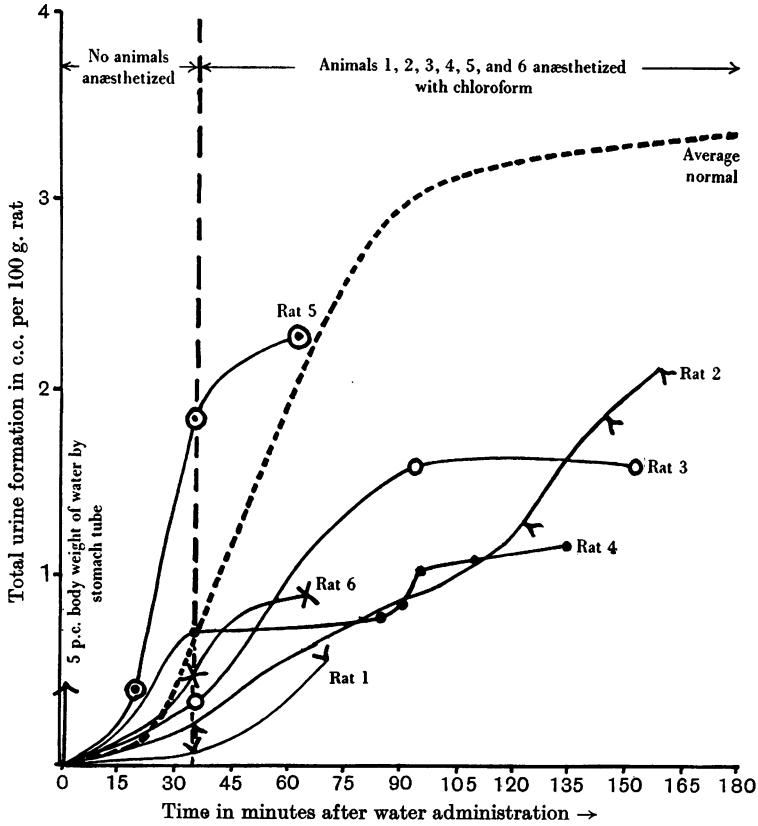

Fig. 4. The influence of chloroform anæsthesia upon water diuresis as distinct from its action upon alimentary water absorption.

TABLE VII. Ether and physostigmine. Light ether anæsthesia with usually a positive corneal reflex. Deprived of water overnight. (Record of the dose of physostigmine lost.)

Time after giving 5 p.c. body weight of water	No. of rats used	Weight of the alimentary canal and contents expressed as a percentage of body weight	Average
60 min.	5	9·6, 9·1, 9·3, 8·0, 8·0	8·8

The results are summarized in graphical form on Figs. 2 and 3, on which the normal absorption curves described in Part I are reproduced. Since it is not possible with injected drugs to obtain much uniformity in the degree of narcosis except by repeated trials on the same animal an increase in the variability of results is to be expected.

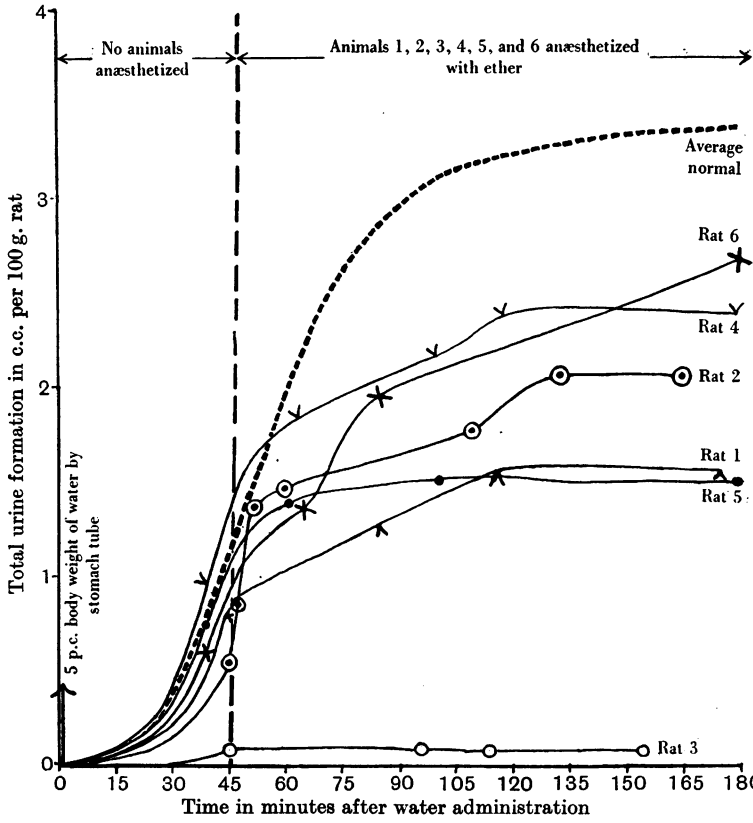

Fig. 5. The influence of ether anæsthesia upon water diuresis as distinct from its action upon alimentary water absorption.

All rats used in these experiments were fed previously on bread and milk for a period of 3 days.

II. *The influences of chloroform and ether upon water diuresis when absorption is complete.* If water is given to an animal and a sufficient time for water absorption is allowed before subsequently administering the anæsthetic, it has been found that a marked inhibition of diuresis is still obtained. This is clearly seen on Figs. 4 and 5, where the diuresis in

each rat which was anæsthetized falls rapidly below the average normal output of the controls. With the exception that no anæsthetic was given the control rats were similarly treated. Figs. 6 and 7 give the average diuresis curves for the anæsthetized and normal rats and indicate the times at which the water absorption may be assumed to have taken place.

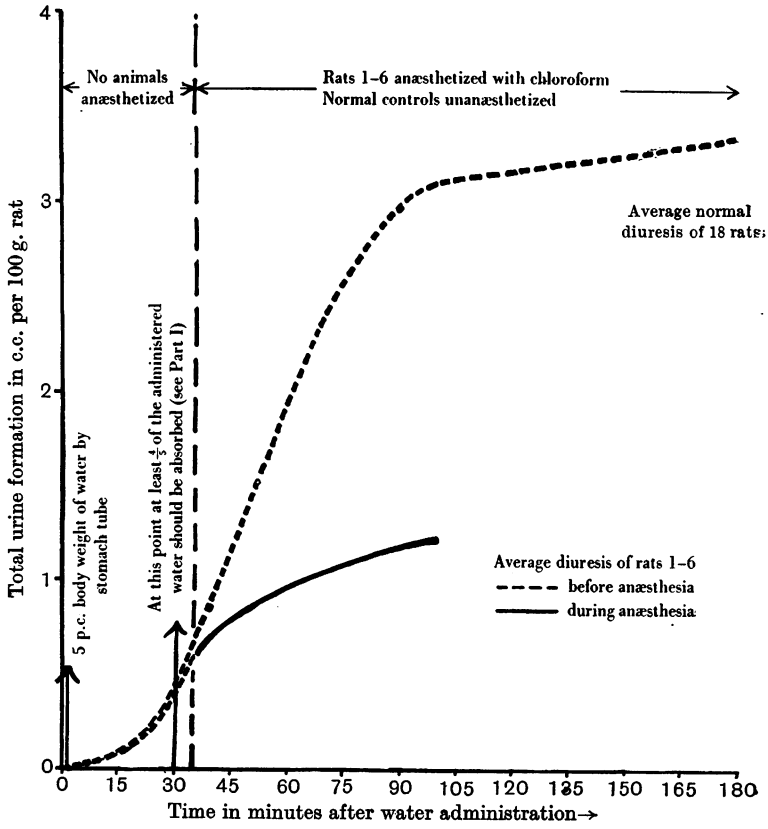

Fig. 6. The influence of chloroform anæsthesia upon water diuresis as distinct from its action upon alimentary water absorption.

From Tables VIII and IX it will be seen that before an anæsthetic was given the average urinary outputs of the two sets of six animals is approximately equal to that of the eighteen normal controls. But during the period when the rats were anæsthetized with ether and chloroform respectively their urinary output fell markedly below that attained by the controls.

Thus at the end of 35 min. the average total urinary output was 0·62 c.c. per 100 g. rat for the normal controls and 0·60 c.c. for the animals which were to be anæsthetized subsequently.

In the next 65 min. the average total output of the normal controls was 2·48, but of the rats anæsthetized with chloroform only 0·61 c.c. per 100 g. rat.

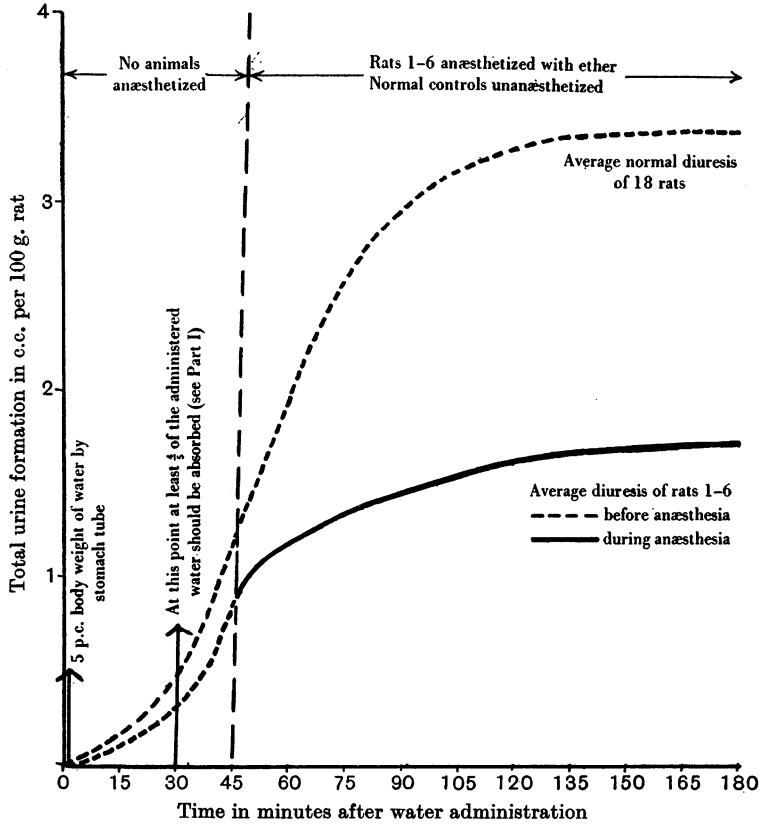

Fig. 7. The influence of ether anæsthesia upon water diuresis as distinct from its action upon alimentary water absorption.

Similar results were obtained using ether anæsthesia.

The water absorption curves for rats in which the previous treatment was similar and which were of the identical breed (Part I) show that water absorption is practically complete within 30 min. after the administration of a 5 p.c. of body weight dose of water by stomach tube.

TABLE VIII.

Time after water administration (min.)	Total urinary output in c.c. per 100 g. body weight of rats which were anæsthetized with ether 45 min. after giving water by stomach tube							Average total urinary output in c.c. per 100 g. rat of 18 normal controls (no anæsthetic given)
	1	2	3	4	5	6	Average	
20	0·13	0·09	0·00	0·26	0·22	0·17	0·15	0·23
40	0·45	0·30	0·04	1·00	0·80	0·66	0·54	0·93
45	0·78	0·54	0·08	1·37	1·10	0·93	0·80	1·17
	Rats Nos. 1–6 now anæsthetized with ether							
50	0·92	1·20	0·08	1·57	1·22	1·08	1·01	1·43
60	1·04	1·46	0·08	1·79	1·37	1·26	1·17	1·95
80	1·23	1·58	0·08	2·00	1·47	1·81	1·36	2·75
100	1·42	1·70	0·08	2·17	1·50	2·10	1·49	3·10
120	1·53	1·88	0·08	2·38	1·50	2·26	1·61	—
140	1·53	2·06	0·08	2·38	1·50	2·41	1·66	—
160	1·54	2·06	0·08	2·38	1·50	2·54	1·68	—
180	1·54	2·06	0·08	2·38	1·50	2·67	1·71	3·35

TABLE IX.

Time after water administration (min.)	Total urinary output in c.c. per 100 g. body weight of rats which were anæsthetized with chloroform 35 min. after giving water by stomach tube							Average total urinary output in c.c. per 100 g. rat of 18 controls (no anæsthetic given)
	1	2	3	4	5	6	Average	
20	0·00	0·04	0·08	0·19	0·40	0·12	0·14	0·23
30	0·02	0·11	0·20	0·50	1·28	0·33	0·41	0·40
35	0·06	0·20	0·32	0·70	1·83	0·47	0·60	0·62
	Rats Nos. 1–6 now anæsthetized with chloroform							
40	0·12	0·30	0·46	0·75	2·00	0·60	0·71	0·93
45	0·17	0·37	0·60	0·77	2·10	0·71	0·79	1·17
50	0·29	0·43	0·72	0·78	2·16	0·78	0·86	1·43
60	0·34	0·54	1·01	0·79	2·26	0·87	0·97	1·95
80	—	0·74	1·40	0·79	—	—	0·98	2·75
100	—	0·98	1·58	1·06	—	—	1·21	3·10
120	—	1·22	1·58	1·12	—	—	—	—
140	—	1·74	1·58	1·17	—	—	—	—
160	—	2·10	1·58	—	—	—	—	—
180	—	—	—	—	—	—	—	3·35

It is clear, therefore, that the results represent the influence of these anæsthetics upon the urinary output after absorption has taken place.

The extrarenal loss of water determined in rats anæsthetized with ether amounted to 3·55, 0·99, 2·97, 3·4, 1·16 and 3·38 per 100 g. rat in 3 hours. In two animals anæsthetized with chloroform it was 2·75 and 3·90 g. per 100 g. rat in 159 and 152 min. respectively. This is not in excess of normal.

The body temperature of the rats fell during anæsthesia, but for reasons described in a previous paper (Part II) it was thought inadvisable to apply heat externally. In any case the inhibition of diuresis takes place before there has been time for any appreciable loss of water or fall in temperature.

Discussion.

In rats the delay in intestinal absorption of water produced by ether and chloroform is so great that this alone would explain the absence of diuresis. But it has also been shown, that even when the induction of anæsthesia is postponed and time is allowed for water absorption there is still a marked inhibition of diuresis. The inhibitory actions of ether and chloroform are therefore twofold: on the alimentary canal delaying absorption and after absorption preventing excretion.

The experiments on rabbits suggest that anæsthetics may also tend to diminish the alimentary absorption in this animal.

In studying the inter-relationship of the nervous system and kidneys and in all diuresis experiments involving the administration of water by the alimentary canal it is clearly necessary to distinguish between enteral and renal phenomena. The parts played by these factors vary and must be separately assessed for each animal and anæsthetic used or a final interpretation of the results may be obscured.

SUMMARY.

In rats: (1) The alimentary absorption of water is delayed to a marked degree by ether and chloroform, to a slighter degree by luminal, paraldehyde and urethane and is not appreciably delayed by chloralose.

(2) Diuresis is inhibited by ether and chloroform even when adequate time for water absorption is allowed prior to the induction of anæsthesia.

(3) The inhibition of diuresis by ether and chloroform is not caused by any increased extrarenal water elimination.

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