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Biologiske Meddelelser. **III,** 1.

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BY

JOHANNES BOCK AND POUL IVERSEN

KØBENHAVN
HOVEDKOMMISSIONÆR: ANDR. FRED. HØST & SØN, KGL. HOF-BOGHANDEL
BIANCO LUNOS BOGTRYKKERI
1921

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Several years ago one of us (Bock) stated that the amount of phosphate in the urine increases by salt diuresis, by sugar diuresis, and especially, by purine diuresis. With regard to water diuresis this was not the same. In most cases Bock[1] found no increase of the phosphate even in profuse water diuresis, in some cases the phosphate was increased but only for short periods. In one experiment (No. 18) by which first water diuresis and afterwards purine diuresis were induced, the amount of phosphate remained quite unchanged during the water diuresis, but was highly increased after theophylline, and the augmentation still continued after the purine diuresis had passed off and the amount of urine returned to its original quantity. Similar results, though not so marked, were obtained in other experiments.

In opposition to Bock's result Baetzner[2] has more recently declared, that in rabbits he almost regularly found the excretion of phosphate in the urine increased during water diuresis. The experiments upon which Baetzner bases his declaration are given in the following table.

A normal estimation before the administration of water has only been made in 4 of Baetzner's 8 experiments, and in each experiment the number of estimations is rather

[1] J. Bock: Archiv f. exp. Pathol. u. Pharmacol. 58 p. 227. 1908.
[2] W. Baetzner: Archiv f. exp. Pathol. u. Pharmacol. 72 p. 309. 1913.

Baetzner's Experiments.

No.	Time	Urine c. c. in 1 hour	P_2O_5 mgm in 1 hour	
1	1. hour	4	1	At the end of the 1st hour 100 c. c. water
	2. —	12	7.6	
	3. —	55	9.6	
	4. —	40	8.8	
2	1. —	1.8	1.5	At the end of the 1st hour 100 c. c. water
	2. —	1.4	2.0	
	3. —	23.3	3.7	
3	1. —	1	1.5	
	2. —	1.2	2.4	100 c. c. water
	3. —	4	5.1	
	4. —	16	6.1	
4	1. —	2.4	2.5	100 c. c. water
	2. —	2.2	6.2	
	3. —	13	7.1	
5	1. —	5	5.3	1 hour before 100 c. c. water
	2. —	20	14.4	
	3. —	75	24.7	
6	1. —	1.8	3.3	1 hour before 100 c. c. water
	2. —	4	5.6	
7	1. —	6	7.5	1 1/2 hours before 100 c. c. water
8	1. —	6	1	1 hour before 100 c. c. water
	2. —	23.5	4.3	

small (4—1). Experiment 7 counts for nothing, comprising only one estimation and no diuresis taking place. — In experiment 4 and 3 in the first hour after the administration of water, respectively none, and only a very slight augmentation of the urine is found, but in both cases a very considerable increase of phosphate is noted, and during the following hour, when diuresis sets in, the further increase of phosphate is but slight. In experiment 6 the amount of urine is so small that it cannot be considered as a diuresis.

In experiment 1 the phosphates increase considerably during the first hour after the administration of water, but the amount af urine only rises from 4 to 12 c. c. and in the following hours, when a profuse diuresis appears, the further increase of the phosphate is only very small. In BAETZNER's experiments 2, 5 and 8 an increase of phosphate was found during the water diuresis, in experiment 5 even a very considerable one. It is however necessary to call attention to a circumstance which makes it impossible to critizise Baetzner's experiments more precisely. In BOCK's experiments the urine was always taken with catheter, and the bladder each time rinsed afterwards with distilled water. This was done partly in order to draw off the last traces of urine, and partly to remove the sediment which is very often present in the bladder of the rabbit and may contain large amounts of phosphate. It was very often necessary, at the commencement of the experiments, to rinse the bladder several times with water before the sediment was entirely removed, a procedure which is absolutely necessary, as we have found that such sediments may happen to be washed out with the urine when a profuse diuresis sets in. BAETZNER states that in his experiments the urine was taken by catheter and by pressing out the bladder. In the last case, at any rate, the bladder has not been rinsed, which we, as already mentioned, must consider an absolutely necessary proceeding in investigating the excretion of the phosphates. According to the above we cannot admit that the experiments of BAETZNER prove the excretion of phosphate to be regularly augmented during water diuresis. —

BOCK's experiments cannot however be directly compared with BAETNER's, BOCK's rabbits being fed partly with oats, which involves an ample excretion of phosphate in the urine, Baetzner's rabbits with green food or with beets, which involves but a slight excretion of phosphate in the urine, the main part of the phosphate being excreted with the fæces.

The fact that after administration of theophylline the amount of phosphate in the urine was always augmented but did not follow the course of the diuresis, and that this augmentation might still continue, when the diuresis had passed off, made Bock suppose that the purine diuretics exercise a stimulating action upon the elements of the kidney by which the phosphates are secreted, and that this action is independent of their action on the mechanism through which the quantity of urine is augmented.

The modern filtration-absorption theory considers the secretion of the urine as the result of a mere filtration of the non-colloid constituents of plasma through the capsule and an absorption of a fluid of unchanging composition very similar to "Locke's fluid" through the tubule cells. We think that this theory must claim that, in water diuresis, very great quantities of water are filtrated and absorbed, the abundant dilute urine containing but a very low percentage of sodium chloride. But if the supposed filtration is increased in water diuresis, the substances which, according to the theory are hardly absorbed — like the phosphates — should be expected to increase always, but this was not the case in Bock's experiments. Furthermore it seems hardly compatible with the said theory that in Bock's experiments the amount of phosphate in the urine was constantly much larger in purine diuresis than in water diuresis and might still be augmented in the later periods, after the purine diuresis had passed off, and the urine was no longer increased.

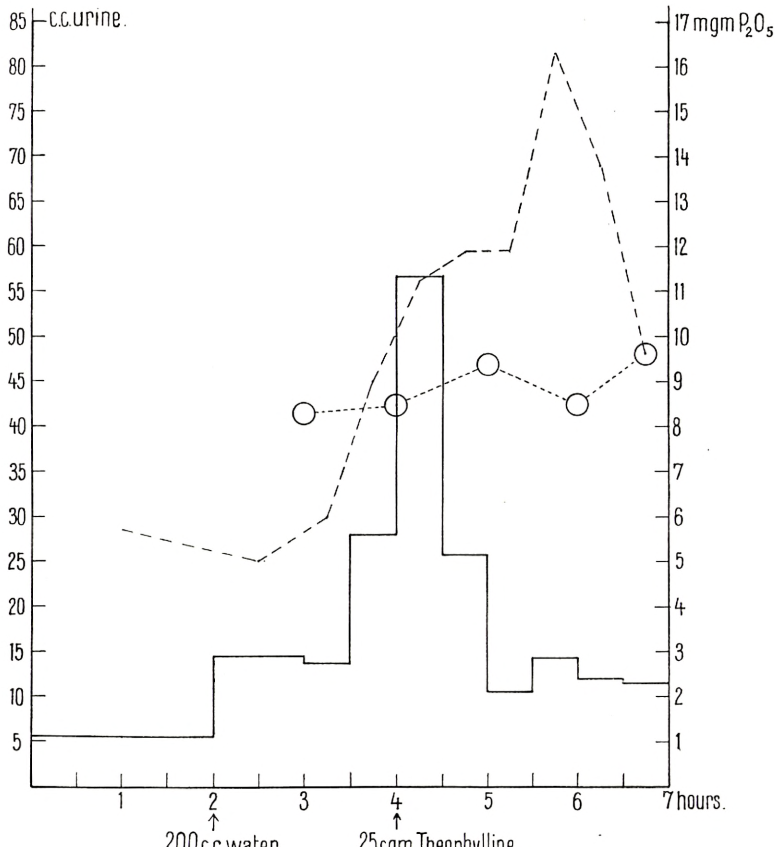
One thing might be able to subvert the above considerations or make them very uncertain. The concentration of phosphate in the blood plasma during diuresis is quite unknown. The phosphate in plasma might possibly be diminished in water diuresis and increased in purine diuresis — in the last case perhaps on account of a concentration of the blood. In order to settle the problem it was therefore necessary to determine the percentage of phosphate in the plasma during the different phases of the diuresis.

Recently one of us (IVERSEN) has described a micro-method[1] for estimating phosphate in small quantities of blood and plasma. The method is based upon the principle of NEUMANN and renders possible the estimation of quantities from 0.15 to 0.03 mgm *P* with an error of 0.003 mgm. The albumen is precipitated with picric acid. The estimation was mostly made in 1—1.5 c. c. plasma. By this method is estimated what is called the acid soluble phosphorus, but GREENWALD[2] has shown that abt. 90 % of the soluble phosphorus in plasma is due to inorganic phosphate, and the difference of 10 % is of no importance for our investigation. In the urine the total amount of phosphate was estimated by the same method, the organic substances being previously removed by oxydation with nitric acid and sulphuric acid. A small percentage of the phosphate, in the urine too, is present in organic combination, but the amount is so small that we can leave it out of consideration.

The experiments were carried out in the following way: We used large rabbits weighing about 3 Kg. The animals were not anesthetised and only tied up when urine and blood were taken. The urine was always taken with catheter mostly every half hour, and the bladder was each time

[1] POUL IVERSEN: Biochemische Zeitschrift Bd. 104. S. 22. 1920.
[2] I. GREENWALD: Jurn. of Biol.-chemistry **25** p. 431. 1916.

rinsed with distilled water. After one or two normal estimations a water diuresis was induced and afterwards a theophylline diuresis. In the urine samples the amount of phos-



Curve 1 (exp. 1). (—) urine c. c. in 30 mins. (---) mgm P_2O_5 in the urine. (O----) mgm P_2O_5 in 100 c. c. plasma.

phate was estimated as described. The blood was taken from a vein in the ear into a few mgm of sodium oxalate, and the plasma at once separated from the blood corpuscles by centrifuting. As only 3. c. c. blood are required for the estimation of the phosphate in the plasma, it was possible to take 4—5 samples during the experiment without depriving the animal of too much blood. The water (200 c. c. tube water) and the theophylline were always given by means of a stomach tube. The rabbits were mostly fed with beets and oats. In several of the experiments no food was given the last 24 hours before the experiment.

In the following protocols and curves the amount of urine and of excreted phosphate is stated for periods of half an hour corresponding to the interval between the collections of the urine. Only in exp. 3 and in the first estimations in the other experiments the urine is collected at intervals comprising two or more periods as indicated in the protocols. The periods succeeding the administration of water and of theophylline are indicated in the following as water-periods and theophylline-periods.

Experiment 1 (curve 1). Rabbit weight 3200 gm, fed on oats and hay.

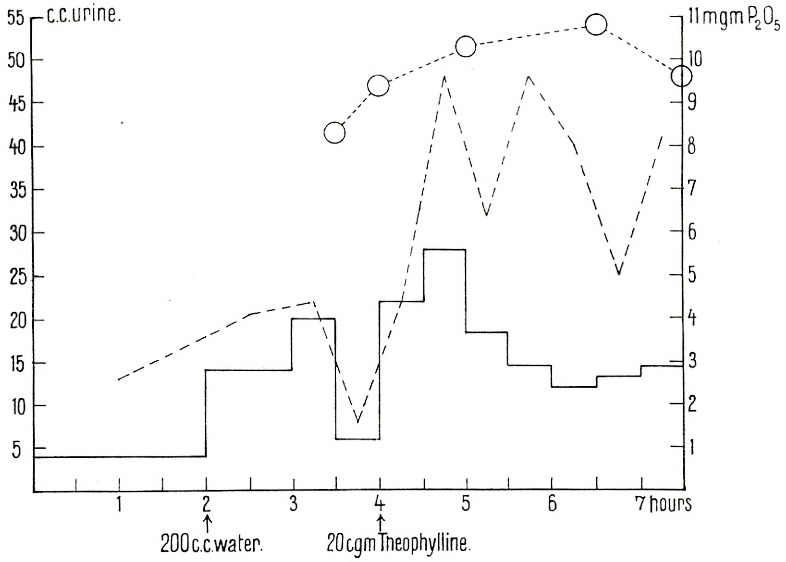
Time	Urine		Plasma	
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	mgm P_2O_5 in 100 c. c.	
$0-2^{00}$	5.5	5.7	..	
2^{00}	...	...	..	200 c. c. water
$2^{00}-3^{00}$	14.4	5.0	..	
3^{00}	...	...	8.3	
$3^{00}-3^{30}$	13.7	6.0	..	
$3^{30}-4^{00}$	28.2	9.1	..	
4^{00}	...	...	8.5	25 cgm theophylline
$4^{00}-4^{30}$	56.7	11.2	..	
$4^{30}-5^{00}$	25.8	11.9	..	
5^{00}	...	...	9.4	
$5^{00}-5^{30}$	10.7	11.9	..	
$5^{30}-6^{00}$	14.2	16.3	..	
6^{00}	...	...	8.5	
$6^{00}-6^{30}$	12.0	13.8	..	
$6^{30}-7^{00}$	11.5	9.6	..	
7^{00}	...	...	9.6	

The phosphate percentage in the plasma varies but little during the experiment. After the administration of water the urine is augmented. Theophylline induces a profuse but short-lasting diuresis, whereupon the urine is rapidly reduced again. The phosphate in the urine, which varies little during the 3 first water-periods, is augmented during the fourth. After theophylline the phosphate in the urine increases during the profuse diuresis but far more when the urine is afterwards considerably diminished.

Experiment 2 (curve 2). Rabbit weight 3200 gm, fed on oats and beets.

Time	Urine		Plasma	
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	mgm P_2O_5 in 100 c. c.	
$0 - 2^{00}$	4.2	2.6	...	
2^{00}	...	..	...	200 c. c. water
$2^{00} - 3^{00}$	14.1	4.1	...	
$3^{00} - 3^{30}$	19.9	4.4	...	
3^{30}	...	..	8.3	
$3^{30} - 4^{00}$	6.0	1.6	...	
4^{00}	...	..	9.4	20 cgm theophylline
$4^{00} - 4^{30}$	22.0	4.4	...	
$4^{30} - 5^{00}$	28.0	9.6	...	
5^{00}	...	..	10.3	
$5^{00} - 5^{30}$	18.4	6.4	...	
$5^{30} - 6^{00}$	14.6	9.4	...	
$6^{00} - 6^{30}$	12.1	8.0	...	
6^{30}	...	..	10.8	
$6^{30} - 7^{00}$	13.3	5.0	...	
$7^{00} - 7^{30}$	14.4	8.3	...	
7^{30}	...	..	9.6	

After the administration of water as well as after theophylline the urine is augmented, but not considerably. The phosphate percentage in the plasma increases somewhat during the last water period and a little more during the early theophylline periods, but is reduced at the end of the experiment. The phosphate in the urine increases a little during the first 3 water-periods and in the fourth is less than during the normal periods. During the theophylline-periods the phosphate is greatly increased and also when, in the subsequent periods, the amount of the urine is less than during the water diuresis.



Curve 2 (exp. 2). (—) urine c. c. in 30 mins. (---) mgm P_2O_5 in the urine. (○----) mgm P_2O_5 in 100 c. c. plasma.

Experiment 3. Rabbit weight 3200 gm, fed on oats and beets.

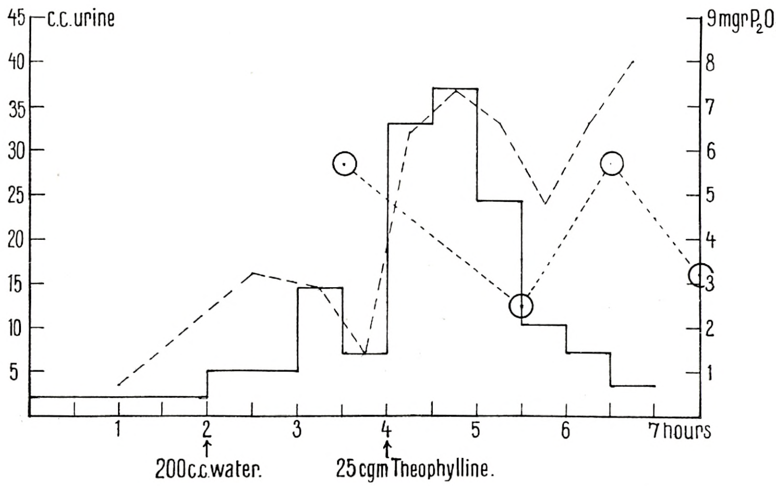
Time	Urine		Plasma	
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	mgm P_2O_5 in 100 c. c.	
0 —2^{00}	4.1	4.6	...	
2^{00}—3^{30}	2.2	5.7	...	
3^{30}	..	..	10.5	20 cgm theophylline
3^{30}—4^{30}	9.5	9.2	...	
4^{30}	..	..	10.8	
4^{30}—5^{30}	4.6	6.9	...	
5^{30}	..	..	8.9	
5^{30}—6^{30}	1.4	6.4	...	
6^{30}	..	..	9.2	

The phosphate percentage in the plasma is almost unchanged during the commencement of the experiment and somewhat lessened at the end. Theophylline induces a rather small increase of the urine but a very marked augmentation of the phosphate in the urine even in the later periods with reduced urine. The two normal estimations show that the phosphate in the urine may vary rather considerably from hour to hour in normal conditions.

Experiment 4 (curve 3). Rabbit weight 2700 gm.

Time	Urine		Plasma	
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	mgm P_2O_5 in 100 c. c.	
0 —2^{00}	2.2	0.7	. .	
2^{00}	. . .	. .	. .	200 c. c. water
2^{00}—3^{00}	5.1	3.2	. .	
3^{00}—3^{30}	14.6	2.9	. .	
3^{30}	. . .	. .	5.7	
3^{30}—4^{00}	6.9	1.4	. .	
4^{00}	. . .	. .	. .	25 cgm theophylline
4^{00}—4^{30}	33.0	6.4	. .	
4^{30}—5^{00}	37.0	7.3	. .	
5^{00}—5^{30}	24.4	6.6	. .	
5^{30}	. . .	. .	2.5	
5^{30}—6^{00}	10.4	4.8	. .	
6^{00}—6^{30}	7.3	6.6	. .	
6^{30}	. . .	. .	5.7	
6^{30}—7^{00}	3.5	8.0	. .	
7^{30}	. . .	. .	3.2	

During the theophylline diuresis the phosphate percentage in the plasma is very considerably reduced, in the following hour it rises and is subsequently reduced. The amount of phosphate is very small in the normal urine and increases after the administration of water, but this increase appears during the first two water-periods (2^{00}—3^{00}), the urine being but slightly augmented. During the 3rd water-period (3^{00}—3^{30}) the phosphate does not increase further, but the urine is considerably augmented. Theophylline induces a profuse diuresis (4^{00}—5^{30}) during which the phosphate in the urine rises greatly, in the following period it is a little diminished, but increases again and reaches the maximum in a period (6^{30}—7^{00}), during which the amount of urine is nearly the same as during the water-periods.

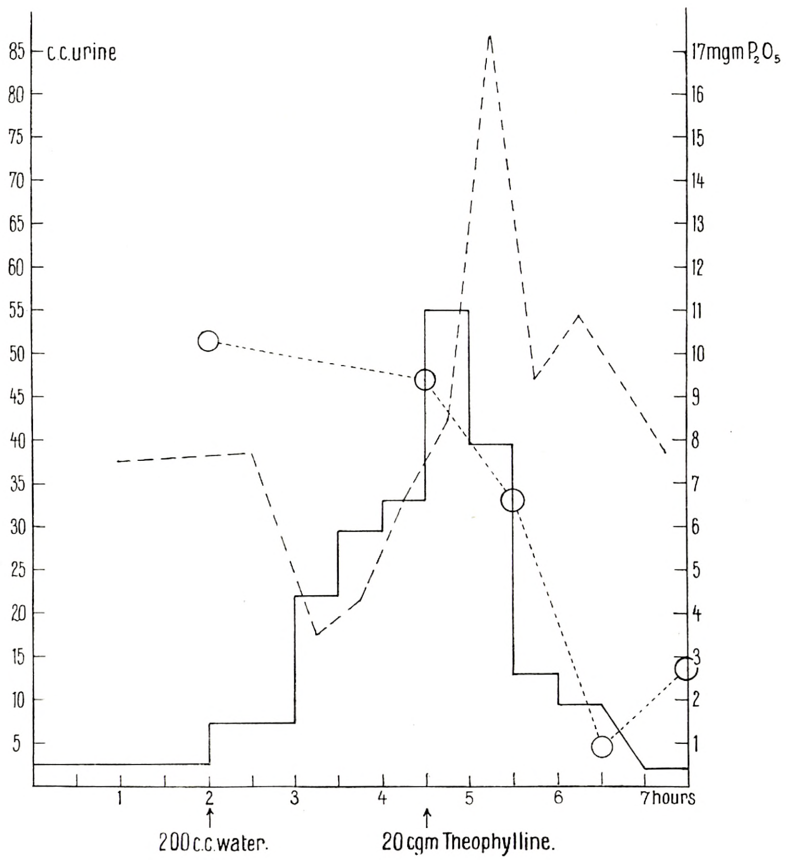


Curve 3 (exp. 4). (—) urine c. c. in 30 mins. (---) mgm P_2O_5 in the urine. (○---) mgm P_2O_5 in 100 c. c. plasma.

Experiment 5 (curve 4). Rabbit weight 2790 gm, no food during 18 hours.

Time	Urine		Plasma	
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	mgm P_2O_5 in 100 c. c.	
0 —2^{00}	2.5	7.5	...	
2^{00}	...	...	10.3	200 c. c. water
2^{00}—3^{00}	7.3	7.7	...	
3^{00}—3^{30}	22.0	3.5	...	
3^{30}—4^{00}	29.5	4.3	...	
4^{00}—4^{30}	33.1	6.6	...	
4^{30}	...	...	9.4	20 cgm theophylline
4^{30}—5^{00}	55.2	8.4	...	
5^{00}—5^{30}	39.5	17.3	...	
5^{30}	...	...	6.6	
5^{30}—6^{00}	13.2	9.4	...	
6^{00}—6^{30}	9.5	10.9	...	
6^{30}	...	...	0.9	
6^{30}—7^{00}	...	...	...	
7^{00}—7^{30}	4.6	7.7	...	
7^{30}	...	...	2.7	

During the water-periods the phosphate percentage in plasma is only little changed, but is greatly reduced during the theophylline-periods. The phosphate in the urine is lessened during the water diuresis. After theophylline the phosphate increases greatly



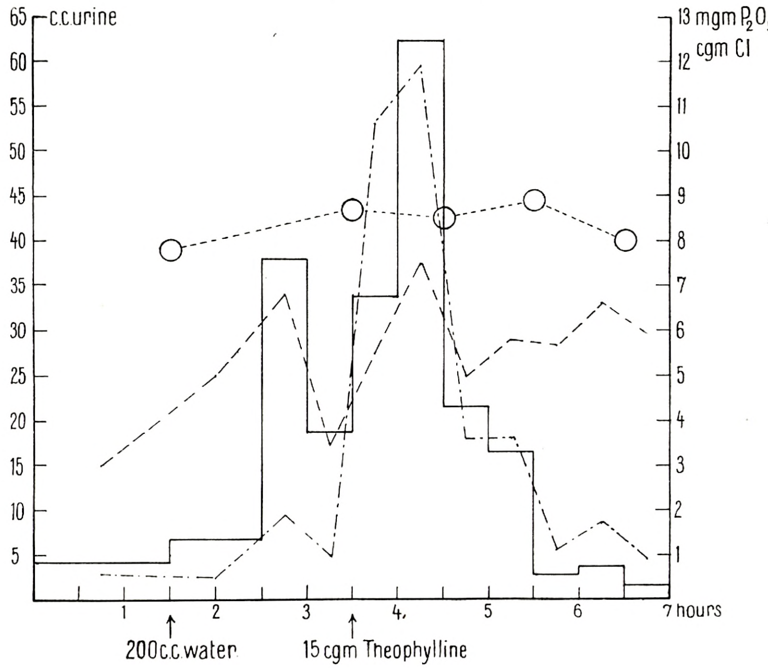
Curve 4 (exp. 5). (—) urine c. c. in 30 mins. (---) mgm P_2O_5 in the urine. (⊙---) mgm P_2O_5 in 100 c. c. plasma.

and the maximum excretion does not coincide with the most profuse diuresis. Though the phosphate percentage in plasma is greatly reduced and the amount of urine is small, the amount of phosphate in the urine during the last periods is much larger than during the profuse water diuresis.

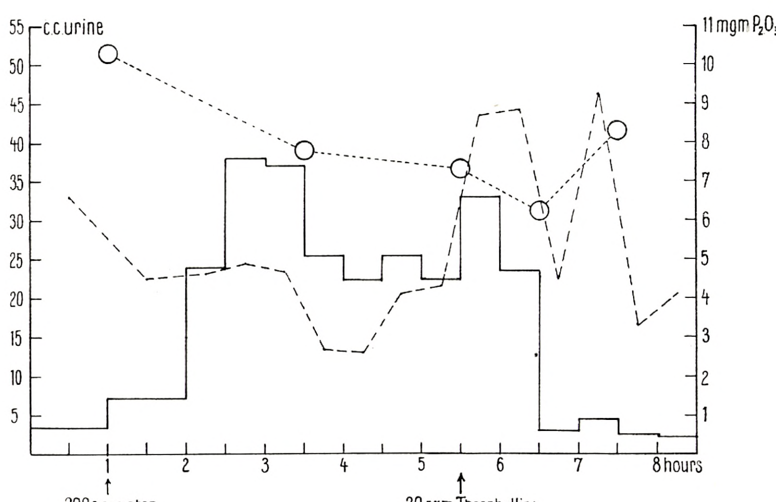
Experiment 6 (curve 5). Rabbit weight 2759 gm no food during 24 hours.

Time	Urine			Plasma	
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	cgm Cl in 30 mins	mgm P_2O_5 in 100 c. c.	
0 —1^{30}	4.2	3.0	0.6	..	
1^{30}	...	..	...	7.8	200 c. c. water
1^{30}—2^{30}	6.8	5.0	0.5	..	
2^{30}—3^{00}	38.0	6.8	1.8	..	
3^{00}—3^{30}	18.6	3.5	1.0	..	
3^{30}	...	..	...	8.7	15 cgm theophylline
3^{30}—4^{00}	33.8	5.4	10.6	..	
4^{00}—4^{30}	62.1	7.4	11.9	..	
4^{30}	...	..	...	8.5	
4^{30}—5^{00}	21.6	5.0	3.6	..	
5^{00}—5^{30}	16.6	5.8	3.6	..	
5^{30}	...	..	...	8.9	
5^{30}—6^{00}	2.9	5.6	1.1	..	
6^{00}—6^{30}	3.1	6.6	1.7	..	
6^{30}	...	..	...	8.0	
6^{30}—7^{00}	1.6	5.9	0.9	..	

The phosphate percentage in the plasma changes but little during the different phases of the experiment. During the first two water-periods the urine is but slightly increased, but the phosphate is considerably augmented and further increases when in the third period, diuresis sets in. In the fourth water-period the diuresis is somewhat lessened and the phosphate reduced to nearly the original amount. The phosphate in the urine increases during the theophylline diuresis and remains high when, during the following periods, the urine is reduced to less than during the normal period. In this experiment the chlorides in the urine are also estimated. During the profuse water diuresis (2^{30}—3^{00}) the chlorine is but little augmented and the concentration in the urine is very low — 0.05 per cent. During the theophylline diuresis the chlorides in the urine increase very considerably and are subsequently reduced, following the changing amount of the urine rather closely.



Curve 5 (exp. 6). (—) urine c. c. in 30 mins. (---) mgm P_2O_5 in the urine. (—·—·—) cgm Cl in the urine. (○---) mgm P_2O_5 in 100 c. c. plasma.



Curve 6 (exp. 7). (—) urine c. c. in 30 mins. (---) mgm P_2O_5 in the urine. (○---) mgm P_2O_5 in 100 c. c. plasma.

Experiment 7 (curve 6). Rabbit weight 2700 gm, no food during 24 hours.

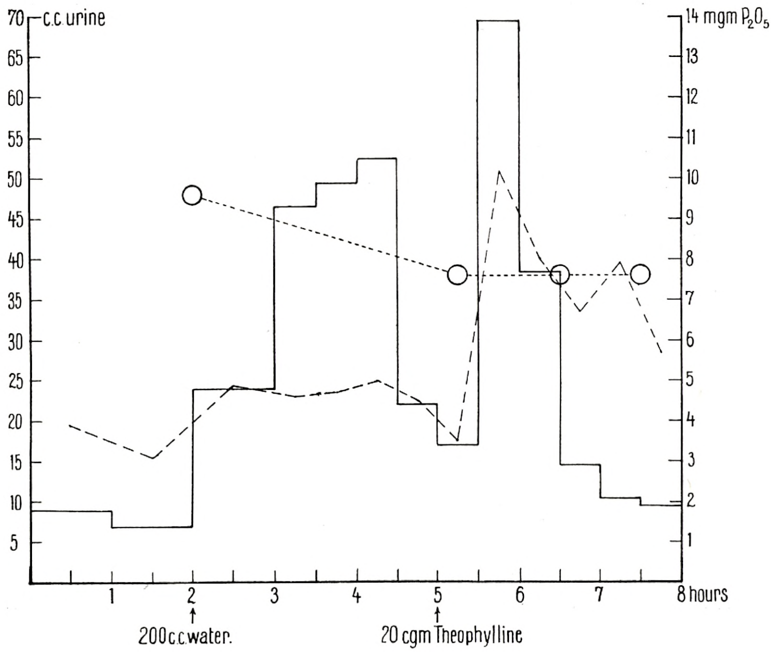
Time	Urine		Plasma	
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	mgm P_2O_5 in 100 c. c.	
$0 - 1^{00}$	3.4	6.6	...	
1^{00}	...	..	10.3	200 c. c. water
$1^{00} - 2^{00}$	7.3	4.5	...	
$2^{00} - 2^{30}$	24.0	4.7	...	
$2^{30} - 3^{00}$	38.1	4.9	...	
$3^{00} - 3^{30}$	36.1	4.7	...	
3^{30}	...	..	7.8	
$3^{30} - 4^{00}$	25.6	2.7	...	
$4^{00} - 4^{30}$	22.1	2.6	...	
$4^{30} - 5^{00}$	25.6	4.1	...	
$5^{00} - 5^{30}$	22.6	4.5	...	
5^{30}	...	..	7.3	20 cgm theophylline
$5^{30} - 6^{00}$	35.3	8.7	...	
$6^{00} - 6^{30}$	23.5	8.8	...	
6^{30}	...	..	6.2	
$6^{30} - 7^{00}$	3.0	4.5	...	
$7^{00} - 7^{30}$	4.6	9.2	...	
7^{30}	...	..	8.3	
$7^{30} - 8^{00}$	2.1	3.3	...	
$8^{00} - 25^{00}$	2.0	4.1	...	

The phosphate percentage in the plasma is reduced during the water diuresis and still more during the theophylline diuresis but increases at the end of the experiment. The administration of water induces a profuse and long-lasting diuresis, the subsequently induced theophylline diuresis being not so profuse as the water diuresis. After the administration of water the phosphate in the urine is reduced and remains so during a long series of water-periods. During the first two water-periods 1^{00}—2^{00}, the diuresis having not yet set in, the amount of excreted phosphate is nearly the same as during the profuse water-diuresis. After theophylline the phosphate in the urine increases to nearly twice as much as during the water diuresis, though the amount of urine is less. The maximum excretion of the phosphate takes place in a period (7^{00}—7^{30}) during which the amount of urine is very small.

Experiment 8 (curve 7). Rabbit weight 3000 gm, no food during 24 hours.

Time	Urine		Plasma	
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	mgm P_2O_5 in 100 c. c.	
0 —1^{00}	8.9	3.9	..	
1^{00}—2^{00}	6.9	3.1	..	
2^{00}	...	...	9.6	200 c. c. water
2^{00}—3^{00}	24.3	4.9	..	
3^{00}—3^{30}	46.6	4.6	..	
3^{30}—4^{00}	49.6	4.7	..	
4^{00}—4^{30}	52.8	5.0	..	
4^{30}—5^{00}	22.0	4.5	..	
5^{15}	...	...	7.6	
5^{00}—5^{30}	17.1	3.5	..	
5^{30}	...	...	..	20 cgm theophylline
5^{30}—6^{00}	69.4	10.2	..	
6^{00}—6^{30}	38.5	8.0	..	
6^{30}	...	...	7.6	
6^{30}—7^{00}	14.7	6.7	..	
7^{00}—7^{30}	10.6	7.9	..	
7^{30}	...	...	7.6	
7^{30}—8^{00}	9.8	5.9	..	

During the water diuresis the phosphate percentage in the plasma lessens somewhat and then remains unchanged during the rest of the experiment. The administration of water induces a profuse and long-lasting diuresis. The amount of phosphate is nearly the same during the different water-periods though the quantity of the urine varies considerably, and is almost the same as in the first normal estimation. During the theophylline diuresis the phosphate in the urine is greatly increased and remains high in the following periods, during which the quantity of the urine is but small.



Curve 7 (exp. 8). (—) urine c. c. in 30 mins. (---) mgm P_2O_5 in the urine. (○---) mgm P_2O_5 in 100 c. c. plasma.

Experiment 9. Rabbit weight 2660 gm, fed on beets, no food during 24 hours.

Time	Urine		Plasma	
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	mgm P_2O_5 in 100 c. c.	
0 —1^{00}	9.7	1.3	. .	
1^{00}—2^{00}	7.5	1.6	. .	
2^{00}	. . .	. .	6.9	
2^{00}—3^{00}	4.3	4.9	. .	
3^{00}	. . .	. .	. .	20 cgm theophylline
3^{00}—3^{30}	22.3	9.1	. .	
3^{30}—4^{00}	21.6	5.7	. .	
4^{00}	. . .	. .	4.8	
4^{00}—4^{30}	9.6	6.6	. .	
4^{30}—5^{00}	8.0	5.9	. .	
5^{00}	. . .	. .	7.6	

Time	Urine		Plasma
	c. c. in 30 mins	mgm P_2O_5 in 30 mins	mgm P_2O_5 in 100 c. c.
$5^{00}-5^{30}$	9.5	5.7	. .
$5^{30}-6^{00}$	3.7	5.2	. .
6^{00}	. . .	. .	7.8
$6^{00}-6^{30}$	2.9	4.9	. .
$6^{30}-7^{00}$	2.2	5.7	. .
7^{00}	. . .	. .	7.6
$7^{00}-7^{30}$	2.3	4.4	. .

The phosphate percentage in the plasma is reduced during the first two theophylline-periods and increases afterwards. During the first normal periods ($0-2^{00}$) the amount of phosphate in the urine is but small, but increases considerably during the normal periods $2^{00}-3^{00}$. During the first theophylline-period the phosphate in the urine is greatly increased, it then lessens somewhat but remains high during a long series of periods, though the urine is gradually reduced to very small quantities.

Our experiment as well as previous investigations, concerning the same question, show that the amount of phosphate in the urine may, in normal animals, sometimes change from hour to hour to a certain extent. Further it must be noted that the same quantity of water or of theophylline may induce diuresis of rather varying profusion in different animals. Consequently the course of the different experiments may vary somewhat. The main-line of the experiments is however easy to see.

In seven experiments 200 c. c. water were given by means of a stomach tube. In two (No. 2 and No. 4) only a rather slight diuresis was induced and in both cases an augmentation of the phosphate was noted. But in experiment 4 (curve 3) this augmentation is present even in the first two periods after the administration of water during which the urine was only augmented to a very slight degree, and when the amount of urine, in the following water-period 3^{00}—3^{30}, reaches its maximum, there is no further increase of the phosphate. As to exp. 2 (curve 2) it is almost the same, the amount of urine in the first periods being however augmented to a somewhat greater extent. In exp. 1 and 6 the administration of water induces a rather considerable increase of the urine. In exp. 1 the amount of the urine is augmented during each of the four water-periods to the greatest degree during the fourth. The phosphate in the urine is a little lessened during the two first water-periods, rather unchanged during the third, and increased during the fourth. In exp. 6 (curve 5) a considerable increase of the phosphate is noted during the two first water-periods during which the urine is but very slightly augmented; when, in the third water-period (2^{00}—2^{30}), a profuse diuresis sets in, the further increase is less, and during the fourth period 2^{30}—3^{00} the phosphates are reduced nearly to the same amount as in the normal estimation, while the diuresis, though less profuse, is still persistent. In experiments 5, 7 and 8 the water induced a profuse and long-lasting diuresis and consequently particular significance must be attached to these experiments. In exp. 5 and 7 (curves 4 and 6) the amount of phosphate was reduced during the water diuresis, and in exp. 8 (curve 7) the phosphates were but slightly augmented, compared with the excretion in the first normal period. In each of these three experiments the excretion of the phosphate was traced through a great number of periods, and it will be seen from the curves that the amount of phosphate by no means follows the quantity of the urine during the different phases of the diuresis. The experiments and especially those by which a profuse and protracted diuresis was induced (5, 7 and 8) convincingly prove that, in water diuresis, there is no connection between the amount of phosphate excreted and the quantity of the urine. In the periods during which the urine was but little augmented, the amount of phosphate was found to be somewhat increased or somewhat reduced, similarly as in the estimations from hour to hour in normal conditions. And in the periods during which a profuse diuresis took place, the amount of phosphate in the urine most frequently remained rather unchanged compared with the excretion during the normal periods and during those water-periods in which the amount of urine was scarcely augmented. Hence we can only confirm the observations of Bock that a profuse water diuresis does not regularly induce an augmented excretion of the phosphate in the urine.

In the 7 experiments mentioned, 2 hours or more after the administration of water, and in most cases at a moment when the water diuresis had passed off, 15—20 cgm theophylline were given by means of a stomach tube. In two experiments (3 and 9) the theophylline was given without previous administration of water. In each experiment theophylline induced an augmentation of the urine which was rather small in exp. 2 and 3, while in the other 7 experiments a profuse diuresis was induced. In each experiment the phosphates in the urine increased — and in most cases greatly — after the administration of theopylline; thus in exps. 1, 2, 4, 5, 7 and 8 the amount of the phosphate rose to twice or thrice the amount of the normal estimations or of any period during the water diuresis. The theophylline diuresis was mostly of a rather short duration but, during the periods with maximum excretion, more profuse than the water diuresis. Yet in exp. 7 (curve 6) the diuresis during the two water-periods 2^{30}—3^{30} is more profuse than during the period 5^{30}—6^{00} in which the theophylline diuresis reaches its maximum. But the amount of phosphate in the urine is almost twice as large during the theophylline period as during any of the two water-periods mentioned.

The experiments prove that the increase of the phosphate induced by theophylline by no means follows the course of the diuresis. In exps. 1, 4, 5 and 7 (curves 1, 2, 3 and 5) the maximum excretion of the phosphate does not coincide with the most profuse diuresis, in exps. 1, 4 and 7 it appears even in periods in which the urine is reduced to nearly the normal quantity. In each of the experiments, during a long series of the later periods with greatly reduced urine, the excretion of the phosphate still remains augmented, being much larger than in the normal estimations and most frequently larger too than in the water-diuresis. After theophylline, the increase of the phosphate in the urine consequently does not follow the course of the diuresis but is much more persistent than the diuresis, and, as already mentioned, the maximum of excreted phosphate need not at all coincide with the most profuse diuresis. The increase of the urine and the augmentation of the phosphate, which both appear after the administration of theophylline, consequently are not connected, but have to be considered as due to different processes entirely independent of each other as Bock has previously asserted in the paper mentioned above. That the excretion of phosphate produced by theophylline has quite another course than the excretion taking place after the administration of large quantities of water becomes evident merely on considering the curves (f. i. 1, 2, 6 and 7).

In each experiment the percentage of phosphate in the plasma was estimated before, as well as at different moments after, the administration of theophylline, most frequently with intervals of an hour. In experiments 1, 3, 6 and 8 the estimated percentages vary very little after theophylline, in exp. 2 the percentage of the phosphate is at first somewhat increased and subsequently lessened, in exps. 7 and 9 the percentage at the commencement is somewhat reduced and subsequently rises. Most marked were the changes in exps. 4 and 5 in which the percentages of phosphate in the plasma are reduced in a very considerable degree. In exp. 4, at the end of the profuse theophylline diuresis the percentage of phosphate is thus reduced to less than half the original value an hour later, the percentage rises to the original amount and after another hour is reduced again. In exp. 5 the percentage of phosphate in the plasma during the first two hours after theophylline is reduced to a very small value and finally increases a little.

In the hours after the administration of theophylline the percentage of phosphate in the plasma thus either remained rather unchanged or was more or less reduced, sometimes very considerably. It is to be seen (curve 3 and 4) that 1 or 2 hours after the administration of theophylline the quantity of the urine as well as the percentage of phosphate in the plasma may be reduced, and still the amount of phosphate excreted in the urine may be much larger than during the normal periods and during the water diuresis. The experiments prove that the augmented excretion of phosphates in the urine after theophylline depends neither on an increase of the concentration of phosphate in the plasma nor on the quantity of the urine, and consequently they lead us to the view, previously advanced by BOCK, that the augmented excretion of the phosphates after the administration of theophylline is due to a specific action of the drug on secretory elements of the kidney, and that these elements are probably not the same as those through which the diuresis is produced.

Our experiments concerning the excretion of phosphate in the urine after the administration of theophylline seem hardly compatible with the modern filtration-absorption theory. And with regard to water diuresis our experiments lead us to a similar result. According to the said theory the phosphates filtrated through the glomerulus are not returned to the blood[1] during the passage through the tubules. Hence if we measure the urine secreted during a certain period and estimate the phosphate percentage in the blood plasma and the amount of phosphate in the urine, we may be able to calculate the amount of fluid filtrated during the same period through the glomerulus. For such a calculation we will choose the period 2^{30}—3^{00} in exp. 6, in which both the phosphate and the chloride in the urine were estimated. During the period 100 c. c. plasma contained 8.4 mgm P_2O_5 (curve 5). According to the theory the amount of phosphate in the urine and in the corresponding glomerular filtrate is the same, and the urine containing 6.8 mgm P_2O_5 $100 \cdot \frac{6.8}{8.4}$ or 81 c. c. fluid ought to be filtrated during the period. The quantity of urine during the period being 38 c. c. $81 \div 38 = 43$ c. c. fluid ought to be absorbed through the tubule cells. According to the theory the absorbed fluid contains chloride in approximately the same concentration in which it is

[1] A. CUSHNY: The Secretion of the Urine. 1917 p. 180.

present in normal plasma. The normal rabbit plasma containing 0.38 per cent chlorine (Abderhalden) the absorbed 43 c. c. fluid must consequently contain 163 mgm *Cl*, and the urine during the period containing 19 mgm *Cl* the filtrated 81 c. c. should contain 163 + 19 = mgm *Cl* or 0.22 per cent, and the plasma should consequently contain the same percentage of chlorine. But it is a well-known fact that even when large quantities of water are taken by the mouth, the dilution of the blood is exceedingly small and undoubtedly the percentage of chlorine in the plasma is but reduced in an insignificant degree, all the more so because the excretion of chlorine is scarcely augmented in the water diuresis. That the percentage of chlorine in plasma should be reduced during the water diuresis to almost half the normal value is impossible to imagine considering the numerous observations concerning the problem of the dilution of the blood by administration of water by the mouth, and a hypothesis leading to this result cannot be correct.

On the other hand, if we assume the percentage of chlorine in the plasma to be but slightly reduced during water diuresis, this will require, according to the theory, that enormous quantities of fluid are filtrated and absorbed to produce in the present case 38 c. c. urine containing 0.05 per cent chlorine. But the phosphate in the urine only corresponding to 81 c. c. glomerulus filtrate, this assumption must necessarily involve the admission that large quantities of phosphate are absorbed through the tubule cells. An example may illustrate the question. Supposing that the chlorine percentage in plasma is reduced during water diuresis to 90 per cent of the original value (a reduction which is undoubtedly rated too high) the absorbed fluid ought to contain 0.38 per cent and the filtrated fluid 0.342 per cent *Cl*. During the period 2^{30}—3^{00} mentioned in exp. 6 38 c. c. urine with 0.05 per cent *Cl* are secreted, and we will suppose x c. c. getting filtrated through the glomerulus and consequently $(x - 38)$ c. c. being absorbed through the tubule cells. The amount of chlorine in the glomerular filtrate being equal to the sum of the chlorine in the absorbed fluid and in the urine, we shall have the following equation

$$\frac{0.342}{100} \cdot x = \frac{0.05}{100} \cdot 38 + \frac{0.38}{100} \cdot (x - 38)$$

which gives $x = 330$ c. c.

A filtration of 330 c. c. would in the present case (100 c. c. plasma containing 8.4 mgm P_2O_5) involve a filtration of 27.7 mgm P_2O_5 but only 6.8 mgm being excreted with the urine, it will be necessary to admit an absorption of 20.9 mgm P_2O_5 thrice as much as excreted in the urine, which is in direct opposition to the above mentioned theory which claims that the phosphate is scarcely returned to the blood. Provided, as is most likely, that the chloride in the plasma, during the water diuresis is less reduced than supposed in the example above, the calculation will give far larger amounts of absorbed fluid and absorbed phosphate.

The results of our investigations concerning the excretion of phosphate under different conditions thus seem hardly compatible with a theory regarding the urine as merely a product of a filtration of deproteinized plasma through the glomerulus and an absorption of a fluid of constant composition through the tubule cells. The investigations being limited to the elimination of the phosphate we shall not try to educe general views as to the activity of the kidney on this base. But our experiments suggest that the excretion of the phosphate is due to an active secretory process taking place in elements of the kidney upon which the purine diuresis may exercise a stimulating effect. The elements through which the excretion of the phosphate is accomplished are most likely not the same as those by which the elimination of water is produced.

Forelagt paa Mødet den 26. Marts 1920.
Færdig fra Trykkeriet den 18. Februar 1921.

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