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THE DIURETIC ACTION OF ALCOHOL AND ITS RELATION TO PITUITRIN.

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That alcohol has a diuretic action is well known, but the way in which it produces its effect is not fully understood. Alcohol put into the circulation of a heart-lung-kidney preparation causes a cessation of urine flow according to Loewy and Bornstein [1927]. Hence it would seem probable that its action as a diuretic is extrarenal.

The experiments to be described represent an attempt to investigate the mechanism of alcohol diuresis. They fall into two series:

(I) Experiments on normal human subjects.

(II) Experiments on cats under amytal.

Part I. Experiments on human subjects.

Firstly, the diuretic effects of alcohol and certain of the more common diuretic drugs were compared. All experiments were carried out under comparable conditions; that is, at constant room temperature first thing in the morning, the subjects having no breakfast. In every experiment the volume of liquid taken was 300 c.c. at 29° C. Control experiments were done, water alone being drunk. The results in Table I show the comparative diuretic effect of alcohol (10 p.c. by volume), urea (5 p.c.), diuretin (theobromine sodium salicylate, 0·3 p.c.) and whey (made by clotting milk with rennin). It can be seen from these figures that alcohol has a very definite and rapid diuretic action. Adolph and Ericson [1926] considered that there are three types of diuresis: (1) water diuresis due to hydræmia, (2) saline diuresis, (3) drug diuresis. The rapidity of action of alcohol is like simple water diuresis. This latter is due to hydræmia and the resulting lowered osmotic pressure. It is antagonized by the antidiuretic hormone of the pituitary.

Experiments were carried out to show the relation of pituitrin to alcohol diuresis. Four different types of experiments were performed,

TABLE I.

No. and type of exp.	Urine flow per ½ hour before, c.c.	Urine flow in successive ½ hours after, c.c.				Total in 2 hours after, c.c.
Subject A						
31. Water, 300 c.c.	15	28	155	115	18	316
27. do.	19	50	216	136	12	414
24. do.	11	21	140	95	11	267
25. Alcohol, 300 c.c. 10 p.c.	17	19	134	214	148	515
28. do.	25	91	227	256	120	694
18. Urea, 300 c.c. 5 p.c.	15	Collected at the end of 2 hours				165
Glucose, 300 c.c. 25 p.c. (av. of 4 exps.)	16	do.				230
Glucose, 300 c.c. 25 p.c. and 10 p.c. alc. (av. of 6 exps.)	18	do.				444
Subject B						
24. Water, 300 c.c.	26	112	202	29	24	367
23. do.	18	56	233	52	10	351
25. Alcohol, 300 c.c. 10 p.c.	22	22	126	230	124	502
27. do.	16	68	235	265	43	611
10. Diuretin, 1 g. in 300 c.c. water	25	Collected at the end of 2 hours				365
Glucose 300 c.c. 10 p.c. (av. of 4 exps.)	21	do.				260
Glucose, 300 c.c. 25 p.c. and 10 p.c. alc. (av. of 6 exps.)	22	do.				485

all under the conditions mentioned above. The urine was collected every half-hour till the rate was constant, then an experiment of one of the following types was performed:

(A) 300 c.c. of tap water at 29° C. was drunk.

(B) 300 c.c. of tap water at 29° C. was drunk and an injection of 0·1 unit pituitrin was given.

(C) 300 c.c. of 10 p.c. alcohol at 29° C. was drunk.

(D) 300 c.c. of 10 p.c. alcohol was drunk and an injection of 0·1 unit pituitrin was given.

Subsequently the urine was collected at half-hourly intervals till the rate had returned to normal again. The results of these experiments are set out in Table II.

The pituitrin was Parke-Davis's posterior lobe extract (10 units per c.c.) diluted with sterile water 1 in 20 so that an injection of 0·2 c.c., which was the usual dose given, was equal to 0·1 unit. The small dose given in two experiments was half this (0·05 unit). The pituitrin was injected subcutaneously.

The results of these experiments show again the marked diuretic action of alcohol and also that this diuretic effect is able to overcome to a certain extent the antidiuretic effect of pituitrin. This point is brought

out by a comparison of Exps. 35 and 34, the small dose of pituitrin has a considerable effect on water diuresis. In Exp. 35 the time of maximum excretion is delayed by 1½ hours, the time of return to the normal rate by 1½ hours and the total excretion decreased by 110 c.c. In Exp. 34 the effect of the small dose is certainly weaker, the time of maximum excretion and the return to normal are only delayed by ½ hour and the total excretion only decreased by 27 c.c.: that is, the pituitrin is almost ineffective. It seems therefore that the alcohol antagonizes the antidiuretic action of pituitrin.

TABLE II.

No. and type of exp.	Urine vol. in c.c. per ½ hour: Before	Urine vol. in c.c. per ½ hour: Successive ½ hours after	Time of max. excretion (hours)	Time to return to normal (hours)	Total excretion till return to normal (c.c.)
Subject A					
31. A. Water diuresis	15	28, 155, 115, 18	1	2	316
27. do.	19	50, 216, 136, 12	1	2	414
30. B. Water, pituitary injection	16	14, 15, 13, 10, 19, 20, 19, 30, 61, 8	4½	5	209
25. C. Alcohol diuresis	17	19, 134, 214, 148, 6	1½	2	521
26. do.	25	91, 227, 256, 120, 21	1½	2	715
29. D. Alcohol, pituitary injection	13	13, 10, 11, 14, 75, 160, 58, 31, 21	3	4½	393
32. do.	11	12, 12, 11, 9, 85, 147, 128, 60, 28	3	4½	492
Subject B					
24. A. Water diuresis	26	112, 202, 29	1	1½	343
23. do.	18	56, 233, 52, 10	1	2	351
28. B. Water, pituitary injection	16	15, 18, 17, 20, 14, 17, 36, 38, 9	4	4½	184
29. do.	20	17, 25, 16, 10, 21, 39, 59, 25, 6	3½	4½	218
35*. do.	30	25, 16, 16, 14, 135, 22, 10	2½	3½	238
25. C. Alcohol diuresis	22	23, 126, 230, 124, 15	1½	2½	518
27. do.	16	68, 235, 265, 43, 17	1½	2½	628
33. D. Alcohol, pituitary injection	23	23, 15, 17, 22, 121, 42, 58, 15	3	4	313
34*. do.	20	30, 30, 126, 273, 69, 18	2	3	546

* Indicates where small dose of pituitrin was used, Exps. 34 and 35.

This could be brought about in several ways. We know from the work of Krogh that one of the most important functions of the posterior lobe of the pituitary gland is to maintain a normal degree of permeability of the capillaries. The absence of pituitrin in a perfusion liquid causes their permeability to increase. An injection of pituitrin into a normal animal probably makes the capillaries more impermeable. This may be the explanation of the antidiuretic effect of pituitrin in suppressing water diuresis. The blood is diluted to the same extent as in water diuresis [Priestley, 1921], but the urine is scanty because the water cannot be filtered through the glomerulus. Now the diuretic action of alcohol and

its antagonism to the antidiuretic action of pituitrin could be explained in several ways:

(1) That alcohol causes a greater hydræmia than water and thereby can overcome the impermeability due to pituitrin.

(2) That alcohol actually destroys or inhibits the secretion of the capillary substance of the pituitrin.

(3) That alcohol increases capillary permeability directly.

(4) That alcohol increases kidney volume and blood flow.

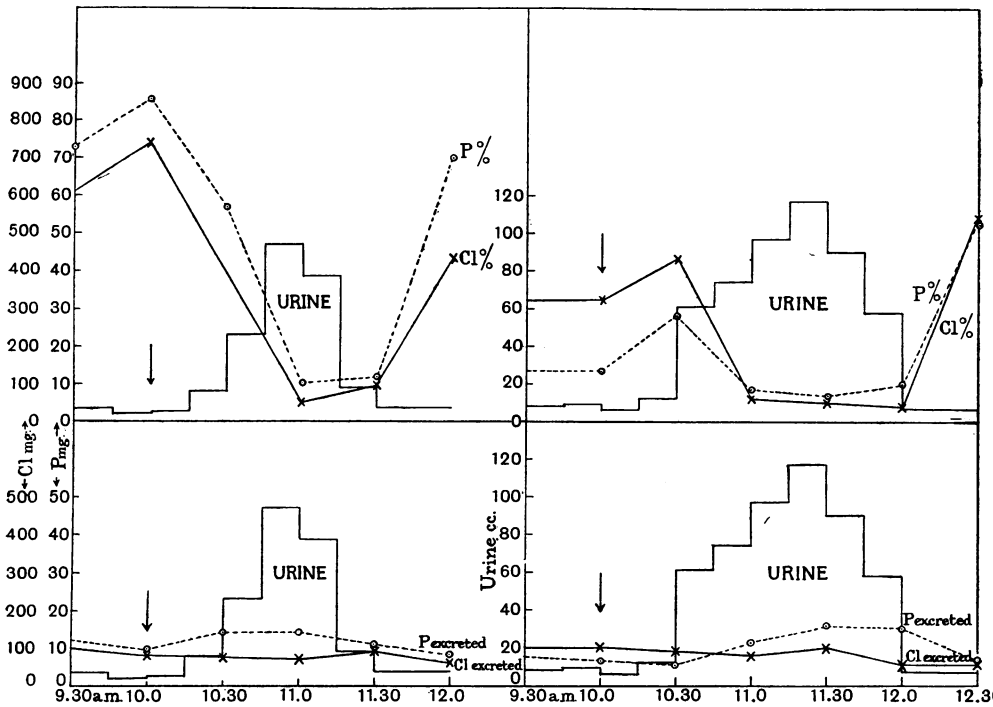
(5) That alcohol increases diffusion pressure in the glomerulus by increasing the blood-pressure, so that the decrease in permeability due to pituitrin is overcome.

Taking the last consideration first, the rise in blood-pressure from such a relatively small dose of alcohol is very slight or non-existent and, if this were the reason for alcohol diuresis, then a similar effect should have been obtained when alcohol was injected into anæsthetized cats in doses sufficient to give blood-pressure rise of about 10 mm. Hg. Here the alcohol did not produce diuresis. The experiments to show this are quoted in more detail later. Alcohol did not cause diuresis in the experimental animals, so the fourth point could not be tested.

Since the result of all the other three possibilities is ultimately the same, these effects cannot be dissociated. It is generally accepted that alcohol increases cell permeability. There is so far no good evidence that alcohol inhibits the secretion of the pituitary gland, but that alcohol and pituitary functions seem to be antagonistic was suggested by Edkins and Murray [1931]. With regard to the possible hydræmic effect of alcohol, attempts were made to investigate this by determining the osmotic pressure of the blood in these experiments, but the results were not consistent. Analyses of the urine were made in all cases, the results of four typical experiments are given in Figs. 1 and 2.

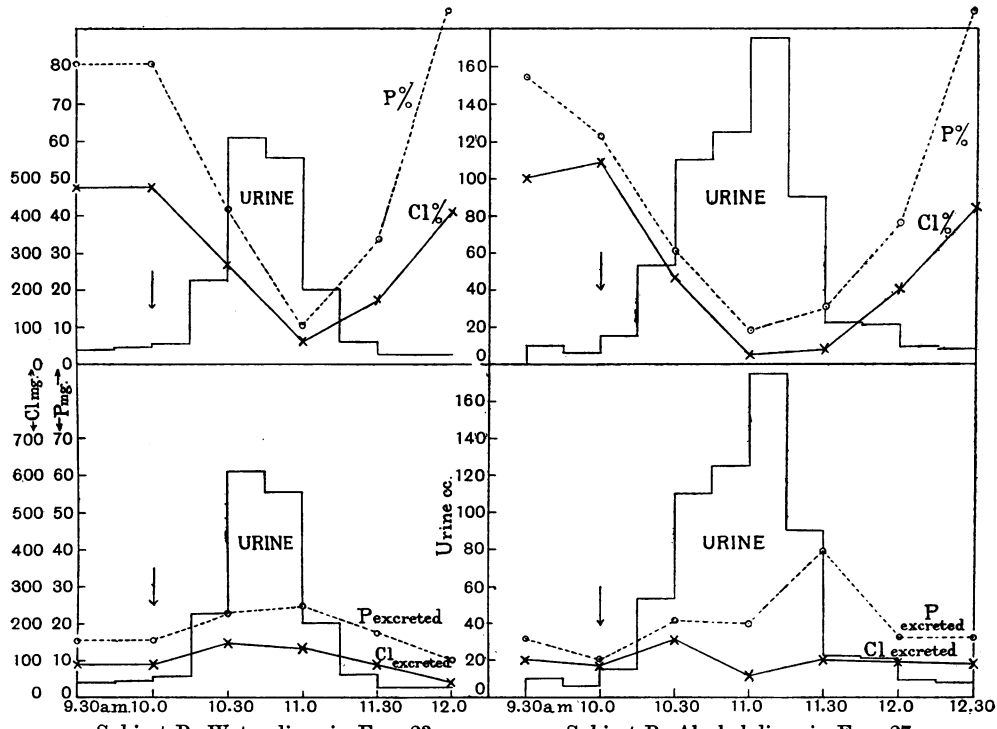
The variations in concentration seem to depend entirely on the urine volume, that is, alcohol causes an exaggerated water diuresis. The output of chloride and phosphate did not suffer much variation, though there was generally a small increase in phosphate output. In subject B there was a slight rise in chloride output and a more marked increase of phosphate; this was probably due to the very rapid rate of secretion.

The graphs of the urine excretion for alcohol experiments and simple water ingestions are very similar, suggesting a similar type of diuresis.



Subject A. Water diuresis, Exp. 24 — Subject A. Alcohol diuresis, Exp. 25

Fig. 1.



Subject B. Water diuresis, Exp. 23 — Subject B. Alcohol diuresis, Exp. 27

Fig. 2.

Part II. Experiments on cats under amytal.

Because of the reverse effects of pituitrin on the urine secretion in anæsthetized animals, as compared with unanæsthetized animals, a series of experiments was done to investigate the effect of alcohol on the urine secretion in cats under amytal, and the relation of alcohol effects and pituitrin injection in these animals. In all experiments the bladder was catheterized and the original rate of urine secretion determined. First of all control experiments were made, giving warm water by means of a tube tied into the œsophagus, to determine whether a water diuresis could be established in these animals. In most cases 20 c.c. water were given, this is for the average sized cat (2·7 kg.), 8 c.c. water per kg. body weight which is much more proportionally than 300 c.c. for a human subject averaging 60 kg., making 5 c.c. per kg. body weight. The figures given in Table III show that there is no diuresis after water ingestion in cats under amytal. In other experiments, alcohol (20 c.c. of 20 p.c.) was given, again a bigger dose than was given to the human subjects. Here again there is no diuresis as seen by the figures in Table III.

Table III. The secretion of urine in cats after administration of:

A. Water 20 c.c.				B. Alcohol 20 c.c. 20 p.c.			
No. of exp.	Urine before per ½ hour c.c.	Urine 1st ½ hour after c.c.	Urine 2nd ½ hour after c.c.	No. of exp.	Urine before per ½ hour c.c.	Urine 1st ½ hour after c.c.	Urine 2nd ½ hour after c.c.
20	1·2	1·3	1·1	20	1·2	1·2	0·4
23	0·8	1·0	0·45	23	1·0	1·3	1·4
24	1·6	1·4	1·0	24	1·9	1·9	2·0
26	0·6	1·0	0·8				
27	0·7	0·8	0·7	27	1·75	0·7	0·7
30	2·0	3·6					
				12	4·0	3·5	4·8
				13	3·8	3·6	
				16	2·7	2·0	2·0
				19	0·5	0·4	0·5
				22	1·6	1·0	0·9
				28	0·3	0·2	0·4
				31	2·7	2·3	2·0
				37	1·0	0·9	0·9
				38	0·3	0·3	0·3

In two of these alcohol experiments a record of the blood-pressure was taken. A slight rise in blood-pressure was noted after giving the alcohol. It seems that the kidney in anæsthetized animals is not capable of responding to a slight degree of hydræmia produced by water ingestion.

These animals responded in the usual way to pituitrin injections. Giving a dose of 0·5–0·75 c.c. of pituitrin intravenously to the animals

1 hour after the administration of water the following results were obtained (see Table IV, column A). Fifteen such experiments were performed, giving an average increase of urine in the first hour after injection of 13·4 c.c. This increase is to be compared with the figures in Table IV,

TABLE IV. Effect of pituitrin on diuresis in cats under amytal. Increase in urine excretion 1 hour after injection of 0·5 to 0·75 c.c. P.D. pituitrin.

	A. After 20 c.c. water ingestion		B. After ingestion of 20 c.c. 20 p.c. alcohol	
No. of exp.	A (i) 1st injection pituitrin c.c.	A (ii) 2nd injection pituitrin c.c.	B (i) 1st injection pituitrin c.c.	B (ii) 2nd injection pituitrin c.c.
22			0·0	
12	15·0	—	2·6	
13	19·0	—	−2·3 (decrease)	
16	7·0	—	6·2	
20	13·5	—	1·0	
23	15·5	—	8·7	
24	23·0	—	14·2	
27	13·0	—	2·3	
Average (7)	15·0	—	4·1	
38	—	—	—	3·3
37	—	—	—	7·2
Average	—	—	—	5·0
8	4·7	5·1		
14	13·0	3·5		
15	11·0	12·0		
20	13·5	16·0		
32	9·0	4·8		
33	19·2	6·0		
35	8·9	12·2		
36	15·4	15·0		
Average (8)	11·8	9·4		
Average of all A (i) exps. (15)	13·4			

column B, where the injection of pituitrin after the giving of alcohol gave a urine increase in the first hour on an average (eight experiments) of 4·1 c.c. Since these results after alcohol were obtained on a second injection of puitrin into animals which had previously given a diuresis for a first dose, the point might be raised that there was less diuresis after alcohol because it was a second dose of pituitrin. To show that this was not the cause of the decrease in effect of the pituitrin, experiments showing the result of two successive injections after water ingestion were performed. The results of these are also given in Table IV, and an average of eight experiments gave 11·8 c.c. increase for the first and 9·3 c.c. urine increase for the second dose. In these cases no further water was given

before the second injection of pituitrin. Hence it is seen that the decreased effect of pituitrin after alcohol is not due to the fact that it is a second injection. It would appear therefore that whatever is the mechanism of pituitrin diuresis in these animals, it is antagonized by previous ingestion of alcohol. The concentration of alcohol in the blood in the animals was estimated in many cases, the usual concentration was 25 mg. per 100 c.c. blood.

Now whether these two sets of results:

(*a*) those on human subjects showing that alcohol is a potent diuretic and has an action antagonistic to the antidiuretic substance of pituitrin,

(*b*) those on cats in amytal anæsthesia showing that alcohol has no diuretic effect in these animals and that it antagonizes the diuretic action of pituitrin,

can be correlated is very difficult to say.

If alcohol antagonizes both antidiuretic and diuretic action, and, as will be shown in another communication, it also inhibits pituitrin hyperglycæmia, its effect seems to be very general. It also appears that alcohol, besides being able to antagonize these hormonic effects on blood sugar when pituitrin is injected, can also possibly antagonize the normal effect of the pituitry gland in these respects as well [Edkins and Murray].

Summary.

1. The diuretic action of alcohol on normal human subjects was compared with that of certain recognized diuretic substances and found to have a rapid and powerful diuretic action.

2. The diuretic effect of alcohol antagonized that of an injection of pituitrin in normal human subjects.

3. It is considered from the results that the effect of alcohol is an exaggerated water diuresis, not a specific effect on the kidneys.

4. In amytalized cats alcohol does not act as a diuretic.

5. Alcohol antagonized the diuretic effect of pituitrin injection in these cats.

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