J. Physiol. (1946) 104, 312–320 612.464

URINE ACIDITY IN ALCOHOL DIURESIS IN MAN

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(*Received* 15 *May* 1945)

Available evidence suggests that the diuresis following ingestion of ethyl alcohol is of the same nature as water diuresis mediated by the pituitary gland (Eggleton, 1942*b*). In an effort to establish further points of similarity or difference between the two types of diuresis, a class experiment on the effects of exercise on urinary excretion was performed identical with those previously reported (Eggleton, 1942*a*, 1943) except for the substitution of alcohol as the diuretic in place of water or tea. The main results of the experiment confirmed those obtained when water had been used as the diuretic, but one unexpected difference suggested that alcohol *per se* might lead to the excretion of an acid urine. The matter has therefore been investigated in a number of subjects by observing the *p*H of the urine during water diuresis and during alcohol diuresis under strictly comparable conditions.

Methods

The class experiment was performed in the manner already described (Eggleton, 1942*a*), 40 g. alcohol in 250 c.c. solution being taken as the diuretic and exercise superimposed when the diuresis was well established. In the remaining experiments, each subject performed the two experiments (water ingestion 560 c.c., and alcohol ingestion 40 g. in 200 or 250 c.c., respectively) at the same time of day, usually on two successive days; in three cases, water was taken on the first day, and in four cases, alcohol. The same preliminary routine was followed on the two occasions: overnight fasting followed by an experiment in the morning, or an afternoon experiment following a 6 hr. fast, on each occasion a glass of water being taken 2½ to 3 hr. beforehand.

Immediately the urine samples had been collected and measured, the *p*H was determined by the simple comparator, using the indicator range phenol red, brom-thymol-blue and methyl red. Readings could be made within 0·1 unit.

Results

I. *Class experiment on the effect of exercise during alcohol diuresis*

The average changes in the urine of eight subjects following a 60 sec. sprint during an alcohol diuresis are shown in Fig. 1, together with the results, reported earlier (Eggleton, 1942*a*), of a similar experiment made during water diuresis. On the main points of difference observed in such experiments with

water and with tea as the diuretic (Eggleton, 1943), the alcohol is seen to behave in the same way as water; both chloride and total N output remain far below the resting values by the end of the experiments. The results also suggest that vaso-constriction in the kidney (as indicated by a fall in the creatinine excretion), during or immediately following the exercise, was much less pronounced when alcohol was used as the diuretic. This is probably connected with the known fact that alcohol is a vaso-dilator, and with the observed fact that the exercise taken was not so violent; the subjects were clearly incapable, after taking alcohol, of making so great an effort as those

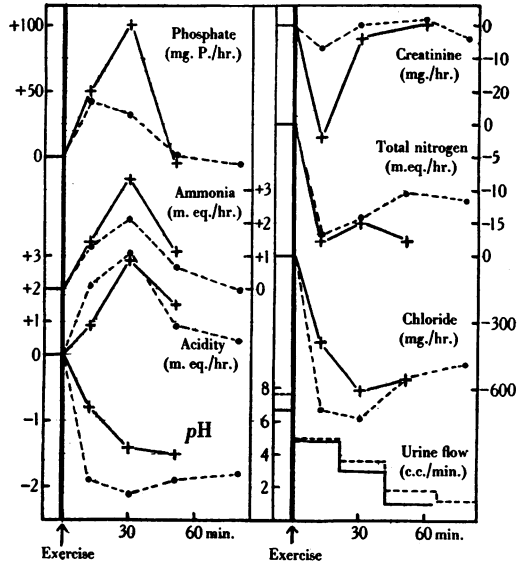

Fig. 1. Average changes in urinary excretion following exercise during alcohol and during water diuresis. •------• Alcohol diuresis (average of eight subjects). +——— + Water diuresis (average of seven subjects).

who had previously ingested only water. In spite of this, the results suggest that, with alcohol as the diuretic, the output of titratable acidity was rather greater, that of ammonia rather less, and the *p*H lower than when water was used as the diuretic. The differences are not statistically significant (the two experiments were performed on two different groups of individuals at an interval of two years, and all analyses were made by students), but appeared sufficiently suggestive to warrant a further, more careful, examination. It had been noted also that a change towards acidity occurred in the urine after alcohol ingestion before the exercise was taken, the effect being most definite in two subjects who, from symptoms and subjective sensations, were the most rapid absorbers.

II. *Comparison of alcohol diuresis with water diuresis in the same subjects*

Of the many factors known to affect urine *p*H, as many as possible were eliminated by comparing the effect of alcohol with that of water at the same time of day, under the same conditions of fasting and body hydration, and at similar rates of urine flow. The necessity for such precautions is demonstrated by the results shown in Fig. 2. In one subject, the urine *p*H, starting at 8·2, fell to 7·0 with the onset of diuresis and remained at that value throughout the experiment; in two subjects, the low initial *p*H (5·0 and 5·7 respectively) rose sharply with the onset of diuresis, and fell again later; and in the four

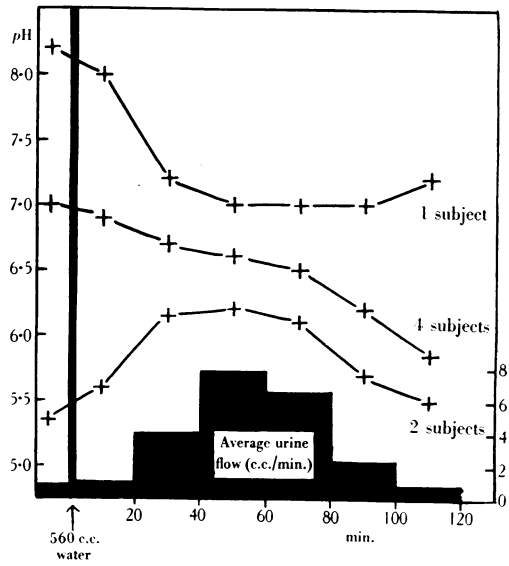

Fig. 2. Changes in urine *p*H during water diuresis in different subjects.

subjects starting at *p*H 6·9 or 7·0 there was a steady drift downwards, the *p*H falling more sharply as the diuresis died away. The success of the precautions taken is shown by the fact that, in only one of the subjects investigated, did the initial *p*H on the two days of experiment differ by more than 0·5 unit, the average difference in the remainder being 0·25 unit. The results of this anomalous subject were therefore discarded. The remaining seven sets of values come from six subjects, on one of whom a pair of morning and a pair of afternoon experiments were performed.

In every subject the *p*H of the urine after ingestion of alcohol was lower than that observed during the water diuresis, although the difference varied widely from one subject to another. The greatest difference occurred 40–60 min. after the drink, at which time the *p*H was, on the average, 0·9 unit lower in

the alcohol than in the water experiment. These results are summarized in Table 1.

TABLE 1. The change in urine *p*H during water diuresis and during alcohol diuresis in different individuals

	Water diuresis			Alcohol diuresis		
Subject	Initial *p*H	After 40–60 min.	Change	Initial *p*H	After 40–60 min.	Change
F. (M.)	8·2	7·2	−1·0	8·0	6·6	−1·4
B. (A.)	6·9	6·8	−0·1	6·4	5·3	−1·1
E. (A.)	7·0	6·4	−0·6	7·4	6·2	−1·2
G. (M.)	7·0	7·1	+0·1	6·7	4·8	−1·9
J. (A.)	7·0	6·7	−0·3	7·0	6·2	−0·8
A. (A.)	5·7	6·6	+0·9	5·7	5·8	+0·1
G. (A.)	5·0	5·7	+0·7	5·4	5·1	−0·3
		Average	−0·05			−0·95

(M.) = morning experiment; (A.) = afternoon experiment.

In five of the seven alcohol experiments, the early fall in urine *p*H was not maintained, although the urine remained more acid than that secreted during the water diuresis. This effect is seen when the average curve for the seven

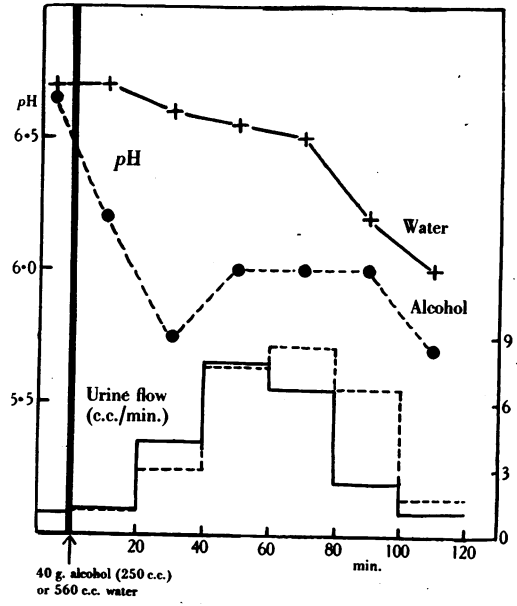

Fig. 3. The average changes in urine *p*H during water diuresis and during alcohol diuresis in six subjects.

alcohol experiments is compared with the average curve of the seven experiments with water (Fig. 3). The average rates of urine flow in the two sets of experiments are also shown. They are not dissimilar, but the alcohol diuresis is slightly later in onset than the water diuresis and is somewhat greater in

magnitude. The average output of urine in 2 hr. following ingestion of 560 c.c. water was 485 c.c. (varying from 310 to 630 c.c.), and that following ingestion of 40 g. alcohol in 200 or 250 c.c. was 630 c.c. (varying from 520 to 790 c.c.).

III. *Possible causes of increased urine acidity during alcohol diuresis*

(*a*) *Excretion of acetic acid.* In attempting to find the cause of this increased acidity of the urine during an alcohol diuresis, attention was first directed to the possible excretion of acetic acid. This substance is known to be produced by the liver during the metabolism of alcohol (Lundsgaard, 1938; Leloir & Muñoz, 1938), but it has not been detected in the blood stream (Himwich, Nahum, Rakieten, Fazikas, Du Bois & Gildea, 1933) although some workers (quoted by Sendroy, 1938) have observed a tendency to acidosis of metabolic type, with alkali deficit, both in chronic and in experimental alcoholism. The specific lanthanum test (Krüger & Tschirch, 1929) was used for its detection.

According to the authors of this test it should yield a positive colour with amounts of acetate as small as 0·1 mg. (in 1–3 c.c. of solution), but under present conditions, a definite positive result could not be obtained with less than 0·5 mg. Moreover, this degree of sensitivity was considerably reduced when the acid had first to be distilled from urine. Other volatile substances (not alcohol itself) interfered with the reaction, whether HCl or H_2SO_4 were used to acidify the urine, and no definite positive test could be obtained on the concentrated distillate if less than 10 mg. acetic acid had been present in the 50 c.c. urine distilled.

The test was applied in three separate experiments on a subject known to absorb alcohol rapidly. The urine sample collected during 30–45 min. following the ingestion of 1 g. alcohol/kg. registered the lowest *p*H in each experiment and was therefore used for the test. This was unequivocally negative in all three experiments. If any acetic acid was excreted, less than 10 mg. were present in the urine secreted during the early stages of the alcohol metabolism, i.e. less than 1/5000th part of the alcohol ingested.

On several occasions also the acid urine secreted immediately after ingestion of alcohol was tested for the presence of aceto-acetic acid by Rothera's reagent. The only positive result recorded was a very faint one, considerably less than that given by 1 : 100,000 dilution of aceto-acetic acid.

(*b*) *Reduced excretion of ammonia.* The second possible cause of the increased acidity of the urine after ingestion of alcohol, suggested by the results of the class experiment, was a diminished production of ammonia by the kidney, but any direct attack on the problem was rendered difficult owing to lack of knowledge concerning the factors involved in the production of ammonia. From long-term experiments on the acidosis produced by fasting, the conclusion has been drawn that 'ammonia production follows the induction of acidosis only after an interval of hours or days' (Smith, 1937); yet it is clear from the results presented in Fig. 1 that, with the acidosis resulting from exercise, no appreciable lag in ammonia production is discernible. Hubbard (1923) came to the conclusion that the *concentration* of ammonia in the urine was related to its *p*H, and that, at constant *p*H, the rate of ammonia

excretion was related to rate of fluid output. His results, obtained on one human subject by varying food and fluid intake, did not agree with those obtained by Marshall & Crane (1922) when the rate of flow was varied in the dog by section of the sympathetic supply to one kidney; they found no correlation between water and ammonia output at constant *p*H. It seemed advisable, therefore, to observe the ammonia concentration and total output over a wide range of flow and of *p*H before coming to any conclusion in regard to the possible action of alcohol, and with this end in view the study was restricted in the main to observations on one subject.

The quickest method of ammonia estimation is titration of the neutralized urine (phenolphthalein faint pink) after addition of neutralized formol, but this titration value also includes the amino-acids present. In several experiments a comparison was made of the results obtained by this method and by the aeration method in which ammonia only is estimated; the results of one such experiment are shown in Fig. 4. The amino-acid fraction varied from 0·16 m.eq./hr. at slow rates of urine flow to 0·28 m.eq./hr. at fast rates. On another occasion a variation from 0·26 to 0·51 m.eq./hr. was observed in the same subject, and one from 0·12 to 0·44 m.eq./hr. in a second subject. This range of variation, partly caused by the analytical errors inherent in the methods, is small in relation to the observed changes in ammonia excretion, and the main body of results has been obtained by use of the formol titration method. The relative inaccuracy of the end-point in the titration is offset by the fact that a reasonably high titration value can be obtained under all conditions by varying the volume of urine used, from 5 c.c. of a concentrated urine, diluted to 50 c.c. before titration, to 50 c.c. of the most dilute urine.

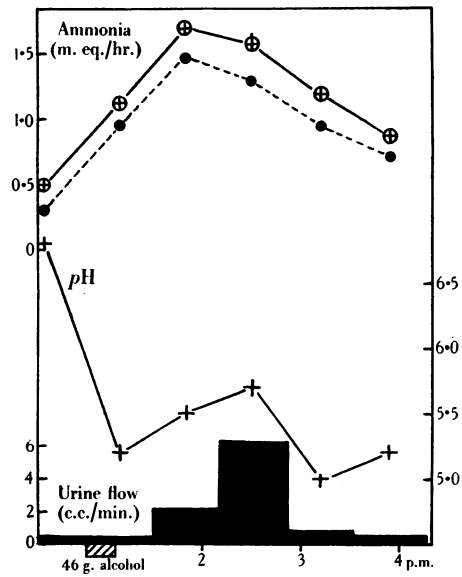

Fig. 4. The relationship between ammonia excretion and urine *p*H after ingestion of alcohol. ⊕——⊕ Ammonia + amino-acids (formol titration). ●------● Ammonia (aeration method).

It will be noted in Fig. 4 that it is the ammonia output and not its concentration which has been plotted, and that this output varies roughly inversely with the urine *p*H. The correlation is not absolute: e.g. the sudden increase of rate of flow from 0·4 to 2·0 c.c./min. (a 5-fold change) is accompanied by a 50% increase in ammonia output although the *p*H has risen

0·3 unit, and the equally sudden decrease in flow from 6·0 to 0·8 c.c. min. is accompanied by a 25% decrease in ammonia output although the *p*H has fallen by 0·7 unit. In this particular experiment, the ammonia concentration also varies inversely with the *p*H, but the relationship is fortuitous. The results of another alcohol experiment plotted in Fig. 5 show again the fairly close inverse relationship between ammonia output and *p*H, and in addition the entire lack of correlation between ammonia *concentration* and *p*H. On the

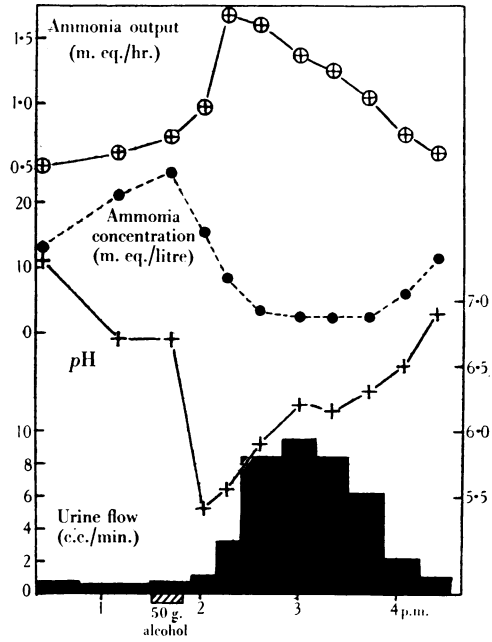

Fig. 5. Showing the lack of consistent relationship between ammonia *concentration* and urine *p*H during alcohol diuresis.

basis of this and many similar results, a graph has been constructed to show the relation between ammonia output and urine *p*H under resting conditions, during water diuresis, and during alcohol diuresis (Fig. 6). The scatter of the points is due largely to the variations in rate of urine flow (a 40-fold range), those to the right of the line occurring during diuresis, those to the left at low rates of flow. There is no indication that the ammonia output after ingestion of alcohol is less than that occurring under other conditions.

Discussion

The observed reduction in urine *p*H following the ingestion of alcohol is an unexpected result which is not easily explained. The well-known action of alcohol in stimulating gastric secretion would, in fact, have led one to expect

a change in the reverse direction. The increased acidity observed is not due to excretion of acetic acid as was at first surmised, nor is it due to a diminished production of ammonia, as the results of the class experiment on the effects of exercise had tentatively suggested. The only remaining possibilities would seem to be either the excretion of some acid product of metabolism other than

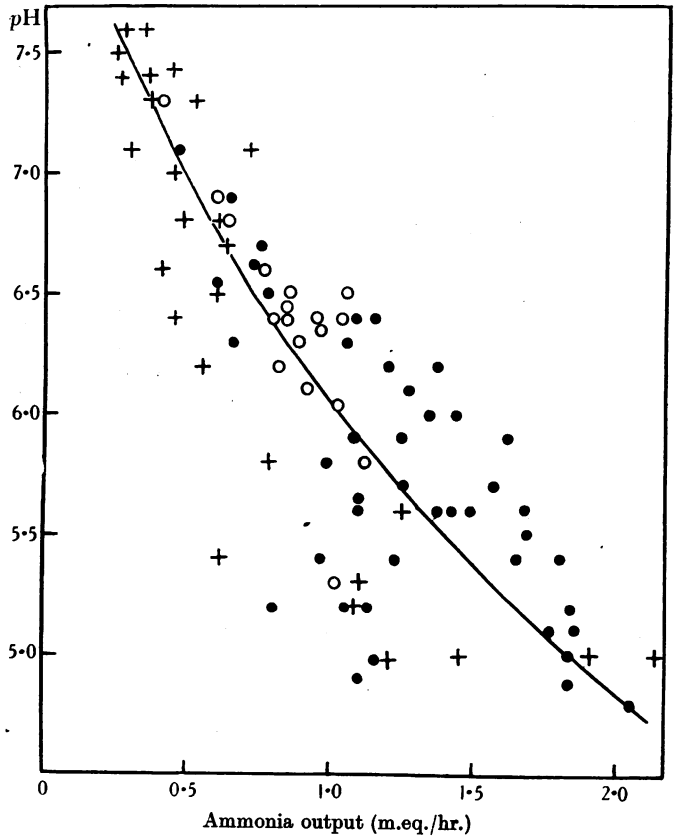

Fig. 6. The relationship between ammonia excretion and urine *p*H under resting conditions (+), during water diuresis (o) and during alcohol diuresis (•) in one subject: covering a 40-fold range in rate of urine flow.

acetic acid, or an acidity induced by some chain of events connected with the physical properties of alcohol, including its rapid rate of absorption. Any conclusion as to its mode of action, therefore, must await more detailed knowledge of possible different types of urine acidity induced by such agents.

Summary

1. A short period of severe exercise superimposed on an alcohol diuresis produces essentially the same effect on the urine as that observed during a water diuresis (Fig. 1).

2. During a water diuresis (uncomplicated by exercise), the *p*H of the urine rises from a low resting value and falls from a high resting value (Fig. 2).

3. In each of six subjects, the urine was consistently more acid during an alcohol diuresis than during a water diuresis (Fig. 3, Table 1).

4. This increased acidity of the urine in alcohol diuresis was not due to excretion of acetic acid, or of aceto-acetic acid.

5. An inverse relationship between urine *p*H and rate of ammonia excretion was observed, the result being unaffected by inclusion of amino-acids with the ammonia (Fig. 4).

6. The relationship was also relatively unaffected by large changes in rate of urine flow, and no consistent relationship was found between urine *p*H and ammonia concentration (Fig. 5).

7. The relationship between ammonia output and urine *p*H observed in resting samples and during water diuresis was not disturbed by ingestion of alcohol (Fig. 6).

I am indebted to Miss I. G. Smith for assistance with the ammonia determinations by the aeration method.

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