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THE RENAL EFFECTS OF URETHANE AND COLCHICINE IN ADULT RATS

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A study of the mode of action of sodium cyanate on the kidneys of adult rats has shown that its diuretic effect is due mainly to a decrease in the rate of water reabsorption by the tubules (Dicker, 1950). As Dustin (1947) and Schütz (1949) had shown that sodium cyanate has a pronounced antimitotic activity, it was thought of interest to investigate whether other antimitotic substances like urethane or colchicine would have a similar diuretic effect and if so how they would affect the renal mechanism.

METHODS

Experimental animals.—Adult male albino rats (weight 250–300 g.) were used; they were fed on a commercially prepared diet, described in a previous paper (Dicker, 1949a).

Experimental procedure for the determination of inulin clearances.—The routine procedure for inulin clearance estimations conformed with that described previously (Dicker and Heller, 1945; Dicker, 1949b): rats were injected subcutaneously with 2 ml./100 g. body weight of a 5 per cent (w/v) solution of inulin in saline. The beginning of the "urine collection period" was started 50–60 min. after the injection of inulin (Friedman, Polley, and Friedman, 1947; Dicker, 1949b), whether water was administered or not. Immediately after the end of the "collection period," the animals were anaesthetized, and blood was obtained from the carotid and jugular vessels and mixed with heparin. The inulin used was that of T. Kerfoot and Co.

Administration of water.—When given lukewarm tap water by stomach tube, the animals received either *one* dose of 5 ml./100 g. (Heller and Smirk, 1932a; Dicker and Heller, 1945; Dicker, 1946) or *three* doses of 5 ml./100 g. at hourly intervals (Birnie, Jenkins, Eversole, and Gaunt, 1949; Dicker and Ginsburg, 1950). The volume of urine excreted after administration of one dose of 5 ml./100 g. body weight was expressed as a percentage of the amount of water administered. In rats which received three doses of the standard amount of water, the urine volume was expressed as a percentage of the water load, i.e., as a percentage of the total water given minus that excreted before injection of the drug (Birnie *et al.*, 1949).

Analytical methods.—Inulin in plasma and urine was determined by the method of Smith, Goldring, and Chasis (1938). Chloride, sodium, and potassium in plasma and in urine were estimated as described previously (Dicker, 1949a).

Drugs.—Urethane was injected subcutaneously in a dose of 50 mg./100 g. rat (5 per cent w/v in saline). Colchicine solutions were prepared as described by Fleischman (1939) and injected intramuscularly in a dose of 0.1 mg./100 g. body weight.

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Methods of calculation.—The rates of tubular reabsorption of water and electrolytes were expressed in two different ways: (*a*) as the reabsorption of water or electrolytes by the renal tubules *as a whole*; (*b*) as the reabsorption of water and electrolytes by the more distal parts of the tubules. This later method of calculation is based on the assumption that about 80 per cent of the glomerular filtrate is reabsorbed iso-osmotically in the proximal segment of the mammalian nephron, regardless of the filtration rate. (Walker, Bott, Oliver, and McDowell, 1941; Wesson and Anslow, 1948; Wesson, Anslow, and Smith, 1948; Duggan and Pitts, 1950.)

The rate of reabsorption in the tubules *as a whole* was expressed as percentage of the glomerular filtration rate (Dicker, 1946 and 1948). Thus for water reabsorption (T_w):

$$T_w = \frac{C_{In} - U}{C_{In}} \times 100 \qquad (1)$$

Where C_{In} = inulin clearance/min./100 g. = glomerular filtration rate (or GFR), U = urinary volume/min./100 g. body weight.

For the calculation of the tubular reabsorption of electrolytes the following formula was used (Dicker, 1948):

$$T = C_{In} \times E_p - U \times E_u$$

which when expressed as percentage of the amount of ion E filtered became:

$$T_E = \frac{T}{C_{In} \times E_p} \times 100 \qquad (2)$$

Where E_p = concentration of the ion E per 100 ml. plasma, E_u = concentration of the ion E/100 ml. urine.

In order to calculate the absorption of either water or electrolytes by the *distal* portion of the tubules the amount of filtrate which had been reabsorbed by the proximal tubules had to be taken into account. The proximal reabsorption $Pr = \frac{C_{In} \times 80.}{100}$

Hence, the amount available for distal reabsorption (F) was:

(*a*) for water: $$F_w = C_{In} - \frac{C_{In} \times 80}{100}$$

(*b*) for an electrolyte: $$F_E = C_{In} \times E_p - \left[\frac{(C_{In} \times E_p) \times 80}{100}\right]$$

The reabsorption by the distal portion of the tubules was then:

(*a*) for water: $$Tw_D = \frac{F_w - U}{F_w} \times 100 \qquad (3)$$

(*b*) for an electrolyte: $$Te_D = \frac{F_E - U \times E_u}{F_E} \times 100 \qquad (4)$$

Statistical treatment.—Results are given as means and standard errors. Fisher's (1944) test for small samples was used for estimating the significance of means. The probability of P for t was obtained from the tables of Fisher and Yates (1943).

RESULTS

Non-hydrated rats. I. Urethane

General effects of urethane on rats.—Rats injected with urethane showed signs of sleepiness and drowsiness, but no real anaesthesia: they reacted to prodding; their movements, however, were slow. No lachrymation was observed as with sodium cyanate (Birch and Schütz, 1946).

TABLE I

RENAL EFFECTS OF INJECTIONS OF URETHANE, COLCHICINE, AND SODIUM CYANATE IN HYDRATED AND NON-HYDRATED RATS

The figures are mean results with their standard errors. Number of animals in parentheses

		GFR (inulin clearance) ml./100 g./min.	Mean amounts of filtrate available for distal reabsorption. *F.* ml./100 g./min.	Mean urine flow ml./100 g./min.	Distal reabsorption as percentage of *F.*	
					of water %	of Cl %
Non-hydrated rats	Controls	0.53±0.043 (11)	0.11	0.0137±0.0024 (11)	87.3±1.89 (11)	97.3±0.19 (10)
Non-hydrated rats	Urethane	0.64±0.087 (14)	0.13	0.0242±0.0059 (14)	77.7±4.90 (14)	94.9±0.77 (9)
Non-hydrated rats	Colchicine	0.29±0.017 (11)	0.06	0.0526±0.0069 (11)	19.8±5.50 (11)	89.9±1.12 (11)
Non-hydrated rats	Sodium cyanate*	0.31±0.034 (14)	0.06	0.0173±0.0030 (14)	72.8±0.76	75.9±1.99
Hydrated rats	Controls: 5 ml. water/100 g.	0.49±0.018 (14)	0.10	0.0342±0.0034 (14)	65.0±3.10 (14)	96.0±0.57 (14)
Hydrated rats	Controls: 15 ml. water/100 g.	0.79±0.021 (15)	0.16	0.0811±0.0052 (15)	33.1±4.85 (15)	95.3±1.57 (9)
Hydrated rats	Urethane: 5 ml. water/100 g.	0.75±0.050 (9)	0.15	0.0296±0.0050 (9)	81.4±2.91 (9)	94.5±0.60 (9)
Hydrated rats	Urethane: 15 ml. water/100 g.	0.73±0.018 (9)	0.15	0.0736±0.0061 (9)	49.4±4.60 (9)	96.8±1.06 (9)
Hydrated rats	Colchicine: 5 ml. water/100 g.	0.30±0.019 (11)	0.06	0.0606±0.0070 (11)	14.2±4.73 (11)	87.5±1.01 (11)
Hydrated rats	Colchicine: 15 ml. water/100 g.	0.33±0.028 (9)	0.07	0.0424±0.0034 (9)	31.4±7.36 (9)	95.3±0.65 (9)

* Data about sodium cyanate have been taken from Dicker (1950).

Effects of urethane on urinary excretion.—Water and food were withheld from rats for at least six hours before they were injected subcutaneously with urethane. Fig. 1 shows the results of a dose of 50 mg. urethane per 100 g. on the urinary volume of 18 rats, compared with that of controls injected with comparable volumes of saline.

Urethane had a significant diuretic effect which started about 60 min. after the injection and lasted for about one hour. It had also a significant effect on the urinary excretion of Cl and Na: the concentration of both ions increased, and hence their excretion was enhanced (Table II). There was no significant effect on the urinary concentration of K.

Inulin clearance estimations.—The mean value for inulin clearances (=GFR) in rats injected with urethane amounted to 0.64±0.087 (S.E. of mean of 14 observations) ml./100 g./min. and was thus higher than that of controls (Table I; $t = 2.150$, $P = 0.05(23)$).

TABLE II

EFFECTS OF URETHANE AND COLCHICINE ON THE VOLUME OF URINE AND ITS IONIC COMPOSITION IN NON-HYDRATED RATS

Results are means and their standard error. Number of animals in parentheses.

	Urine volume ml./100 g./3 hr.	Cl mg./100 ml.	Cl mg./100 g./3 hr.	Na mg./100 ml.	Na mg./100 g./3 hr.	K mg./100 ml.	K mg./100 g./3 hr.
Control rats ..	0.78 ±0.24 (26)	77.2 ±4.31 (26)	0.66 ±0.10 (26)	36.0 ±2.01 (10)	0.28 ±0.05 (10)	100.7 ±13.40 (10)	0.78 ±0.26 (10)
Rats injected with urethane, 50 mg./100 g. s.c.	1.70 ±0.12 (18)	111.4 ±8.51 (18)	1.89 ±0.12 (18)	50.0 ±5.76 (9)	0.85 ±0.12	134.3 ±11.35 (14)	2.28 ±0.64 (14)
Rats injected with colchicine 0.1 mg./100 g. i.m.	1.14 ±0.074 (18)	92.0 ±7.00 (18)	1.04 ±0.10 (18)			105.7 ±14.15 (9)	1.20 ±0.13 (9)

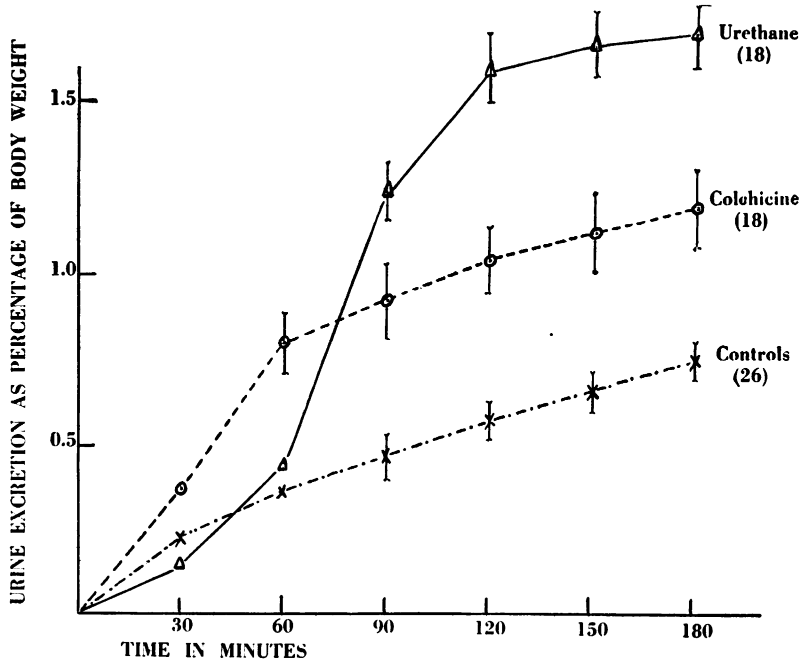

FIG. 1.—Effect of urethane and colchicine on the urine excretion of non-hydrated rats: Δ———Δ : rats injected with 1 ml./100 g. of a 5% solution of urethane; ⊙— — — — ⊙ : rats injected with 0.1 ml./100 g. of colchicine (0.1% sol.); ×—·—·—·× : control rats injected with equivalent amounts of saline. The vertical lines indicate the standard errors. Number of animals in parentheses.

The tubular water reabsorption by the distal portion of the tubules was calculated on the assumption that 80 per cent of the filtrate was reabsorbed passively by its proximal portion (see equation 3): Tw_D amounted to $77.7 \pm 4.90(14)$; this value was not significantly different from that found in control animals (Table I; $t = 1.814$, $P > 0.05$).

In the same way, it could be shown that the mean value for the distal tubular reabsorption of chloride (TCl_D) was much the same in rats injected with urethane and in controls (Table I; $t = 0.425$, $P > 0.6$).

It can thus be concluded that the injection of urethane (50 mg./100 g. rat) had a marked diuretic effect in non-hydrated rats (Fig. 1) and that both the increased urinary volume and the enhanced chloride excretion were the result of an increased glomerular filtration rate, without any significant changes in the tubular reabsorptive activity for either water or chloride (Table I).

Non-hydrated rats. II. Colchicine

General effects of colchicine in rats.—Colchicine injected in a dose of 0.1 mg./100 g. rat had no immediate toxic effect. It had, however, a pronounced delayed toxic action: 12 rats out of 42 died eight to ten days after a single injection. Examination *post mortem* revealed haemorrhages in the small intestine of all these rats and large areas of congestion in the liver and the spleen; no macroscopical changes were seen in the kidneys.

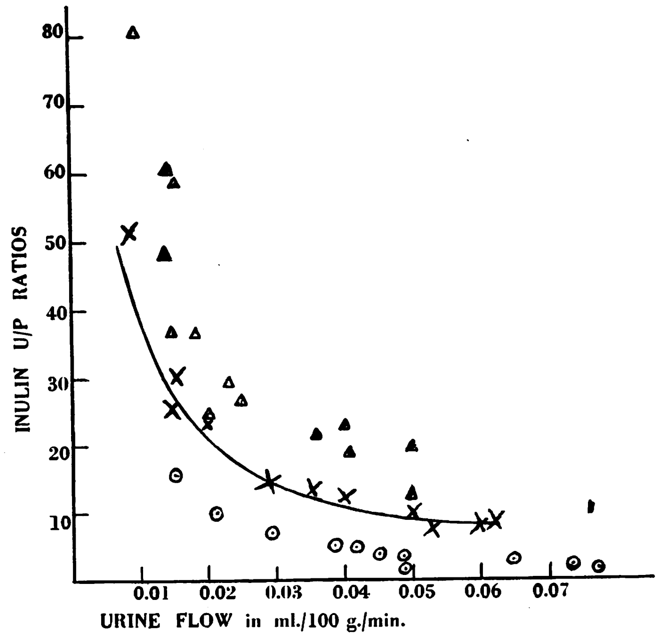

FIG. 2.—Effect of urethane and colchicine on the inulin *U/P* ratios, in non-hydrated rats. Δ : rats injected with urethane. ⊙ : rats injected with colchicine. × : control rats.

When, by mistake, the standard amount of water (5 ml./100 g.) was administered to the surviving animals about ten days after the injection of colchicine, about a third of them had an abnormally high urine output: 100 per cent of the administered water was excreted in less than 60 min.

Effects of colchicine on urinary excretion.—Water and food were withheld from rats for at least six hours before the rats were injected intramuscularly with colchicine. Fig. 1 shows the result of the injection of 0.1 mg. colchicine per 100 g. on the urinary excretion. There was a clear, though fleeting, diuretic effect: it started almost immediately after the injection and lasted for about 60 min. (Fig. 1).

Inulin clearance estimations.—The values for *U*/*P* ratios for inulin, and therefore the values for glomerular filtration rate, were lower than in controls (Fig. 2): the mean value for GFR in colchicine treated animals amounted to $0.29 \pm 0.017(11)$ ml./100 g./min. as compared with $0.53 \pm 0.043(11)$ ml./100 g./min. in controls. Concurrently the rate of water reabsorption was smaller than that of controls. Expressed as the rate of water reabsorption by the distal portion of the tubules, the mean value for Tw_D amounted to $19.8 \pm 5.50(11)$ per cent only (Table I). This result

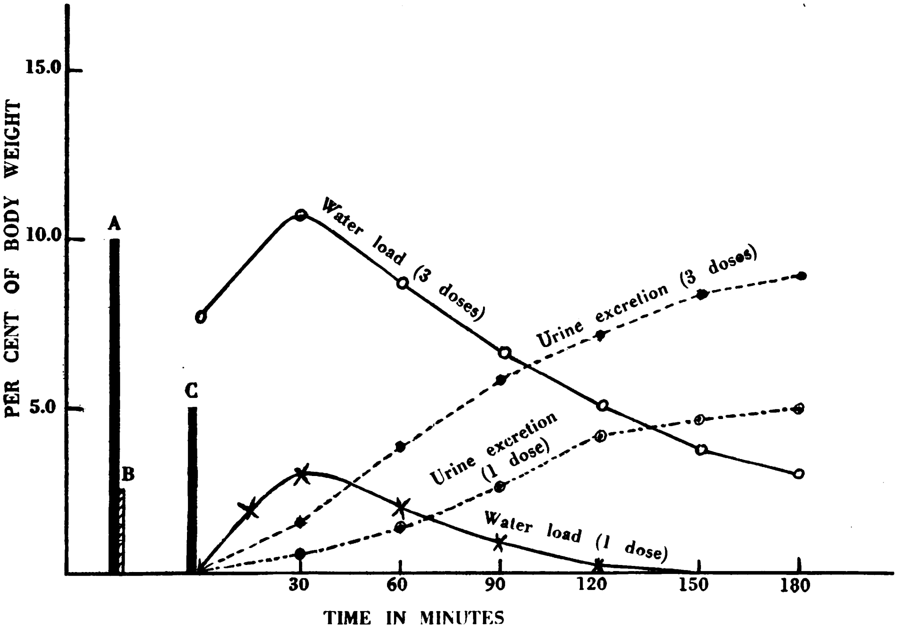

FIG. 3.—A comparison of the effects of the administration of one and three doses of 5 ml. water per 100 g. on the water load and urinary excretion of rats. A: amount of water given in 2 hours (= 10% body weight). B: amount of urine excreted in 2 hours (in % of the body weight). C. = volume of 5 ml./100 g. water: it represents either the third dose of water in rats receiving 15 ml./100 g. of water or the sole dose of water in rats receiving 5 ml./100 g. of water only. O——O: water load (% of body weight) of rats given 3 doses of water. ×——×: water load (% of body weight) of rats given 5 ml./100 g. of water. ●———● and ⊙—·—·—⊙ urine excretion (% of body weight) of rats hydrated with 3 and 1 doses of water respectively. Note the considerable increase of water load in rats which received 3 doses of water.

indicates that very little water was reabsorbed by the distal portion of the tubules. This was also suggested by the following facts observed at moderately high ranges of urine flow (e.g., beyond 0.05 ml./100 g./min.): (*a*) the values for *U/P* ratio for inulin did not change significantly (Fig. 2); (*b*) the mean value for the water reabsorption by the tubules as *a whole* ($=T_w$) amounted to 81.4±2.06(11) per cent, a figure which is very near to the theoretical value attributed to the iso-osmotic reabsorption by the proximal tubules; and (*c*) the calculated values for Tw_D were equal to zero (Fig. 4).

Effect of colchicine on excretion of chloride.—No significant increase of the chloride excretion could be noted in experiments where the urine collecting period extended up to 180 min. (Table II). Even during the short period when colchicine had its full diuretic effect (i.e., during periods when clearances were estimated) the chloride concentration of the urine of rats injected with colchicine remained comparable with that of controls, in spite of the fact that the mean filtration rate was decreased by about 40 per cent. This finding suggested that the chloride reabsorption by the tubules was decreased: Table I shows that values for TCl_D amounted to 89.9±1.12(11) per cent as compared with 97.3±0.19 per cent (t=4.378, P>0.001) in control animals.

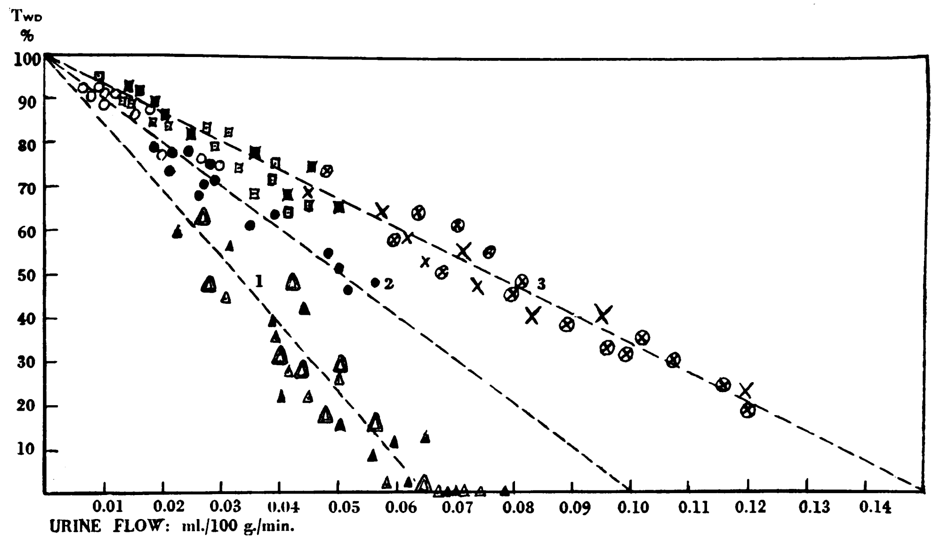

FIG. 4.—Relation between rates of water reabsorption by the distal portion of the tubules and rates of urine flow. The rates of water reabsorption are expressed as percentages of the amounts of filtrate available after 4/5 of it has been reabsorbed passively by the proximal portion of the tubules. 1, line representing mean results of water reabsorption for values of GFR = 0.3 ml./100 g./min.; 2, line representing mean results of water reabsorption for values of GFR = 0.5 ml./100 g./min.; 3, line representing mean results of water reabsorption for values of GFR = 0.75 ml./100 g./min. O: non-hydrated control rats, ● and ⊗ rats hydrated with 1 or 3 doses of 5 ml./100 g. of water, respectively. Δ: non-hydrated rats injected with colchicine, ▲ and ◬ rats injected with colchicine and hydrated with 5 or 15 ml./100 g. of water, respectively. □: non-hydrated rats injected with urethane, ■ and × rats injected with urethane and hydrated with 5 and 15 ml./100 g. of water respectively.

Thus it would seem that during the diuretic effect of colchicine there was a very pronounced decrease of the reabsorptive capacity of the tubules for water, and to a lesser degree for chlorides.

Hydrated rats

Effect of an increased water load on the urine excretion

Urethane and colchicine had a clear diuretic effect in rats which had received no extra water (Fig. 1); they were, however, not dehydrated. The same observation had been made when investigating the action of sodium cyanate on the urine excretion of adult rats (Dicker, 1950). It was therefore of interest to see whether an increased water load would enhance the diuretic effect of these drugs. In order to increase the water load rats were given either *one* or *three* doses of 5 ml. tap water per 100 g. by stomach tube.

(*a*) *One dose of* 5 *ml. water per* 100 *g.*: The effects of this dose of water on the diuresis, water load, and renal functions have been described in detail in previous papers (Heller and Smirk, 1932a; Dicker and Heller, 1945; Dicker, 1946, etc.).

(*b*) *Three doses of* 5 *ml. water per* 100 *g.*: When expressed as a percentage of the actual water load, the urine excretion followed the usual pattern of a normal water diuresis. It will be seen, however, from Fig. 3 that the water load after administration of the third dose of water, i.e., at the beginning of the urine collection, was significantly higher than that observed after the administration of 5 ml. water per 100 g. only.

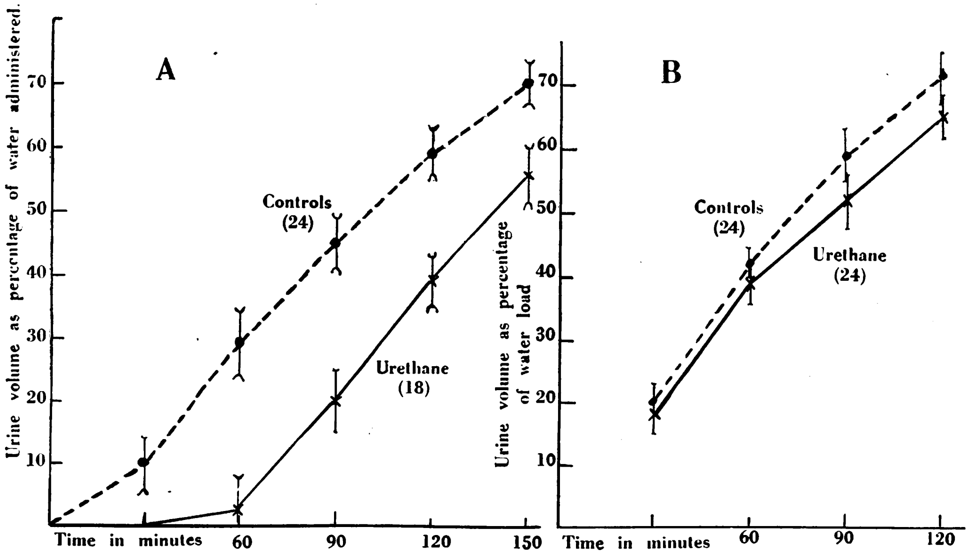

FIG. 5.—Effect of urethane on the urinary volume of rats which had received (A) 5 ml./100 g. of water, (B) 15 ml./100 g. of water. The urine volume is expressed in (A) as percentage of the amount of water administered; in (B) as a percentage of the water load. (For details see text.) The vertical lines indicate the standard errors.

The rate of glomerular filtration of rats which were given 15 per cent of their body weight of water was significantly raised. It amounted to $0.79 \pm 0.021(15)$ ml./100 g./min. Fig. 4 shows the values of water reabsorption by the distal portion of the tubules compared with those of rats which had received one dose of water only: it will be seen that at comparable rates of urine flow there was more water reabsorbed by the tubules of animals which were given 15 ml. water per 100 g. than by those which had received 5 ml. water per 100 g. only. This finding is consistent with that of an increased water load and explains why in the former series 75 per cent only of the initial water load was excreted after 180 min.

Effects of urethane on the renal functions of rats which received 5 *ml. water per* 100 *g.*

(1) *Water diuresis.*—The administration of urethane to hydrated rats (5 ml./100 g.) decreased their urine flow. It will be seen from Fig. 5A that there was a considerable delay in the onset of the water diuresis and that 50 per cent of the water administered was excreted after 140 min. only. This, however, could be explained by the fact

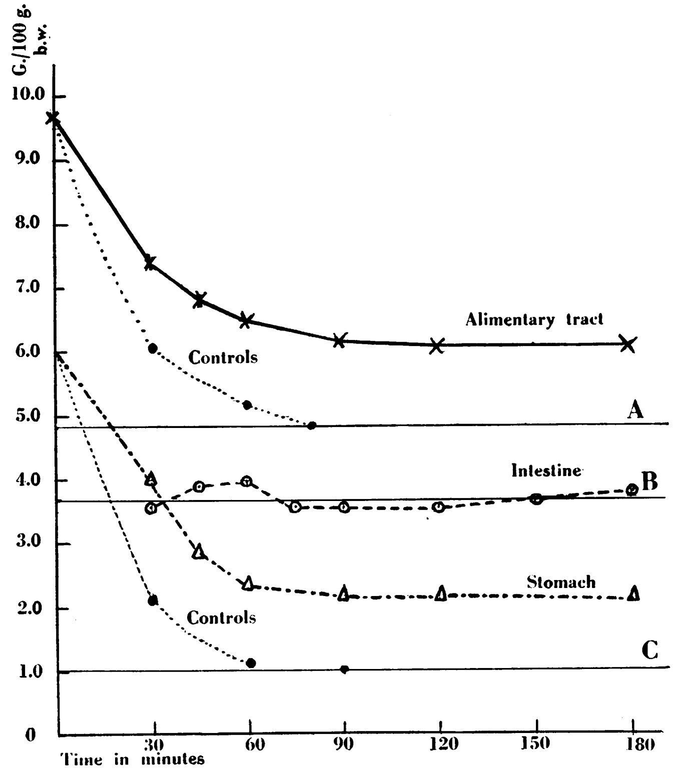

FIG. 6.—Average water absorption curves in rats injected with urethane. The average weight of the empty gastro-intestinal tract (A) was 4.7 g./100 g. body weight; 5 ml./100 g. of water was given, making 9.7 ml./100 g. the starting point of the absorption curve. The average weight of the empty intestine (B) was 3.7 g./100 g. rat and that of the empty stomach (C) was 1 g./100 g. rat. ×——× alimentary tract. ⊙— — —⊙: intestine. △—·—△: stomach. ●····●: water absorption in control rats.

that urethane retarded significantly the absorption of water from the stomach (Fig. 6). These results confirm those of Heller and Smirk (1932b).

(2) *Inulin clearances.*—The mean glomerular filtration rate of this series of animals amounted to $0.75 \pm 0.05(9)$ ml./100 g./min., which is not significantly different from that observed in non-hydrated rats injected with urethane (Table I).

It is thus clear that the administration of 5 ml. water per 100 g. did not increase the diuretic effect of urethane.

Effects of urethane on the renal functions of rats hydrated with three doses of water

In order to minimize any impairment of the absorption of water from the alimentary tract, urethane was injected one hour after the administration of the third dose of water. The mean water load at that time amounted to $8.9 \pm 0.49(36)$ ml./100 g. rat (Fig. 3). It will be seen (Fig. 5B) that the urine volume, expressed as a percentage of the water load, was much the same in rats injected with urethane as in controls. Likewise, no significant difference could be found between the rate of glomerular filtration and the rates of water and chloride reabsorption and the ionic concentration of urine ($\triangle$) in rats treated with urethane and in controls.

Effects of colchicine on the urine excretion of hydrated rats

(*a*) *In rats hydrated with* 5 *ml. water per* 100 *g.*—Colchicine was injected at the same time as water was administered. The total urine volume excreted in 180 min. was comparable with that of control animals. There was, however, a significant increase of the diuresis during the first hour following injection of the drug (Fig. 7A).

In contrast with urethane and sodium cyanate (Dicker, 1950), colchicine had no action on the absorption of water from the stomach and the gut.

Estimations of inulin clearances, of T_w and Tw_D showed that they were comparable with those found in non-hydrated rats: there was a marked decrease of the glomerular filtration accompanied by a pronounced decrease of values for T_w and Tw_D (Table I).

(*b*) *In rats hydrated with* 15 *ml. water per* 100 *g.*—(i) *Water diuresis*: Colchicine was injected 60 min. after the administration of the third dose of water, i.e., at a time when the water load was at its maximum (mean water load: $8.9 \pm 0.49(36)$ ml./100 g.). No significant difference could be noted in the rate of urine flow of rats whether injected with colchicine or not (Fig. 7B).

Chloride concentration as well as the freezing point ($\triangle$) were estimated in samples of urine collected at 1 hr. intervals in rats injected with colchicine and in controls: there was a significant decrease of the concentration of Cl in rats treated with colchicine ($t=2.202$) and the decrease of the freezing point, expressed in milli-osmol (C) indicated that the urine samples of colchicine treated animals were less concentrated than those of controls.

(ii) *Inulin clearances*: In spite of the administration of 15 ml. water per 100 g., the mean rate of urine flow and the mean values for GFR, T_w, Tw_D, T_{Cl}, and TCl_D were all comparable with those found in non-hydrated rats or in rats hydrated with one dose (5 ml./100 g.) of water only (Table I).

It is thus clear that colchicine acted quite independently of the degree of hydration of the animal and that in all animals the urine excretion was the result of a marked

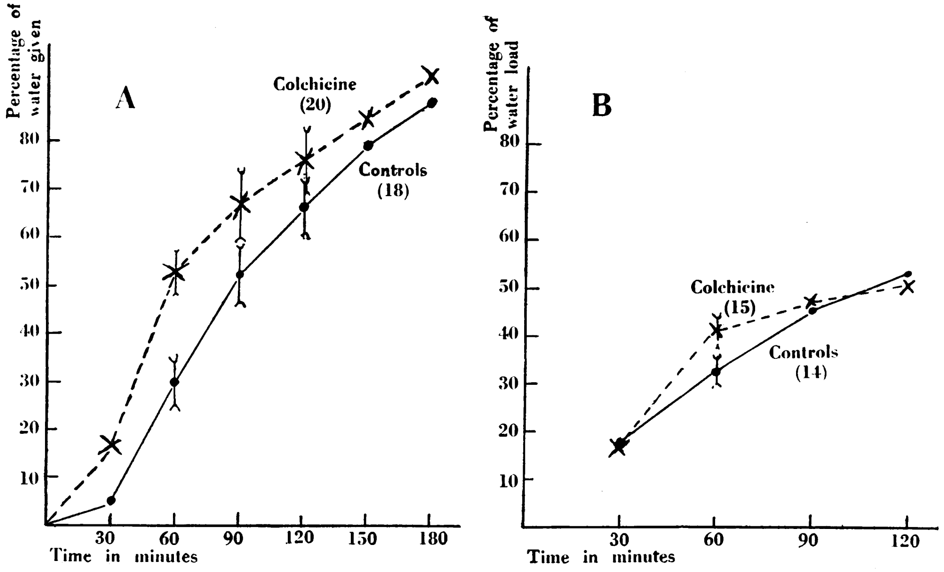

FIG. 7.—Effect of colchicine on the urinary excretion of hydrated rats. A: rats which received 5 ml./100 g. of water and were injected with colchicine. B: rats which received 3 doses of 5 ml./100 g. of water and were injected with colchicine 60 min. after the administration of the third dose of water. The urinary excretion is expressed in A as percentage of the amount of water administered; in B as percentage of the water load. ×— — —×: rats injected with colchicine. ●——●: controls. The vertical lines represent the standard errors. Number of animals in parentheses.

decrease of the tubular water reabsorption which counteracted the effect of a sharp fall in the glomerular filtration rate.

DISCUSSION

Urethane and colchicine both have an antimitotic activity, a property which they share with sodium cyanate (Dustin, 1947; Schütz, 1949) and to a certain extent with mercurial derivatives (Lettré, 1946; Meier and Schär, 1947). Though it is not known whether their antimitotic effect has any relation to their renal effects, it would appear that all four substances have a diuretic effect when injected into rats; however, mercurial derivatives have a diuretic effect in *hydrated* rats only (Dicker, 1946), while sodium cyanate increases the urine output when no extra water has been administered (Dicker, 1950). Urethane seems to act like sodium cyanate, while colchicine has a diuretic effect in non-hydrated rats and in rats which received one dose of water only (Fig. 7A). Further investigation has shown that colchicine produces a significant decrease of the filtration rate and that its diuretic effect seems to be due almost entirely to a decreased rate of water reabsorption by the tubules; this mode of action is reminiscent of that of sodium cyanate (Dicker, 1950). Urethane in non-hydrated rats on the other hand owes its diuretic effect both to an increase of the glomerular filtration rate and a decrease of the tubular water reabsorption; in this respect its action resembles that of mercurial derivatives (Dicker, 1946).

Is it permissible, or even correct, to assume that about 80 per cent of the glomerular filtrate is iso-osmotically reabsorbed by the proximal tubules, irrespective of the filtration rate? So far there has been only indirect evidence of such passive reabsorption of four-fifths of the glomerular filtrate (Walker *et al.*, 1941; Wesson *et al.*, 1948; Duggan and Pitts, 1950). However, even if this assumption were invalidated or had to be modified, the actual calculation used in this investigation (see equation 3), which consists in a uniform decrease of 80 per cent of the filtration rate, does not alter the conclusions materially. Presentation of the results in terms of this hypothesis has the advantage (or disadvantage) of magnifying changes in the rates of tubular reabsorption of water and chloride.

Changes in glomerular filtration rate raise an important issue, namely, the validity of inulin clearance estimations in animals injected with toxic drugs. Little criticism can be levelled against the finding of an *increase* of the filtration rate. In a *decrease* of the filtration rate, however, the decreased value of inulin clearance may be the result of a back diffusion of that substance, and if so inulin clearances would no longer represent a measure of filtration. No experiments were specifically carried out to investigate this question, but certain findings suggest that the decrease of inulin clearance found in rats injected with colchicine (or sodium cyanate) represents a real decrease of the filtration rate. Firstly, in rats injected with sodium cyanate, it has been shown that the filtration fraction was significantly lower than that of control animals, indicating a dilatation of the glomerular vessels, which would lead to a decrease of the glomerular filtration rate (Dicker, 1950). Secondly, in rats injected with colchicine, it was found that for the *same* volume of urine flow, the urine was regularly less concentrated (in terms of osmotic pressure). This could be due either to an intoxication of the tubular cells resulting in a back diffusion of solutes and of inulin, or to a decreased rate of water reabsorption. The hypothesis of a severe tubular intoxication leading to back diffusion of the solutes is ruled out by the finding that the urinary concentration of Cl and K remained unaffected (Table II) and that values for TCl_D were very much the same as those found in control rats (Table I). It would therefore seem more probable that colchicine acts specifically on the water reabsorption. At least one other drug, vasopressin, is known to have such a specific effect; it increases the rate of water reabsorption but has no effect on the chloride excretion (Dicker and Heller, 1946; Heller and Stephenson, 1950). If it be assumed, therefore, that colchicine affects the water reabsorption only, it is difficult to believe that the decreased value for the inulin clearance was due to a back diffusion of inulin through the tubular cells.

Summary

The effects of two antimitotic drugs (urethane and colchicine) on urine excretion were investigated (*a*) in non-hydrated adult rats, (*b*) in adult rats which had been given either 5 ml./100 g. or 15 ml./100 g. of water, the latter at hourly intervals.

A. Non-hydrated rats

1. The subcutaneous injection of urethane (1 ml./100 g. of a 5 per cent (w/v) solution of urethane) produced a significant increase of the urine excretion accompanied by an enhanced excretion of Cl and Na. The increased volume of urine was mainly the result of an increased glomerular filtration rate.

2. The intramuscular injection of colchicine (0.1 mg./100 g. rat) produced an increased urinary excretion, which started soon after the injection and ended in about an hour. There was no significant effect on the urinary excretion of Cl or Na. The enhanced diuresis was the result of a pronounced decrease of the tubular water reabsorption, the glomerular filtration (=inulin clearances) being markedly depressed.

B. Hydrated rats

1. The administration of 5 ml./100 g. of water had no effect on the glomerular filtration rate which remained comparable to that of non-hydrated rats. However, the administration of three doses of the standard amount of water produced a marked increase of the glomerular filtration rate.

2. The injection of urethane into hydrated rats (with one or three doses of water) resulted in a decreased water diuresis, due mainly to a decreased absorption of water from the alimentary tract.

3. The injection of colchicine did not impair the water absorption from the stomach and intestine. It produced a fleeting increase of the water diuresis. It had the same depressing effect on the glomerular filtration as in non-hydrated rats.

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