From the chemical analysis of the medulla, it is known that the concentration of potassium does not increase in the medulla (ULLRICH and JARAUSCH[2]). The distribution of iodides in the kidney has not yet been studied.

For our test we used 5 dogs with the average weight of 20 kg. They were fed on a mixed diet without limitation of liquids. From 200 to 1000 μc of the isotope were injected intravenously 60 min before the exstirpation of the kidneys. 15 min before nephrectomy the pituitrin was applied intramuscularly. The exstirpated kidneys were immediately put in the mixture of the concentrated alcohol and solid CO_2 for 30 min. The kidneys were cut longitudinally by a circular saw which was cooled before. Then the slices of the kidneys were attached to an X-ray film (Agfa Sino) from which they were separated by a polyethylen sheet. The time exposure was 3 days for K^{42} and 14 days for I^{131}. The frozen kidneys were kept in the refrigerator under a temperature of −20°C during the exposure.

Distribution of K^{42}. Figure 1 represents a radioautogram of the kidney after the application of 1000 μc $K^{42}Cl$. This Figure reveals that this ion is collected predominantly in the cortex. The concentration in the medulla is lower. This is most probably caused by the fact that potassium is reabsorbed almost completely in the proximal tubule. The radioautogram is similar to that concerning Rb^{86}.

Distribution of I^{131}. Figure 2 shows a radioautogram of the kidney after the application of 200 μc KI^{131}. The concentration in the medulla is greater than in the cortex. The maximum concentration is on the tip of the papilla. We deduce that the excretion of I^{131} by the kidney is realized by means of the counter-current system.

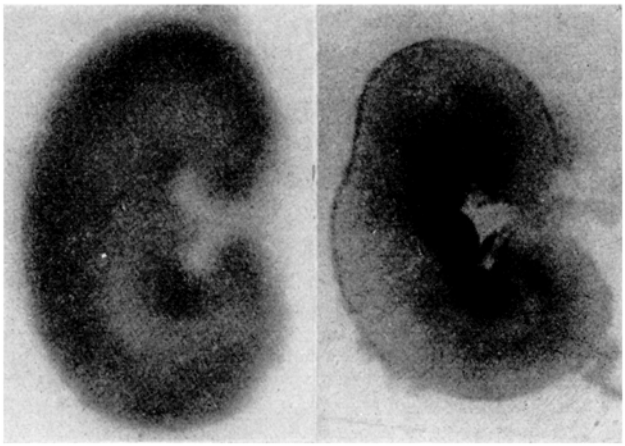

Fig. 1. A macroradioautograph of the canine kidney after 1000 μc $K^{42}Cl$ injection.

Fig. 2. A macroradioautograph of the canine kidney after 200 μc KI^{131} injection.

Zusammenfassung. Mittels der makroautoradiographischen Methode wurde festgestellt, dass die höchste Konzentration von K^{42} in der Nierenrinde, die maximale Konzentration von I^{131} im Nierenmark auftritt.

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The Effect of Ethionine on the Increased Metabolism of some Drugs and Increased Urinary Excretion of Vitamin C Induced by Pretreatment with Chloretone or Phenobarbital

A marked increase in the urinary excretion of vitamin C in rats pretreated with phenobarbital or chloretone was recently reported, and at the same time, a marked increase of pentobarbital and meprobamate metabolisms in the pretreated rats was observed[1-8]. On the other hand, some experiments carried out by BURNS et al.[1,2], and also some of us[9], have demonstrated that many drugs which can induce an increase in the metabolism of other drugs, also increase the urinary excretion of vitamin C.

It is therefore reasonable to think that there are analogous mechanisms concerned in the induced increase in the metabolism of the drugs and the increased urinary excretion of vitamin C.

It is also well known that the induced increase in drug metabolism is due to an increase in biosynthesis of the specific liver enzymes and it has been observed that the administration of ethionine, 30 min before the injection of the inducing drugs, can inhibit their effect[3-6, 10-12].

In the work reported here, we have examined the possibility of inhibiting the increased urinary excretion of vitamin C induced by the administration of phenobarbital or chloretone by prior administration of ethionine.

The experiments were carried out using rats of the Sprague-Dawley strain, weighing about 160 g, maintained on a standard diet chow. Phenobarbital 60 mg/kg or chloretone 50 mg/kg were injected intraperitoneally daily for 3 days. Ethionine was also injected intraperitoneally 30 min before the other drug in the following doses; first day: 200 mg/kg, second day: 100 mg/kg, third day: 150 mg/kg. The animals were sacrificed on the fourth day and *in vitro* metabolisms of pentobarbital and meprobamate were determined in liver slices.

The urine was collected for 24 h, starting 12 h after the last injection of the inducing drugs. The determinations of pentobarbital and meprobamate were carried out according to the methods of BRODIE et al.[13] and HOFFMAN and LUDWIG[14] respectively. The incubation of liver slices was

[1] A. H. CONNEY and J. J. BURNS, Nature *184*, 363 (1959).
[2] J. J. BURNS, A. H. CONNEY, P. G. DAYTON, C. EVANS, G. R. MARTIN, and D. TALLER, J. Pharm. exp. Therap. *129*, 132 (1960).
[3] A. H. CONNEY, C. DAVIDSON, B. GASTEL, and J. J. BURNS, J. Pharm. exp. Therap. *130*, 1 (1960).
[4] R. KATO, Atti Soc. Lomb. Sci. Med. Biol. *14*, 777 (1959).
[5] R. KATO, Med. exp. *3*, 95 (1960).
[6] R. KATO and E. CHIESARA, Brit. J. Pharmacol., in press.
[7] R. KATO, E. CHIESARA, and P. VASSANELLI, Atti Accad. Med. Lomb. *15*, 443 (1960).
[8] H. REMMER, Arch. exp. Path. Pharmak. *276*, 296 (1959).
[9] R. KATO, A. BOLEGO, and G. FRONTINO, Atti Accad. Med. Lomb., in press.
[10] R. KATO and E. CHIESARA, Atti Accad. Med. Lomb. *15*, 392 (1960).
[11] R. KATO, G. FRONTINO, and P. VASSANELLI, Jap. J. Pharmacol., in press.
[12] J. M. FUJIMOTO and G. L. PLEA, J. Pharm. exp. Therap. *131*, 282 (1961).
[13] B. B. BRODIE, J. J. BURNS, L. C. MARK, P. A. LIEF, E. BERNSTEIN, and E. M. PAPPER, J. Pharm. exp. Therap. *109*, 26 (1953).
[14] A. J. HOFFMAN and B. J. LUDWIG, J. Amer. pharm. Assoc. *68*, 740 (1959).

The effect of ethionine on the induction of the increased metabolism of pentobarbital and meprobamate and the increased urinary excretion of vitamin C induced by the pretreatment with phenobarbital or chloretone

Pretreatment	Pentobarbital metabolism (μg/g/2 h)	Meprobamate metabolism (μg/g/2 h)	Total vitamin C excretion (μg/100 g/day)	Ascorbic acid excretion (μg/100 g/day)
–	138 ± 3.3 (6)	145 ± 4.1 (6)	635 ± 48 (16)	481 ± 35 (16)
Phenobarbital	389 ± 5.3 (6)[a]	421 ± 5.4 (6)[a]	1885 ± 204 (8)[a]	1423 ± 118 (8)[a]
Chloretone	242 ± 4.5 (4)[a]	250 ± 4.8 (4)[a]	4641 ± 345 (12)[a]	3838 ± 209 (12)[a]
Ethionine	133 ± 4.0 (4)	141 ± 4.3 (4)	889 ± 78 (8)[c]	743 ± 82 (8)[b]
Ethionine + phenobarbital	148 ± 4.1 (6)	154 ± 3.9 (6)	2282 ± 305 (12)[a]	1731 ± 129 (12)[a]
Ethionine + chloretone	136 ± 3.2 (4)	138 ± 4.3 (4)	5236 ± 491 (12)[a]	4345 ± 269 (12)[a]

Pentobarbital and meprobamate metabolisms are represented by μg of the drugs metabolized by 1 g of liver slices in 2 h. Urinary excretion of ascorbic acid and total vitamin C are represented by μg of the acid or total vitamin C excreted in 24 h per 100 g body weight. The numbers of rats used is shown in the brackets. Probability = [a] $P < 0.001$, [b] $P < 0.01$, [c] $P < 0.05$.

carried out as described previously[6]. Ascorbic acid and total vitamin C were determined by 2,4-dinitrophenylhydrazine method and the 2,6-dichlorophenolindophenol method respectively.

The Table shows that ethionine has a potent inhibitory action on the induction of an increase in the drug metabolism in liver, while, on the contrary, it does not show any inhibitory effect on the increase in urinary excretion of vitamin C.

On the other hand, it was also observed that phenobarbital has a marked action on the increase in the metabolism of drugs, but it has a moderate effect on the increase in the urinary excretion of vitamin C. Chloretone, on the contrary, has a marked effect on the increase in the urinary excretion of vitamin C, but it has little effect on the metabolism of the drugs.

The results indicate that if some analogies between the mechanism of the increase in drug metabolism in liver and the increase in urinary excretion of vitamin C exist, the mechanism of the latter cannot be the same as that of the former.

Further experiments with different doses of ethionine showed that the administration of 150 mg/kg, 75 mg/kg, and 100 mg/kg for three successive days inhibited the chloretone induced increase of the drug metabolism, but even the high doses of 300 mg/kg, 200 mg/kg, and 250 mg/kg failed to inhibit the chloretone-induced increase of urinary excretion of vitamin C.

Riassunto. L'etionina è capace di inibire l'aumentata attività metabolica del fegato sul pentobarbital e sul meprobamato indotta da un pretrattamento con fenobarbital o cloretone. Essa invece non inibisce l'induzione dell'aumento dell'eliminazione urinaria di vitamina C causata da un analoge prettamento con fenobarbital o clorotone. Si conclude che i meccanismi delle due induzioni non possono considerarsi identici.

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The Effect of Temperature Variation on Spontaneous Potential Production from Explants of Brain Tissue in Culture[1]

This is the first report of the quantitative response of spontaneous potentials from explants of brain tissue in culture to variations in environmental temperature. It concerns the separate but simultaneous responses of two similar explants of the superficial part of the posterior-lateral aspect of the telencephalon of 14-day chick embryos to the same variation in temperature. The results provide some information concerning the nature of these spontaneous potentials.

Each explant was procured in the usual way[2,3] and each placed on a separate coverglass between and touching the upper surface of a cellulose sponge and a 36 gauge bare platinum electrode. Each coverglass with its sponge, explant and electrode was placed in a separate Kahn tube which had a 36 gauge platinum wire cemented on its wall to serve as a reference electrode. Sufficient supernatant (balanced salt solution TDL1[2] and 0.25% human serum protein) was added to each Kahn tube to cover the end of the reference electrode and come half-way up the cellulose sponge without touching the explant. A serum stopper containing an air filter was inserted into the upper end of each tube in such a way as to allow the egress of the electrodes. The two explants in their separate but identical tubes were then placed in similar places in a double-walled copper incubator with a water jacket heated by an alcohol lamp. When the walls of the incubator were grounded they made a very satisfactory shield against artefacts from transients and interference. The pair of electrodes from each culture tube was connected to separate but identical amplifier systems and paper strip recorders by shielded cables.

After the explants had been 24 h in culture the temperature in the incubator was altered and observations made on the frequency and magnitude of the potentials produced by each explant per unit of time (30 sec). The temperature was altered as follows (Figures 3, 4, and 5); lowered from the original 39°C to 32°C and then brought back to 35°C, observations being made at every half degree change in temperature. From 35°C the temperature was raised slowly to 47°C with continuous recordings being made on the strip chart recorder from each explant. When all activity had ceased in both explants the tem-

[1] This research was supported by a grant from the Office of Naval Research, U.S. Navy Contract NONR 1598(04).

[2] A. W. B. CUNNINGHAM, M. DOUGHERTY, and B. J. Rylander, Nature *186*, 477 (1960).

[3] A. W. B. CUNNINGHAM, Nature *190*, 816 (1961).