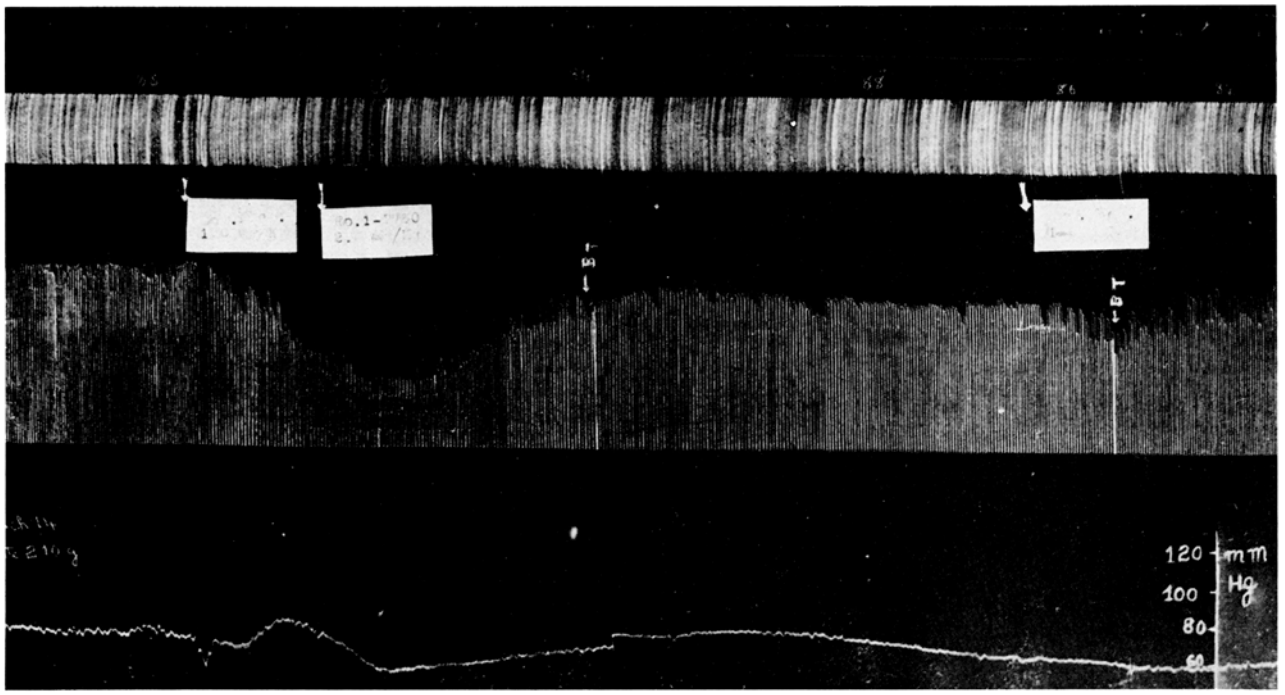

Fig. 2. Exp. No. 14; Dt. 9/2/1931; Weight of rat 210 g. Other items are as described under Figure 1. Expl. = Even a single dose of Ro 1-7780 adequately antagonized the action of codeine on the respiratory centre and raised the respiratory volume to 88 to 90% of the original. A second lethal dose of Cod. phos. injected after Ro 1-7780 shows no influence on respiration. 1st and 3rd arrows 150 mg/kg i.p. Cod. phos., 2nd arrow 2.0 mg/kg i.p. Ro 1-7780.

the original volume was not recovered. A second dose of 1.5 mg/kg Ro 1-7780 administered after 8 to 10 min increased the volume to 66% of the original. But a single dose of 2.0 mg/kg i.p. raised the respiratory volume to 88% of the original; still higher doses could not restore the original volume. Under the influence of Ro 1-7780, the respiratory rate usually recovered the values existing before codeine phosphate administration. In all the trials, the antagonist had to be administered to rats under the effect of codeine when the respiratory volume was reduced to 50% of the original, whatever the respiratory rate and blood pressure. Ro 1-7780 had no antagonizing effect when the volume became as little as 30 to 40% of the original. Another dose of codeine phosphate (150 mg/kg i.p.) injected even 20 min after Ro 1-7780 (2 mg/kg i.p.) did not show any influence either on respiration or on blood pressure. The influence of Ro 1-7780 on blood pressure was indiscriminate. Codeine phosphate lowered the blood pressure to about 60% of the original value. Administration of Ro 1-7780 brought about first a transient increase in blood pressure, and then, either maintained the levels under the influence of codeine, or gradually increased the levels to 80 to 85% of the original. It may be concluded that (−) 3-hydroxy-N-propargylmorphinan possesses the same influence as levallorphan[9] in antagonizing the respiratory depression produced by codeine in rats, and that it should be administered in doses (2 mg/kg i.p.) twice those of levallorphan (1 mg/kg i.p.)[10].

Zusammenfassung. Es wird festgestellt, dass Ro 1-7780 die atemdepressive Wirkung von Codein aufhebt. Die Dosis muss zweimal so gross wie die von Levallorphan sein. Das Dosisverhältnis zwischen Ro 1-7780 und Codein ist 1:50 bis 1:75.

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[10] *Acknowledgement:* We wish to thank F. Hoffmann-La Roche & Co. A.G. for their generous supply of the substances Ro 1-7780 and Lorfan.

Macro-Radioautographic Localization of K^{42} and I^{131} in the Canine Kidney

The existence of the counter-current system in kidneys is based upon the fact that the concentration of some material is greater in the medulla than in the cortex and that this concentration increases from the basis toward the tip of papilla. This type of dislocation was proved in sodium (KRAKUSIN and JENNINGS[1], ULLRICH and JARAUSCH[2]), chlorides (GLIEMSTEDT[3]), urea (LEVINSKY and BERLINER[4]), bromides (ANDRYSEK, SCHÜCK, and ANDRYSKOVÁ[5]), exogenous creatinine and aminoacids (ULLRICH and JARAUSCH[2]).

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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.

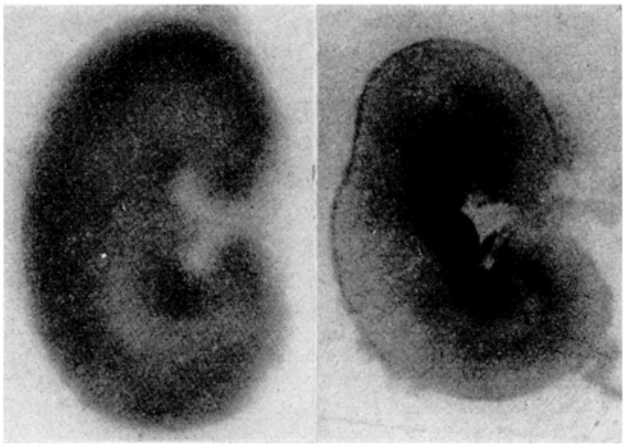

Fig. 1. A macroradioautograph of the canine kidney after 1000 μc $K^{42}Cl$ injection.

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

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