der Glukose-6-Phosphatase durch Phenobarbitalvorbehandlung wesentlich gesteigert werden.

GARNER und MCLEAN[12] konnten durch Nachweis von $^{14}CO_2$ in der Atemluft mit $^{14}CCl_4$ behandelter Tiere zeigen, dass Tetrachlorkohlenstoff in vivo abgebaut wird. Auch unsere Untersuchungen deuten darauf hin, dass nach Gabe von CCl_4 durch die Arzneimittel-metabolisierenden Enzyme ein toxischer Metabolit gebildet wird, der die Endoxydase dieses Enzymsystems, das Cytochrom P_{450}, zerstört. Der toxische Metabolit beeinflusst jedoch nicht nur dieses Cytochrom, sondern auch seine lipophile Umgebung. Dadurch kommt es nicht nur zu einer verminderten Bindungsfähigkeit für Substanzen vom Typ II wie Anilin, die direkt an das Cytochrom P_{450} gebunden werden, sondern auch für Substanzen vom Typ I wie Hexobarbital, deren Bindung durch die lipophile Umgebung vermittelt wird.

Summary. Isolated damage of the drug-metabolizing enzyme system, the binding power of the endoplasmic reticulum for hexobarbital and aniline, and glucose-6-phosphatase, appears 3 h after oral administration of carbon tetrachloride. The damage is evidently dependent on the dose and can become enlarged after phenobarbital pretreatment.

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Enhancement of the Positive Inotropic and Pressor Effects of Ouabain in Nephrectomized Dogs

Bilateral nephrectomy in dogs was shown to enhance the pressor effects of renin, angiotensin or norepinephrine. This increased response to pressor agents was attributed to an increase in vascular reactivity typical for a prehypertensive state. The increase was not mediated through the central nervous system and was not dependent on the excretory function of the kidney. It has been suggested that a nonexcretory renal function and specifically the absence of an antihypertensive substance of renal origin may be responsible for an increase in vascular reactivity after nephrectomy[1-3]. We recently found that not only the pressor but also the positive inotropic effects of ouabain are enhanced in dogs by nephrectomy.

Mongrel dogs of either sex and of 6.8 to 11.2 kg body weight were anesthetized with sodium vinbarbital, 50 mg/kg i.v. Bilateral nephrectomy was performed by retroperitoneal approach. The duration of the procedure did not exceed 40 min. The animals were tracheotomized and vagotomized; they were respired artifically with a respiratory pump Model AR-2 (Electro-Med, Inc., Minneapolis, Minn.) at the rate of 18 per min. The thorax was opened bilaterally at the fourth intercostal space. A BRODIE-WALTON[4] strain gauge was sutured on the right ventricle. The left ventricular wall was punctured with Teflon No. 6437 tubing, 0.066 inches O.D. The right femoral vein and artery were catheterized. The left ventricular and femoral arterial pressures were recorded through Statham Model 23Db pressure transducers. Heart rate was measured with a cardiotachometer driven from the amplified pressure signal. The first derivative of the left ventricular pressure, dp/dt max, was obtained with Lexington Model A-111 differentiator (Lexington Instruments Co. Waltham, Mass.). All variables were recorded on a Hewlett-Packard 8-channel recorder of 7700 series. Ouabain was dissolved in distilled water at 1 mg/ml and administered i.v. at 60 to 75 min after nephrectomy. Student's *t*-test was used for evaluation of significance of the differences in the effects of ouabain in normal and nephrectomized dogs.

The results are summarized in the Table. Under our experimental conditions ouabain had a relatively rapid onset of action. The maximal effect was usually seen within 15 min after administration of the drug. The data in the table refer, therefore, to the maximal effects of ouabain observed within 15 min after treatment. At 25 µg/kg ouabain had slight positive inotropic and pressor

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Effect of ouabain on right ventricular contractile force, left ventricular dp/dt max, mean arterial pressure and heart rate in anesthetized dogs[a]

Group No.	Dogs	Dose of ouabain (µg/kg i.v.)	No. of dogs	Right ventricular contractile force (*g*)		Left ventricular dp/dt max (mm Hg/sec)		Mean arterial pressure (mm Hg)		Heart rate beats/min	
				Before ouabain	Change[b]	Before ouabain	Change[b]	Before ouabain	Change[b]	Before ouabain	Change[b]
1	Normal	25	4	51	+ 5[d]	2376	+ 270[d]	85	+ 9[d]	159	−11
2	Normal	50	8	65	+33[c]	1652	+ 805[c]	88	+26[c]	140	−10[d]
3	Nephrectomized	25	4	54	+31[c,f]	1620	+ 270[c]	86	+11[d]	135	− 8
4	Nephrectomized	50	8	55	+82[c,e]	1674	+2398[c,e]	103	+63[c,e]	120	+24[d,e]

[a] Average values for 4 or 8 animals. [b] Maximal change within 15 min after ouabain. [c] Post-treatment values were significantly different from control values in the same animals, $p < 0.01$. [d] Same as [c], but $p > 0.01$ and < 0.05. [e] Significantly different from the corresponding changes in dogs of group No. 2 ($p < 0.05$). [f] Significantly different from the corresponding changes in dogs of group No. 1 ($p < 0.05$).

effects in normal or in nephrectomized animals. At 50 μg/kg ouabain produced significant increases in the right ventricular contractile force, left ventricular dp/dt max, and mean arterial pressure. These effects were considerably more pronounced in nephrectomized than in normal animals, the differences were significant statistically ($p < 0.05$). Heart rate was decreased by ouabain, 50 μg/kg in normal and increased in nephrectomized dogs. In addition, experiments were performed in which ouabain was administered at 75 μg/kg i.v. to 2 normal and 2 nephrectomized dogs. At this dose ouabain produced ventricular arrhythmias in all four animals at 8 to 15 min after administration. These experiments were not used for comparative evaluation of positive inotropic and pressor effects of the glycoside.

A possibility was considered that plasma Ca^{++} levels may determine the magnitude of the positive inotropic effect of ouabain. The total plasma Ca^{++} was determined in normal and nephrectomized dogs before and after ouabain utilizing the atomic absorption spectroscopy method of WILLIS[5]. The average total plasma level in 6 normal dogs before administration of ouabain was 5.13 mEq/l with a standard deviation of 0.33. In 10 nephrectomized dogs the average total plasma Ca^{++} was 5.26 mEq/l with the standard deviation of 0.44. There was no significant difference in total plasma Ca^{++} levels in both groups of dogs. Our experiments did not exclude, however, a possibility that myocardial Ca^{++} levels may have differed in the 2 groups of animals.

The renal excretion of ouabain is not likely to account for the observed difference in the positive inotropic effects of ouabain in normal and nephrectomized dogs. Only a relatively small portion of ouabain is known to be rapidly excreted by the kidneys. The 50% excretion time for ouabain in man was estimated to be 8 h[6]. Also, a greater enhancement of the effects of ouabain at 25 μg/kg would have been expected in nephrectomized animals if the renal excretory function were responsible for the observed differences in the effects of the drug.

It is conceivable that a humoral factor of renal origin, possibly an antihypertensive substance, antagonizes not only the pressor effects of angiotensin or norepinephrine, but also the pressor and the positive inotropic effects of ouabain. After nephrectomy the absence of this factor leads to the enhancement of ouabain effects.

Zusammenfassung. In nephrectomierten Hunden erhöht Ouabain den Blutdruck und die Kontraktionskraft des Herzens mehr als in intakten anaesthesierten Tieren.

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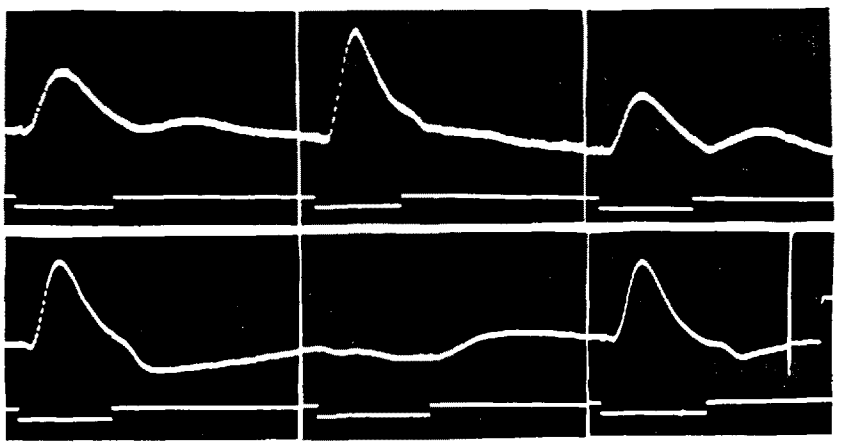
Effect of Strychnine on the Electroretinogram of the Isolated Rabbit Retina

Strychnine influences both *b*- and *d*-wave in frog[1,2]. However, no such influence could be shown as yet in ERG of rabbit and cat[3,4], although spike activity is altered in optic fibres of these animals[3,5]. From this the question arises whether strychnine may act on the second neuron of the mammalian retina and, therefore, on its ERG.

The eyes of 8 rabbits (anaesthetized by urethane 2 g/kg) were enucleated after dark adaptation of at least 1 h duration. The isolated retinae (17 preparations) were perfused by plasma saline-mixture kept at 30 °C[6] and the ERG recorded by an oscilloscope (OG2-18, VEB Messtechnik Berlin, dc-amplification).

Normal ERG of the isolated rabbit retina is shown in the Figure (upper row, left). After application of strychnine $3.5 \times 10^{-5} M/l$ the *b*-wave increases (upper row, middle). The transitory effect is reversible as shown in the right ERG (upper row). With higher concentration of strychnine ($7 \times 10^{-4} M/l$) the effect is just the opposite, the *b*-wave of the control ERG (Figure, lower row, left) practically abolished (lower row, middle). Complete restoration occurs after application of plasma-saline-mixture without strychnine (lower row, right). Strychnine in a moderate concentration ($7 \times 10^{-5} M/l$) results only in slight reduction of the *b*-wave. The dependence of the drug's effect of its concentration and of the adapta-



Influence of strychnine on the ERG of the isolated rabbit retina in concentration $3.5 \times 10^{-5} M/l$ (upper row, middle) and $7 \times 10^{-4} M/l$ (lower row, middle). Left and right ERGs are controls before and after application of strychnine to the perfusion fluid. Calibration 200 μV, light stimulus 50 mlx, approximately 1 sec.