The possibility of studying the TETD-ethanol reaction in animals opens the way for a better experimental analysis of its mechanism, and also for a better evaluation of the various counter-measures which have been proposed to alleviate the sometimes serious circulatory complications during TETD-ethanol reactions in man[3].

A detailed description of this work will be presented in the near future[4,5].

Zusammenfassung. Vorbehandlung mit Tetraäthylthiuramdisulfid (Disulfiram, Antabus) ändert die Reaktivität von Kaninchen auf Äthanol. Selbst durch kleine Dosen von Äthanol hervorgerufene Symptome (Hyperventilation, Hypotension) stimmen weitgehend mit der Antabus-Alkohol-Reaktion des Menschen überein.

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Mechanism of the Hypotension During the Antabuse-Alcohol Reaction in Rabbits

Recent work has shown that an equivalent to the human Antabuse-alcohol reaction can be produced in rabbits by administration of small amounts of ethanol after pretreatment with tetraethylthiuramdisulfide (TETD, disulfiram, Antabuse). Hyperventilation and a long-lasting decrease in arterial pressure are prominent features of this reaction. The mechanism of the arterial hypotension has been studied in more detail in view of the clinical importance of the corresponding hypotension in man[1].

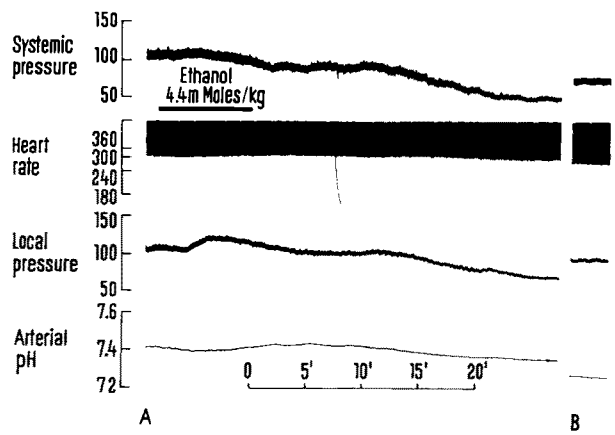
Methods. Male albino rabbits weighing 2–4 kg were used. For pretreatment 1.0 g TETD (Antabuse, Dumex Ltd.) was given by stomach tube (in a gum arabic suspension) 26 and 2 h prior to experiments. The animals were anesthetized with urethane (1.4 g/kg i.v.). The following physiological functions were studied *in vivo:* systemic arterial pressure, heart rate, vascular resistance in the hind limb and pH of arterial blood. A polygraph (Grass) was used for recording. The systemic arterial pressure was recorded from the right femoral artery via a pressure transducer (Statham). The heart rate was recorded by an ordinate writer. A measure of the vascular resistance in the hind limb was obtained with the following technique. Polyethylene tubing was inserted into the left femoral artery, allowing the blood to flow in an extracorporal loop. The blood flow in the loop was maintained constant by a pump (Sigmamotor). The perfusing pressure was recorded via a pressure transducer, and the flow rate in the loop was adjusted so that at the beginning of the experiment the perfusing pressure equalled the systemic arterial pressure. Changes in perfusing pressure during the course of the experiment accordingly reflected changes in the vascular resistance of the perfused region. Arterial pH was determined with a pH-electrode in the loop recording via a pH-meter (Radiometer PHM 22). Ethanol was administered intravenously diluted in saline (0.9%).

Pieces of intestine from pretreated and non-pretreated rabbits were studied in *in vitro* experiments. Finkleman's[2] preparation was used in these experiments, and ethanol or acetaldehyde was added directly to the intestine bath.

Results. The ethanol-induced hypotension was not prevented by maintaining constant ventilation (after neuromuscular blockade with decamethonium), indicating that hyperventilation is not a primary cause of the hypotension. During the hypotension stimuli acting at different levels of the sympathetic vasoconstrictor system (carotid occlusion, hypoxia, hypercapnia, administration of sympathetic transmitter) all produced a rise in systemic pressure. Ethanol also induced a marked hypotension in pretreated rabbits after ganglionic blockade with hexamethonium (2–5 mg/kg i.v.).

The vascular resistance in the perfused hind limb of pretreated animals decreased during the ethanol-induced fall in systemic pressure (Figure). A decrease in vascular resistance following administration of ethanol was seen also in experiments where the sympathetic nerves to the perfused region had been cut. It was noted that the fall in systemic pressure preceded the decrease in vascular resistance of the perfused hind limb when the extracorporeal loop had a large capacity. It seems probable that this was due to the 'delay' caused by the loop. These results therefore suggest that the decrease in vascular resistance is primarily due to a blood-borne factor with peripheral action.

There was a slight transitory (20 min) increase in heart rate during the initial phase of the hypotension; no change in heart rhythm was observed. There was a slight initial increase in arterial pH probably related to the concomitant ventilatory increase.



Rabbit pretreated with TETD. Urethane anesthesia. From above downwards: systemic arterial pressure in mm Hg; signal; heart rate in beats per min; local pressure in mm Hg in the left hind limb, perfused at constant flow rate (6 ml/min) with blood from the same animal (= vascular resistance); arterial pH; time scale in min. Capacity of loop: 9 ml. (B) 80 min after end of ethanol infusion.

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Intestines from pretreated rabbits responded in an apparently normal way to sympathetic nerve stimulation *in vitro* in the presence of ethanol (< 1.0% w/v) or acetaldehyde (< 0.01% w/v).

Conclusions. The results suggest that a decrease in peripheral vascular resistance is a major contributing cause of the hypotension during the Antabuse-alcohol reaction. No evidence of any impaired function in the sympathetic nervous system was obtained. This indicates that the hypotension is not primarily due to a blockade of the vasoconstrictor system. However, the homeostatic regulation of the blood pressure is notoriously poor in the rabbit, and this probably explains why the hypotension during the Antabuse-alcohol reaction is so pronounced in this animal.

The present findings seem to provide some experimental support for the clinical observation[3] that exogenous administration of the sympathetic transmitter (= noradrenaline i.v.) may be an adequate supportive therapy for the serious hypotension which can occur during Antabuse-alcohol reactions in man.

A more detailed report[4] of these studies will appear in the near future[5].

Résumé. Nos études sur le système circulatoire des lapins anesthésiés à l'uréthane montrent que la baisse de la résistance vasculaire périphérique, provoquée par un facteur transporté par le sang, est une cause majeure contribuant à l'hypotension pendant la réaction Antabuse-Alcool. Aucune évidence de la présence d'un bloc primaire au niveau du système vasoconstricteur n'a été constatée.

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In vitro Guanidino-Resistance and Guanidino-Dependence of Poliovirus

The discovery of the *in vitro* antipolio activity of guanidine[1,2] has been quickly followed by the observation that the poliovirus becomes easily resistant to this chemical[3,4]. It seemed to us useful, from the view-point of viral biology and from that of chemotherapy, to study in detail some features of this resistance.

The technical procedure employed in these *in vitro* experiments has been described in detail elsewhere[5]. In brief, we have been able to confirm that a guanidine-resistance easily develops in poliovirus 1 and 2. As shown in Table I, it is possible to obtain an appreciable degree of resistance after only 4–5 transfers in HeLa cell cultures containing increasing amounts of guanidine HCl (from 1/16000 to 1/4000 which is the maximum dose tolerated by the cultured cells). However, when the initial amount of guanidine in the medium is very high (1/4000) it is never possible to isolate resistant viruses.

The stability of the guanidine-resistance was then investigated. A strain of guanidine-resistant poliovirus was subjected to passages in guanidine-free HeLa cell cultures. After 10 transfers (Table II), a clear diminution of its guanidine-resistance was observed and after 30 transfers the resistant virus had a guanidine-sensitivity very similar to that of the original sensitive virus.

These results suggest that the guanidine-resistance evoked *in vitro* should be considered as an adaptative character of the virus-cell system rather than a genetic one. Other experiments have demonstrated that the virus which has become guanidine-resistant in HeLa cell cultures shows the same degree of resistance even when propagated in other cell-lines. It seems, therefore, that the resistance we induced is a property acquired by the virus or by a virus-cell system not limited to a single cellular type – for instance the virus plus the 'receptor' described by HOLLAND and MCCLAREN[6].

Finally, we have observed that guanidine not only interferes with, but even enhances the viral growth. In fact, if the transfers of a resistant virus in cell cultures

Tab. I. Guanidine resistance induced in poliovirus strains (CPU present in culture media after 4 or 5 serial passages[a])

	Virus	CPU[a] without guanidine	with guanidine γ/ml	
1 S:	Polio 1 Strain (Brunhenders)	10^6	250	<10
			125	10
			83	10^2
			62	10^3
			50	10^5
			33	10^6
1 R:	1 S propagated in HeLa cells once with 62 and 3 times with 250 γ/ml of guanidine HCl	10^6	250	10^6
1 Rx:	1 S propagated in HeLa cells 4 times with 250 γ/ml of guanidine HCl	10^3	250	<10
			125	<10
			83	<10
			62	<10
			50	10
			33	10
2 S:	Polio 2, MEF 1; mouse adapted	10^6	250	<10
2 R:	2 S propagated in HeLa cells once with 15, twice with 62 and twice with 250 γ/ml of guanidine HCl	10^6	250	10^6

[a] End-point method, performed in HeLa stationary cultures

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