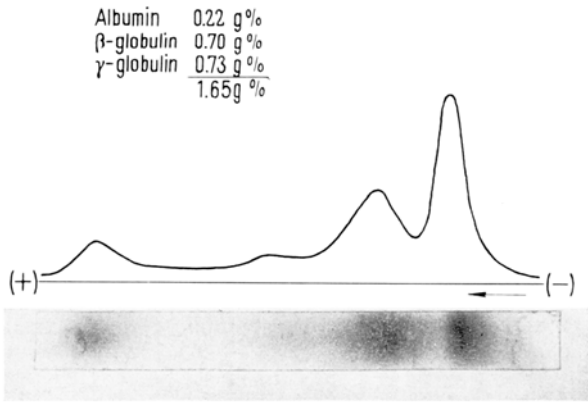


Zusammenfassung. Es wird festgestellt, dass der Magensaft von Menschen mit Achlorhydrie die cytopathogene Wirkung der Poliomyelitis-Viren in HeLa-Gewebekultur neutralisiert. Die neutralisierende Wirkung des Magensaftes scheint vom homologen Antikörpertiter des Serums abhängig.

V. BALÁZS and E. SZÖLLÖSY

1st Department of Medicine, University Medical School of Szeged, and Public Health Institute, Szeged (Hungary), May 21, 1962.

Antabuse-Alcohol Reaction in Rabbits

It is well known that a small amount of ethanol produces a characteristic, unpleasant reaction (hyperventilation, hypotension, etc.) in human subjects pretreated with tetraethylthiuramdisulfide (TETD, disulfiram, Antabuse)[1]. However, several workers[2] have found it difficult or impossible to demonstrate a similarly altered response to ethanol in animals. This has made the experimental analysis of the TETD-ethanol reaction difficult, and its mechanism is still to a large extent obscure.

This study shows that a TETD-ethanol reaction can be produced in the rabbit, and that it corresponds well to the human reaction in several important features.

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. In experiments on urethane-anesthetized (1.4 g/kg i.v.) rabbits, arterial pressure and ventilation were recorded on a smoked drum with standard methods. Experiments were also carried out on un-anesthetized rabbits. In these experiments the blood pressure was recorded from the ear artery with a strain gauge manometer coupled to an ink-writer, and the technique permitted repeated recordings from the same animal during several days. Ethanol (diluted in saline) was administered intravenously by infusion (infusion time 6–9 min).

Results. Pretreatment with TETD did not by itself appreciably affect the general condition of the animals or the parameters under study. In pretreated animals, however, small ethanol doses (1.1–4.4 m Moles/kg) regularly produced marked hypotension and hyperventilation lasting 2–3 h (Figure 1). Similar ethanol doses induced hypotension also in pretreated, un-anesthetized rabbits, and this altered 'sensitivity' to ethanol persisted for several days after pretreatment (Figure 2). In un-pretreated rabbits, similar ethanol doses did not affect blood pressure or ventilation.

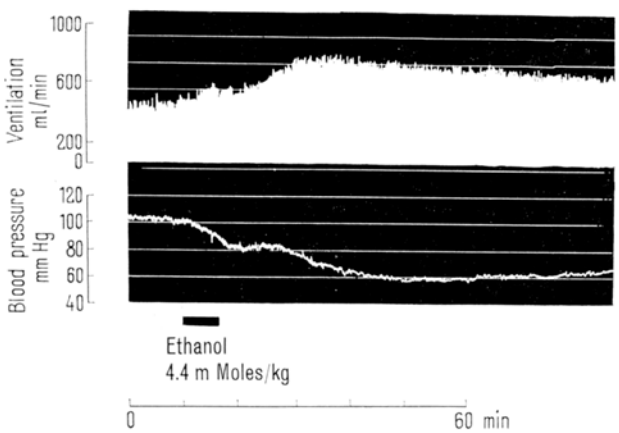


Fig. 1. Rabbit (3 kg) pretreated with 1 g TETD 26 and 2 h prior to experiment. Urethane anesthesia (1.4 g/kg i.v.). Ethanol (4.4 m Moles/kg = 0.2 g/kg) infused i.v. during signal.

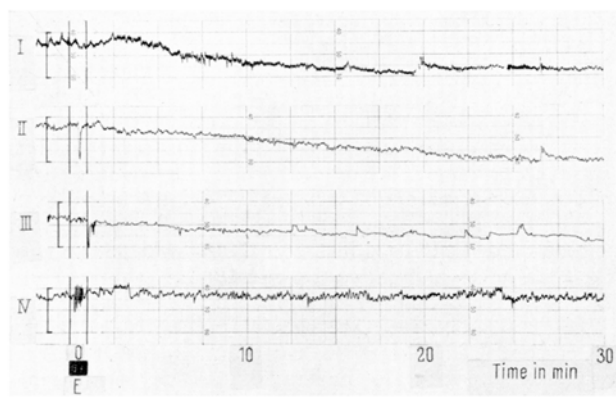


Fig. 2. Rabbit (3 kg) pretreated with 1 g TETD twice with an interval of 24 h. No general anesthesia. Recordings of ear artery pressure on 4 consecutive days. Scale: upper limit 100 mm Hg, lower limit 60 mm Hg. At E (between markings) ethanol infusion, 4.4 m Moles/kg i.v. I: First day, 4 h after the second TETD dose. II: Second day. III: Third day. IV: Fourth day.

[1] J. HALD, E. JACOBSEN, and V. LARSEN, Acta pharmacol. (Kbh.) *4*, 285 (1948).

[2] V. LARSEN, Acta pharmacol. (Kbh.) *4*, 321 (1948). – G. P. CHILD, J. Pharmacol. exp. Therap. *101*, 6 (1951). – R. A. SEIBERT, R. A. HUGGINS, and A. R. BRYAN, Arch. int. Pharmacodyn. *89*, 426 (1952). – E. ZIEGLER and H. J. MEYER, Arch. int. Pharmacodyn. *123*, 34 (1959).

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.

E. S. PERMAN

Department of Physiology, Karolinska Institutet, Stockholm (Sweden), April 27, 1962.

[3] E. JACOBSEN, Quart. J. Stud. Alcohol *13*, 16 (1952).
[4] E. S. PERMAN, Acta physiol. scand. *55*, Suppl. 190 (1962).
[5] A research grant from the Alcohol Research Committee of the Swedish Medical Research Council is gratefully acknowledged.

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].

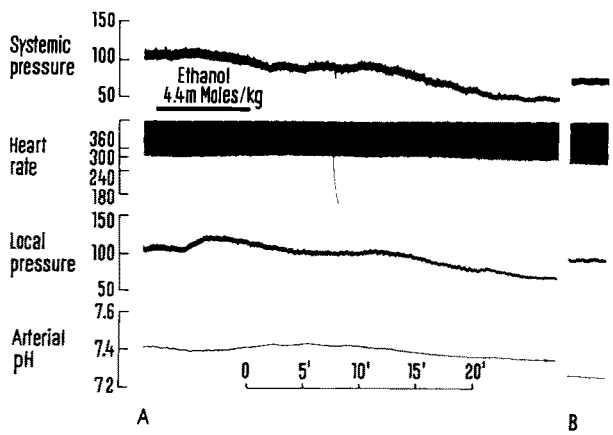
Methods. Male albino rabbits weighing 2–4 kg were used. For pretreatment 1.0 g TETD (Antabuse, Dumex Ltd.) was given by stomach tube (in a gum arabic suspension) 26 and 2 h prior to experiments. The animals were anesthetized with urethane (1.4 g/kg i.v.). The following physiological functions were studied *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.

[1] K. RABY, Dan. med. Bull. *3*, 168 (1956).
[2] B. FINKLEMAN, J. Physiol. (Lond.) *70*, 145 (1930).