Discussion. As already pointed out, if the entry of ^{3}H noradrenaline into the brain tissue is prevented by a capillary wall, the space of ^{3}H noradrenaline in the brain should be approximately equal to the space of ^{131}I albumin. In the intoxicated animals, the space of ^{3}H noradrenaline and ^{131}I albumin would probably change in a parallel way.

On the other hand, if the passage of noradrenaline into the brain is hindered by pericapillary structures, the space of ^{3}H noradrenaline in normal and probably also in the intoxicated animals would be close to the values of ^{14}C sucrose.

Our present experiments seem to speak for the latter possibility, and therefore we suspect that the barrier preventing the entry of noradrenaline from blood into the brain is probably located outside the capillary wall.

Our hypothesis does not correlate well with the observations of BERTLER et al.[6] Using fluorescence microscopy, these authors found that the vascular endothelium in the brain constitutes a barrier for some monoamines closely related to noradrenaline.

Our approach to the investigated problem is based on the hypothesis of the existence of a rapidly equilibrating pericapillary space in the brain[2-4]. However, the existence of the pericapillary space in the brain tissue has not been confirmed by a direct histological method[7].

It seems that the question of the existence of the pericapillary space in the brain and its relation to the rapidly exchanging compartment has to be elucidated before a final evaluation of the present experiment.

	Space ml/100 g of tissue		
	^{3}H noradrenaline	^{14}C sucrose	^{131}I albumin
Controls	2.20 (1.49–2.91)	2.17 (1.92–2.42)	1.21 (0.70–1.72)
Intoxicated animals	8.10 (5.27–10.93)	8.37 (6.31–10.43)	2.57 (2.07–3.07)

The values represent the mean value from 10 animals with their fiducial limits.

Zusammenfassung. Die Autoren untersuchen den transkapillaren Durchtritt von ^{3}H Noradrenalin in das Gehirn der Mäuse. Auf Grund der Versuche scheint es wahrscheinlich, dass die Barriere, die den Eintritt von Noradrenalin in das Gehirn verhindert, sich nicht in der Kapillarwand befindet.

J. ŠTULC, K. MAŠEK and R. FRIEDRICH

Department of Pharmacology, Faculty of Pediatrics, Charles University, and Institute of Pharmacology, Czechoslovak Academy of Sciences, Praha (Czechoslovakia), 17 October 1968.

[6] A. BERTLER, B. FALCK and E. ROSENGREN, Acta pharmac. *20*, 317 (1963).
[7] S. W. KUFFLER and J. G. NICHOLLS, Ergebn. Physiol. *57*, 1 (1966)

Effects of Alcohol Ingestion on the Intercalated Disc in the Mouse Heart

Heart muscle is divided into distinct cellular units by the intercalated disc at the intercellular boundaries[1]. Physiological studies indicate that the electrotonic coupling between the adjacent heart muscle cells is facilitated by the low resistance of the intercalated disc[2-4]. Recent studies of SOHAL et al.[5] and KAWAMURA and KONISHI[6] suggest that the intercalated disc undergoes morphologic alterations in certain physiologic and pathologic conditions. There is some evidence of a direct causal relationship between alcohol consumption and heart disease in man[7]. This study reports the ultrastructural changes of the intercalated disc in the myocardium of mice following prolonged ethanol ingestion.

Hearts of 20 HaM/ICR mice (3 weeks old) that drank water containing 15% ethanol by volume for a period of 3 months were studied. The mice were allowed access to ethanol-free water for a period of 10 min on each alternate day. They were fed on balanced commercial Purina Chow ad libitum. Ten animals from the same stock were kept as controls and given no ethanol. At the end of 3 months the mice were killed by spinal dislocation. Daily alcohol consumption at the time of sacrifice was approximately 5.2 ml/100 g body weight.

Small pieces of left ventricular myocardium were fixed in 3% phosphate buffered glutaraldehyde for 2 h followed by 1% osmium tetroxide for 75 min. Tissues were embedded in Maraglas. Thin sections were cut with an LKB 'Ultrotome' microtome and stained with uranyl acetate and lead citrate. A Siemens 'Elmiskop I' electron microscope was used for observations.

The fine structure of the intercalated disc in control mice was similar to that described by FAWCETT[1]. The disc is structurally differentiated into 4 types of regions without any particular sequential order of location. These regions are designated as (1) macula adherens or desmosome, (2) macula occludens or nexus, (3) fascia adherens or area of myofibrillar insertion and (4) nonspecialized region or intercellular gap region (Figure 1).

In the alcoholic mice the intercellular space in the fascia adherens region was strikingly widened (Figure 2). In the control animals the maximal width of the intercellular space in this region was approximately 250 Å, whereas in the experimental mice the maximal width increased to about 0.3 μ. No significant alterations were observed in other regions of the intercalated disc. Widening of the intercellular space does not seem to be a result of preparatory procedures as the control tissues

[1] D. W. FAWCETT, *An Atlas of Fine Structure. The Cell* (W. B. Saunders Co., Philadelphia 1966).
[2] J. W. WOODBURY, *Handbook of Physiology, Circulation* (American Physiological Society, Baltimore 1962), vol. 1, sec. 2, p. 237.
[3] L. BARR, M. M. DEWEY and W. BERGER, J. gen. Physiol. *48*, 797 (1965).
[4] S. WEIDMANN, J. Physiol. *187*, 323 (1966).
[5] R. S. SOHAL, S. C. SUN, H. L. COLCOLOUGH and G. E. BURCH, Lab. Invest. *18*, 49 (1968).
[6] K. KAWAMURA and T. KONISHI, Jap. Circul. J. *31*, 1533 (1967).
[7] C. S. ALEXANDER, Ann. intern. Med. *67*, 670 (1967).

similarly and simultaneously prepared did not display such changes.

In vitro studies of the heart muscle indicate that high concentrations of alcohol have a direct toxic effect on the membrane potential and the contractile system[8,9]. Loss of enzymes and electrolytes[10,11] from the myocardium of chronic alcoholic patients suggests that ethanol affects the permeability and metabolic pathways of the myocytes. It is thus possible that the structural changes of the intercalated disc are secondary to the metabolic changes induced by chronic ethanol consumption.

The pathogenesis or the effects of the alterations of intercalated disc on myocardial function is unknown. However, in some cardiomyopathic states of man[6] and in chronically exercised rats[5] the nonspecialized region of the intercalated disc was found to be swollen. Macula occludens or nexus has been considered as the region of lowest electrical resistance allowing electrotonic coupling between the myocardial cells[3]. What effect the changes of the intercellular space in adjacent portions of the intercalated disc have on the electrophysiological properties of macula occludens is not known. In any event, it is possible that degenerative changes in the structure of intercalated disc may affect the normal spread of excitation impulse in the heart. Interestingly, a variety of electrocardiographic alterations in association with alcoholic heart disease of man has been reported[12,13].

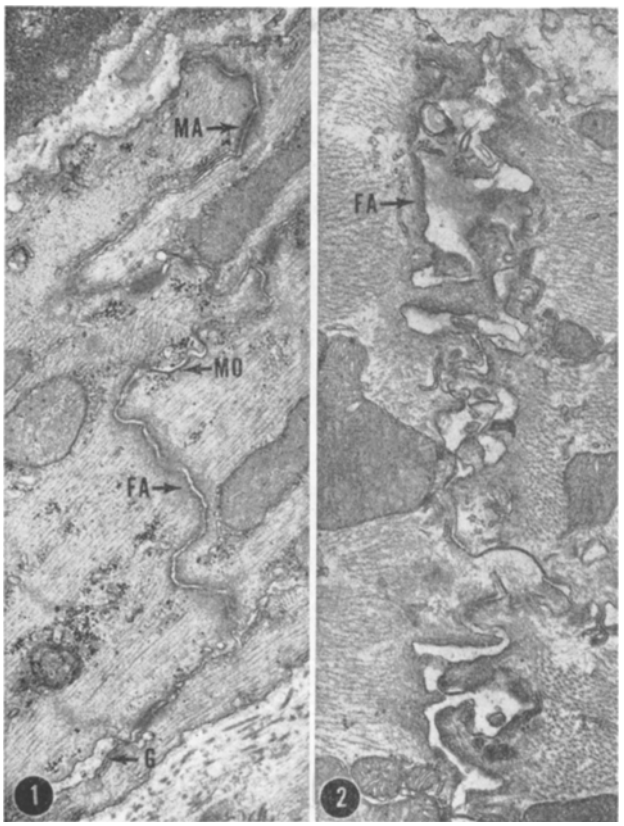

Fig. 1. Intercalated disc from the myocardium of a control mouse showing the 4 types of intercellular contact: macula adherens (MA); macula occludens (MO); fascia adherens (FA); and nonspecialized region (G). × 34,000.

Fig. 2. Intercalated disc of the myocardium of a mouse on ethanol ingestion. Note the vesiculation of fascia adherens (FA). × 23,400.

Résumé. L'examen au microscope électronique du disque intercalaire dans le tissu cardiaque de la souris, après administration orale d'alcool éthylique, ont révélé une augmentation de la distance intercellulaire. Le couplage électrotonique entre les cellules du myocarde est assuré par le disque intercalé. Par conséquent, des changements dégénératifs survenus dans le disque intercalaire diminuent la propagation de l'impulsion excitatrice dans le tissu cardiaque.

R. S. Sohal and G. E. Burch

Department of Medicine
of the Tulane University School of Medicine,
and Charity Hospital of Louisiana, New Orleans
(Louisiana 70112, USA), 2 December 1968.

[8] A. L. Gimeno, M. F. Gimeno and J. L. Webb, Am. J. Physiol. *203*, 194 (1962).
[9] H. W. Haggard, L. A. Greenberg, L. H. Cohen and N. Rakieten, J. Pharmac. exp. Ther. *71*, 358 (1941).
[10] V. E. Wendt, C. Wu, R. Balcon, G. Doty and R. Bing, Am. J. Cardiol. *15*, 175 (1965).
[11] V. E. Wendt, R. Ajluni, T. A. Bruce, A. S. Prasad and R. J. Bing, Am. J. Cardiol. *17*, 804 (1966).
[12] W. Evans, Am. Heart J. *61*, 556 (1961).
[13] This work was supported by grants No. HE0-6769 from the National Heart Institutes of the U.S. Public Health Service, the Rudolph Matas Memorial Fund for the Kate Prewitt Hess Laboratory and the Rowell A. Billups Fund for Research in Heart Disease.

The Effect of Various Beta-Receptor Blocking Agents on Platelet Aggregation

In 1960 Hellem found that a protein-free, heat-stable, dialysable extract of red cells could produce marked platelet aggregation in vitro[1]. This extract, or 'factor R' as Hellem called it, was subsequently identified as adenosine diphosphate (ADP) by Garder et al.[2].

ADP was found to be the most active of a number of nucleotides, lipids, catecholamines and other substances tested for their aggregating activity[3,4].

In recent years an increasing number of substances has been found – besides those with aggregating properties – that inhibit platelet aggregation in vitro. Among these substances the β-receptor blockers seem to be of particular interest, as they are used increasingly in the treatment of heart diseases.

In the following we have explored the inhibitory action of four β-receptor blockers on adenosine-diphosphate induced platelet aggregation.

Method. Blood was obtained from healthy volunteers in fasting condition by punction of an antecubital vein and collected in siliconized (silicone oil: AK 350) glass tubes. Nine parts of blood were added to one part of 3.8% trisodium citrate as anti-coagulant. Platelet-rich