40 Action of Leptodactyline on the Isolated Vagus-Auricle Preparation of the Guinea Pig. A. N. Corbascio and K. Greeff (U.S.A. and Germany).

Leptodactyline (*m*-hydroxyphenethyl) trimethyl ammonium, is a naturally occurring quaternary ammonium base recently isolated from Leptodactylus by Erspamer. Since he has shown it to possess marked nicotinic actions and neuromuscular blocking properties, its effects were studied on the isolated vagus-auricle preparation of the guinea pig and in the rat phrenic-diaphragm preparation. The findings were as follows: (1) Leptodactyline at concentrations of 1–10 μg/ml induces a marked negative inotropic effect on the contractions of the isolated guinea-pig auricle, suspended in Tyrode solution at 28°C. (2) This response is abolished by atropine (0·1 μg/ml). After atropinization, larger doses of leptodactyline (10–25 μg/ml) induced a 50 to 75 per cent increase in amplitude and a 10 per cent increase in the rate of contraction of the auricular muscle. This response was blocked by large doses of hexamethonium (100–200 μg/ml). (3) The threshold to vagal stimulation of the auricle was not appreciably changed by the presence of leptodactyline in the bath (1–50 μg/ml). (4) Total neuromuscular blockade was observed on the isolated phrenic-diaphragm preparation of the rat only after very large doses of leptodactyline (50–500 μg/ml). It therefore appears, under these circumstances, that the nicotinic effects of leptodactyline are more readily elicited than its neuromuscular blocking actions.

41a Uber die Foerderung der Energiegewinnung am erschoepften Herzmuskel durch ein Pyrimidinderivat. W. Kunz und M. Siess (Germany).

Strophanthin führt am überlasteten Herzvorhof des Meerschweinchens nach positiv inotroper Wirkung zu diastolischem Erschöpfungsstillstand, der mit einem Schwund der energiereichen Phosphate um etwa 30 Prozent verbunden ist. Dabei findet eine Na^+-Aufnahme und eine K^+-Abgabe in der Muskelfaser statt. Eine erneute Ansprechbarkeit auf positiv inotrop wirkende Stoffe wie Adrenalin oder Strophanthin findet sich erst nach einer Erholungszeit von etwa einer Stunde, in der das $\sim PO_4$ wieder aufgebaut und die Na^+- K^+-Verhältnisse wieder normalisiert werden. Diese Erholungszeit wird durch 2:6-Bis (diäthanolamino)-4:8-dipiperidino-pyrimido-5:4-D-pyrimidin (Persantin, Thomae) (P.) um etwa 75 prozent verkürzt unter Beschleunigung der Resynthese der $\sim PO_4$. P. verlängert die positiv inotrope Wirkung von Strophanthin am überlasteten Vorhof.

Auch der durch Anaerobiose hervorgerufene Energiemangelstillstand wird durch P. unter Restitution des $\sim PO_4$ aufgehoben. Adrenalin und Strophanthin wirken im Gegensatz zu reiner Anoxie bei P.-Anwesenheit sogar noch positiv inotrop.

Die biochemische Untersuchung ergab, dass eine Anreicherung von DPNH, welche durch Anaerobiose und gleichzeitige Ausschaltung der wasserstoffverbrauchenden Brenztraubensäurehydrierung mittels NaF erzeugt wurde, durch P beseitigt wird. Die Analyse mit ^{14}C markierter Glucose (C_1 oder C_6) ergibt eine Beschleunigung der C_6-Dekarboxylierung bei unveränderter Geschwindigkeit des Glukose-6-Phosphatshunts. In Verbindung mit Metabolitanalysen und Untersuchungen der Atmung und Glykolyse ergibt sich der Schluss, dass die Übertragung des aus dem Tricarbonsäurecyclus stammenden Wasserstoffs durch P als Wasserstoffakzeptor unter Energiegewinnung katalysiert wird.

41b Energy Gains by the Exhausted Heart Muscle with the Aid of a Pyrimidine Derivative. W. Kunz and M. Siess (Germany)

Strophanthin causes diastolic exhaustion-arrest of the overloaded guinea-pig atrium following a positive inotropic effect; this is due to the loss of approx. 30 per cent of the energy-rich phosphates. There is an uptake of Na^+ and a loss of K^+ by the muscle fibres. Renewed reactivity to positively inotropic substances such as adrenalin or Strophanthin only occurs after a recovery period of approximately 1 hour during which the $\sim PO_4$ is again built up and the Na^+ and K^+ relationship has returned to normal. This recovery period is shortened by about 75 per cent by 2:6-bis (diethanol amino)-4:8-dipiperidino-pyrimido-5:4-D-pyrimidin (Persantin, Thomae) (P) with acceleration of $\sim PO_4$ resynthesis. P prolongs the positively inotropic effect of Strophanthin on the overloaded atrium.

Arrest, due to lack of energy caused by anaerobiosis is also abolished by P, through the restitution of $\sim PO_4$. Adrenalin and Strophanthin, in contrast with pure anoxia, have an even positive inotropic effect in the presence of P. The biochemical investigation showed that the accumulation of DPNH, which was caused by anaerobiosis and the simultaneous inhibition of the hydrogen-accepting pyruvic acid by means of NaF, was eliminated by P. Analysis by means of ^{14}C, labelled glucose (C_1 or C_6) results in acceleration of C_6-decarboxylation without change in the rate of the glucose-6-phosphate transfer. The conclusion reached, after combined analysis of metabolites and investigation of respiration and glycolysis, was that the transfer of hydrogen derived from the tricarboxylic acid cycle is catalysed by means of P which acts as a hydrogen-acceptor with a gain of energy.

42 Mechanism of Action of Histamine on the Heart. M. F. Murnaghan (Canada).

Isolated guinea-pig auricles were accelerated with a continuous infusion of histamine and the amount of veratramine require to cause a 50 per cent inhibition of acceleration, i.e. I_{50} dose, deter-

mined. As the minimal rate to which the auricles could be brought with veratramine was less than the initial rate, the I_{50} dose could assume two values depending upon whether the initial or minimal rate was used in calculating acceleration and its percentage inhibition. The terms "corrected" and "uncorrected" refer to the use of the minimal and initial rates respectively in the calculation. The I_{50} dose against histamine was 0·33 μM/l. "uncorrected" or 1·23 μM/l. "corrected". Reiter[1] accelerated isolated guinea-pig auricles with a continuous infusion of adrenaline and obtained an I_{50} value of 0·04 μM/l. "uncorrected" or 0·15 μM/l. "corrected" (the latter value calculated by this author). Evidently, veratramine is approximately 18 times more potent as an anti-accelerator agent against adrenaline than against histamine.

Innes *et al.*[2] have suggested that veratramine exerts two distinct effects, the one that of competitive antagonism towards the accelerator effect of sympathomimetic amines, the other being an independent less sensitive negative chronotropic action. This latter action probably accounts for its antagonism towards the cardio-accelerator effect of histamine.

The results indicate that the chronotropic effect of histamine is due to a direct effect on the sino-auricular node and is not due to catecholamines liberated by the histamine from a storage site in in the heart. Mannaioni[3] has recently reached a similar conclusion from a study of the effect of histamine on auricles treated with reserpine and dichloro*iso*proterenol.

1. Reiter, M. (1956), *Arch. exp. Path. Pharma.*, **229,** 233.
2. Innes, I. R. and Krayer, O. (1958), *J. Pharmacol.*, **124,** 245.
3. Mannaioni, P. F. (1960), *Brit. J. Pharmacol.*, **15,** 500.

43a Activite Pharmacodynamique des Aspartates sur le Coeur Isole. M. Lamarche et M. Tapin (France).

Nous avons étudié l'activité pharmacodynamique sur le coeur isolé des aspartates de magnesium et de potassium (composés racemiques) ainsi que des mélanges des deux. Les coeurs utilisés, prélevés rapidement après saignée de cobayes adultes, etaient maintenus en survie selon la technique de Langendorf et perfusés avec le liquide de Chenoweth et Koelle oxygéné.

Dans ces conditions experimentales, l'addition à une concentration de l'ordre de 10 pour cent au liquide de perfusion d'un des espartates utilisés entraine une nette augmentation de l'amplitude de la contraction du coeur isolé (20–30 pour cent), sans que le rythme cardiaque ne presente de variation notable, sauf pour les concentrations élevées du sel de potassium. Cette action se maintient pendant la durée de la perfusion avec le liquide contenant le produit, mais cesse aussitôt que celui-ci est remplacé par le liquide ordinaire, l'experience étant ainsi reproductible à volonté Enfin, il est à noter que cette action nette sur l'amplitude des contractions, sans modification du rythme ne s'accompagne d'aucune variation du débit du coeur isolé.

Nous avons ensuite recherché l'activité des aspartates sur le comportement du coeur lors d'une anoxie. Celle-ci était réalisée dans nos experiences par le remplacement de notre solution de perfusion oxygénée par une autre non aérée. Dans ces conditions, on observe une diminution progressive de l'amplitude des contractions, qui peut être reversible si l'experience n'est pas trop prolongée. Ces essais nous ont montré que la presence d'aspartate dans le liquide de perfusion retardait notablement l'apparition de ces manifestations d'anoxie cardiaque.

43b The Pharmacodynamic Activity of Aspartates on the Isolated Heart. M. Lamarche and M. Tapin (France).

The pharmacodynamic activity of magnesium and potassium aspartates (racemic compounds) as well as of a mixture of both was studied on the isolated heart. The hearts used were removed soon after adult guinea-pigs had been bled and were kept alive by the Langendorf technique and perfused with Chenoweth and Koelle's fluid which has been oxygenated.

Under these experimental conditions the addition of one of the aspartates added in a concentration of about 10 per cent to the perfusion liquid caused a definite increase in the amplitude of contraction of the isolated heart (20–30 per cent) without causing any marked variation in the cardiac rhythm: except with high concentrations of potassium. This effect continued during the time of perfusion with the fluid containing the substance but stopped as soon as it was replaced by ordinary fluid; the experiment could thus be repeated at will. Finally, it must be noted that this definite action on the amplitude of contractions, which did not affect the rhythm, was not accompanied by any variation in the output of the isolated heart.

Subsequently, the activity of aspartates on the behaviour of the heart during anoxia was studied by replacing an oxygenated perfusion fluid by another, non-aerated one. Under these conditions a progressive decrease of the amplitude of contraction was observed which was reversible if the experiment was not too prolonged. These trials have shown that the presence of aspartate in the perfusion fluid markedly delayed the appearance of anoxic cardiac manifestations.

44 The Relationship between Potassium and the Action of Digoxin in the Guinea Pig. G. A. Stewart (United Kingdom).

Slow intravenous infusion of non-toxic doses of