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

digoxin into guinea pigs increases the K content of the ventricles and serum. Toxic doses produce a further rise in serum K whereas the amount of K in the ventricles does not differ significantly from that of untreated animals.

Intravenous infusion into guinea pigs of KCl solution (8·4–134 mM) simultaneously with digoxin (56 μg/ml) fails to influence the lethal dose of digoxin, but with 268 mM solution of the salt the lethal dose of digoxin is decreased ten-fold.

The time of onset of the positive inotropic response of the isolated right ventricle of the guinea pig, stimulated electrically, to a toxic dose of digoxin is not influenced when the KCl concentration of the bathing fluid is raised from 5·6 to 13·5 mM.

The rate of increase of the amplitude of contraction is markedly reduced but the maximum attained is unaltered and the life of the ventricle is greatly prolonged.

The duration of the therapeutic action of digoxin in the failing heart-lung preparation of the guinea pig is increased if the K content of the circulating fluid is increased from 5·6 to 6·1 mM, but considerably decreased when it is raised to 12·1 mM.

These data suggest that: (1) the extracardiac tissues are more sensitive than the myocardium to the action of digoxin on K flux. and (2) that K, depending on its concentration in the heart, can increase or decrease the cardiotoxicity of digoxin.

45 Pharmacology of Chlordiazepoxide (Librium) and Analogues. L. O. Randall and B. Kappell (U.S.A.).

Chlordiazepoxide (Librium) is the first member of a new chemical class of compounds which has shown unique taming effects in animals[1] and powerful anti-anxiety effects in human subjects.[2] Other pharmacological effects first observed in animals and later confirmed in human subjects include anticonvulsant activity and muscle relaxant effects at low doses, with sedative effects and appetite-stimulating effects at high doses. Certain pharmacological effects which were minimal in animal tests were also minimal in human subjects including effects on blood pressure, heart rate and autonomic nervous system.

Analogues of chlordiazepoxide (7-chloro-2-methylamino-5-phenyl-3H-1:4-benzodiazepine 4-oxide hydrochloride) showed a similar type of activity in muscle relaxant and anticonvulsant tests. Screening tests include the inclined screen test in mice, the fighting mouse test,[3] the anti-strychnine test and the gross behaviour test in cats. Benzodiazepines having activity of interest include 7-chloro-1-methyl-5-phenyl-3H-1:4-benzodiazepin-2(1H)-one; 7-chloro-2-oxo-5-phenyl-1:2-dihydro-3H-1:4-benzodiazepine 4-oxide; 5-phenyl-7-trifluoro-methyl-3H-1:4-benzodiazepin-2(1H)-one; 7-chloro-2-oxo-5-phenyl-1:2-dihydro-3H-1:4-benzodiazepine; 7-chloro-5-(2-chlorophenyl)-3H-1:4-benzodiazepin-2(1H)-one and 7-nitro-5-phenyl-3H-1:4-benzodiazepin-2(1H)-one.

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2. Tobin, J. M. and Lewis, N. D. C. (1960), *J. Amer. med. Ass.*, **174,** 96.
3. Tedeschi, R. C., Tedeschi, D. H., Mucha, A., Cook, L., Mattis, P. A. and Fellows, C. J. (1958), *J. Pharmacol.*, **125,** 28.

46 The Effects of Ethanol and Chlordiazepoxide in Altering Autonomic Responses Evoked by Isocortical and Paleocortical Stimulation. M. N. Carroll, jr., E. C. Hoff, J. F. Kell, jr. and C. G. Suter (U.S.A.).

Unipolar stimulation of the anterior sigmoid gyrus (I), limbic lobe (II), hypothalamus (III), N. Von Bechterew (IV), amygdala (V), and central gray (VI) loci in flaxedilized cats evoked pressor responses, cardiac arrhythmias (nodal and ventricular extrasystoles and ventricular tachycardia with indications of coronary insufficiency), mydriasis and striking inhibition of mobility of the pyloric sphincter and ileum. Salivation was elicited from subcortical loci II, III, IV and VI, and retraction of the nictitating membrane was noted from I, III and VI. Lacrimation was not observed from any of the areas studied.

The intravenous administration of chlordiazepoxide (10–20 mg/kg) elicited a transient hypotention and slight bradycardia whereas 10 per cent ethanol (3 ml/kg, i.v.) produced increased pyloric mobility and slight to marked alterations in the electrocardiogram. Chlordiazepoxide greatly attenuated pressor responses from all brain areas studied whereas ethanol exerted weak anti-pressor effects in areas I, II and strong blocking action against central stimulation of III. Centrally-induced cardiac arrhythmias were completely blocked by chlordiazepoxide in loci II and V whereas ethanol partially attenuated the response only from II. Neither compound showed any activity against centrally evoked salivation, mydriasis or gastrointestinal inhibition.

Inasmuch as chlordiazepoxide lacks the undesirable side effects of ethanol, its prophylactic potential against centrally-induced arrhythmias and pressor responses merits intensive investigation.

47 Effects of Chlordiazapoxide (Librium) and Other Psychopharmacological Agents on "Fixated" Behaviour in Rats. W. T. Liberson, A. Kafka and E. Schwartz (U.S.A.).

Effects of various therapies were investigated on fixation rats[1] with regard to: (1) motor coordination; (2) sensory and symbolic discrimination and speed of their acquisition; (3) reaction times to stimuli during approach, avoidance or escape behaviour; (4) variability of behaviour; (5) compulsive rigidity; and (6) variety of patterns