Nous avons trouvé des taux parfois légèrement inférieurs, parfois légèment supérieurs. C'est ainsi que chez les femelles normales la plus grande quantité de nor-adrénaline observée a été de 0·23 μg/g, la plus faible étant de 0·18; chez les femelles injectées, le maximum est de 0·25 et le minimum de 0·16. La moyenne des différentes valeurs obtenues est de 0·22 μg/g chez les rats normaux et de 0·20 μg/g chez les animaux soumis à l'action de l'I.D.P.N.

Une deuxième série d'expériences a été entreprise sur la souris. Comme chez le rat, nous n'avons observé que de faibles variations—augmentation ou baisse—de la teneur en nor-adrénaline du tissu cérébral de la souris tournante.

Les résultats que nous avons obtenus montrent donc que la nor-adrénaline du tissu cérébral ne subit pas de variations importantes lorsque le syndrome excito-moteur se constitue.

32b Nor-Adrenalin Content of the Cerebral Tissue of Animals under the Influence of Aminodipropionitril. M. Beauvallet and J. Fugazza.

In 1952 Delay *et al.* found that aminodipropionitril;$HN = (CH_2\text{-}CH_2\text{-}CN)_2$ (IDPN) causes permanent motor agitation in the mouse; the animal shows generalized activity and a strong tendency to turn in circles.

Rats, submitted to injections of this substance react in a similar way; they show disturbances of motor co-ordination and loss of equilibrium.

In the present investigation we studied the nor-adrenalin content of the brain tissues of rats and mice before and after the injection of I.D.P.N.

The first experiments were performed on rats of the Wistar strain, weighing 60–100 g; 3 groups of 6 females and 1 group of 6 males received 2 intraperitoneal injections of I.D.P.N. at intervals of 48 hr.

The cerebral tissue was removed as soon as the motor-excitation syndrome appeared. At the same time the brain of a normal animal of the same litter, sex and weight was removed.

The results obtained by us show that the nor-adrenalin level in the cerebral tissue of the male or female rat, subjected to the action of I.D.P.N., is similar to that of normal animals. The values obtained were either slightly lower or slightly higher. Thus, the largest amount of nor-adrenalin found in normal females was 0·23 μg/g, the lowest was 0·18; in injected females the maximum was 0·25 and the minimum 0·16. The mean of the different values obtained in normal rats was 0·22 μg/g and in animals which had been given I.D.P.N. it was 0·20 μg/g.

A second series of experiments was carried out with mice. As in rats, only slight variations (increases or decreases) in the nor-adrenalin content of the brain tissues of revolving mice was found.

The results obtained by us show that nor-adrenalin in the cerebral tissues does not undergo any important variations while the motor-excitation syndrome develops.

33 The Effect of Eserine on the Activity of Adrenergic Nerves in the Rat. V. Varagić, R. Lešić, J. Vuco and B. Stamenović (Yugoslavia).

It has been repeatedly found that eserine raises the blood pressure of the rat anaesthetized by urethane (Varagić, 1955; Dirnhuber and Collumbine, 1955; Hornykiewicz and Kobinger, 1956) as well as of the conscious rat (Medaković and Varagić, 1957). Several factors influencing this effect of eserine have been studied. Pretreatment with reserpine regularly abolished the hypertensive response to eserine. The slow intravenous infusion of noradrenaline, L-DOPA and 5-hydroxytryptamine restored the hypertensive effect of eserine only occasionally. Bretylium and choline 2:6-xylyl ether bromide significantly depressed or abolished the hypertensive effect of eserine. Cocaine was found to antagonize the action of bretylium. In doses which depressed the action of eserine bretylium did not inhibit the hypertension due to excitation of medullary centres induced by clamping the common carotid arteries. Pretreatment with *iso*propylisonizid did not antagonize the inhibitory action of reserpine on the hypertensive response to eserine.

Similar results were obtained by recording the electrical activity in the sympathetic fibres in the mid-cervical region. It is concluded that the available evidence indicates that the hypertensive effect of eserine in the rat is due to central activation of adrenergic nervous elements. Liberation of noradrenaline (and adrenaline) from the adrenals and from the blood vessels by eserine does not play a significant role in causing the hypertensive effect of eserine.

34 The Relation between Structure and Central Nervous Action of some Hydrazine Derivatives. A. Spinks and E. H. P. Young (United Kingdom).

About 300 derivatives of hydrazine have been prepared and examined by several biological tests for activity on the central nervous system and particularly for their ability to cause hyperactivity in mice subsequently injected with reserpine. The compounds tested included both straight and branched chain aralkylhydrazines and their acyl derivatives, bis-aralkylhydrazines and aryloxyalkyhlhydrazines. The effect of these structural changes, and especially of nuclear substitution, on biological activity has been studied and some relationships have been observed.

It was found that the most promising compound in respect of activity and low toxicity was α-methylbenzylhydrazine (α-phenylethylhydrazine). Nuclear substitution in this and other classes usually reduced activity, and 3:4-dichloro-substitution of many

N_1-aralkyl-N_2-acyl hydrazines caused the appearance of powerful sedative, instead of anti-depressant activity.

35 Mode of Action of Antifibrillatory Drugs. E. M. VAUGHAN WILLIAMS and L. SZEKERES (United Kingdom).

Investigators still disagree how antifibrillatory drugs act. The problem is how they prolong the effective refractory period (minimum interval between stimuli for propagation of second action-potential) although they do not affect the absolute refractory period. Some still believe increased duration of action potentials responsible, others that antifibrillatory drugs slow down the recovery of mechanism by which depolarization is achieved.

To test these two hypotheses, measurements were made, on the same preparations of isolated rabbit atria, of: (a) highest frequency stimuli could be followed; (b) threshold current for producing fibrillatory responses; (c) conduction velocity; (d) contractions; and (e) intracellular potentials, during exposure to drugs of dissimiliar structure, quinidine, procaine, procaine-amide, papaverine and dibenamine, from $5 \cdot 10^{-6}$–3×10^{-5}.

All drugs reduced maximum driving frequency and increased fibrillation threshold, dose–response curves being parallel. All reduced conduction velocity, but hardly affected contractions at the concentrations used. The time taken for repolarization to half the full resting potential was unchanged, a fact consistent with absence of change in absolute refractory period. The time for complete repolarization was either unchanged, or slightly prolonged at high doses to an extent insufficient to account for the great prolongation of effective refractory period. The resting potential was unchanged.

In contrast, the rate of rise of the action potential was greatly reduced by all drugs, implying that the property held in common was interference with the phase of depolarization. Such interference would necessitate a longer recovery period before the depolarization mechanism could be reactivated, and so would prolong the effective refractory period.

36 Competition between β-Haloalkylamines and Norepinephrine for Sites in Cardiac Muscle. R. F. FURCHGOTT and S. J. KIRPEKAR (U.S.A.).

Four β-haloalkylamines, *N*-α-napthylmethyl-*N*-ethyl-β-bromoethylamine (SY28), *N*-cyclohexylmethyl-*N*-ethyl-β-chloroethylamine (GD31), phenoxybenzamine (PB), and Dibenamine (DB), have been studied on isolated, left atria of guinea pigs. These agents do not antagonize the cardiac stimulating effects of catecholamines, and therefore it is concluded that they do not react with cardiac β-receptors. However, they do produce certain effects, which are listed below along with postulated mechanisms of action: (1) Prolonged positive inotropic effect and depletion of endogenous norepinephrine (NE) in normal atria. Mechanism: reaction with storage and binding sites for NE. Potency: SY28 > GD131 > PB > DB; (2) Transient positive inotropic effect on atria from reserpinized animals after "repletion" of such atria with NE, followed by irreversible blockade against further "repletion". Mechanism: reaction with binding sites for NE, probably on nerve terminals. Potency: SY28 > GD131 > PB > DB; (3) Marked irreversible potentiation of inotropic effect of added NE. Mechanism: reaction with sites with which NE combines in the process of its active removal or inactivation. Potency: PB > DB > GD131 > SY28.

All of these agents irreversibly block adrenergic α- (excitatory) receptors of smooth muscle (potency: SY28 > PB > DB > GD131). The sites with which they irreversibly compete with NE in heart may have some reactive grouping in common with smooth muscle α-receptor sites. However, the varying orders of potency associated with the different activities may indicate fundamental differences in the nature of the sites under consideration.

(Supported by U.S.P.H.A. Grant H-5237.)

37 Theophylline Structure as Related to Cardiac Inotropic Activity. H. F. HARDMAN (U.S.A.).

The relationship between changes in chemical structure and pharmacological activity is complex. Albert[1] emphasized the importance of drug ionization as a factor to be considered in such relationships.

The methylated xanthines such as theophylline and caffeine have measurable positive inotropic activity on cardiac tissue of several animal species. In the pH range of 6·5–8·5 theophylline ionizes as an anion (p*K*a 8·6) whereas caffeine lacks an ionizable hydrogen and cannot exist in the anionic state. Both drugs exist primarily in the non-ionized state at pH 7·4 suggesting that their cardiac inotropic action may be related to this physical form of the drugs. Halogen substituted derivatives of theophylline which exist primarily in the anionic state at pH 7·4 lack positive inotropic activity.

The isolated perfused turtle heart (*Chrysemys picta*) was employed to evaluate the effect of drug ionization upon cardiac inotropic activity in a series of methylated xanthines having different ionization characteristics. This preparation was chosen because pH per se over the range of 6·5–8·5 does not affect the rate or amplitude of contraction of the preparation. This situation allows one to examine the relative effect of the ionized and nonionized form of the drug.

The conclusion reached was that cardiac positive inotropic activity in the methylated xanthines was directly related to the concentration of nonionized drug presented to the turtle heart. Confirmatory evidence was obtained in mammalian cardiac tissue within a more restricted pH range.

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1. ALBERT A. (1954), *Pharm. Rev.*