early as 15 min after intraperitoneal injection, more than 90% of the activity in the serum was found to be present as free MTX except in the case of the diethyl ester, for which hydrolysis was 81% complete at this time. At the later times, more than 99% of the serum MTX activity was present as the non-esterified parent compound.

Discussion. These studies indicate that while di-*n*-alkyl esters of MTX exhibit significant antitumor activity in the mouse, this activity is due to rapid hydrolysis to the parent drug. A similar conclusion was reached by EISENFELD et al.[5] in studies with the dimethyl ester of MTX. Extension of these studies to other mammalian species would however be of interest: comparative studies have indicated that plasma esterase levels in the mouse are significantly higher than in larger species such as monkey, dog, and man[6], and the possibility therefore exists that in the latter species the esters would persist for a sufficient length of time to reach tumor sites inaccessible to the lipid-insoluble parent drug. Replacement of the ester groups of the present series with chemical structures having equivalent lipid solubility, but resistant to biological hydrolysis, would also appear to offer promise[7].

Résumé. L'action biologique de 6 esters liposolubles di-*n*-alkyle de la méthotrexate (MTX) a été comparée à celle du composé non estérifié. En tant qu'inhibiteurs de la réductase dihydrofolate de cellules leucémiques L1210 de la souris, les esters ont été moins efficaces que la MTX. In vivo, les esters dialkyles ont eu une action égale à celle de la MTX, en prolongeant la survie des souris inoculées par l'injection de cellules leucémiques L1210. Puisque les esters sont rapidement hydrolysés in vivo on conclut que l'action antitumeur chez la souris est due à la libération de la MTX.

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The Effect of Quinidine *bis*-(7-Theophylline Acetate) on the Isolated Papillary Muscle of the Rabbit Heart

In the previous papers, a combination of diphenhydramine and theophylline (dimenhydrinate) was found to have a significant antiarrhythmic action[1,2] with none of the undesirable effects of diphenhydramine alone[3]. These observation caused the authors of the present comminication to investigate the properties of a chemical combination of theophylline and quinidine[4,5].

Methods. Quinidine *bis*-(7-theophylline acetate) (QTA) has been obtained by refluxing quinidine (0.01 *M*) and theophylline-7-acetic acid (0.02 *M*) in ethanol solution. After recrystallisation from ethanol, it melted at 201–203 °C, lit. m.p. being 203–207 °C[6].

The experiments were performed on the papillary muscles isolated from the right ventricle of the rabbit heart, perfused with oxygenated warm (35 °C) Tyrode's solution. The preparations were driven with rectangular, double-threshold pulses at a rate of 1 Hz. The electrical activity was recorded by means of intracellular microelectrodes, and the contractions of the preparations with a transducer RCA 5734. The recordings were taken before and 10–15 min after administration of QTA in a concentration of 5 mg $\times 1^{-1}$.

Results and discussion. The results are shown in the Table and the Figure. As results from Table and Figure, QTA practically does not affect either the amplitude of the resting and action potential or the rapid upstroke in the ventricular fibres. Thus, it cannot cause any significant change in the velocity of the impulses propagation. On the contrary, quinidine alone markedly slows down both the rapid upstroke and the velocity of propagation[7–9]. Prolongation of the refractory period after

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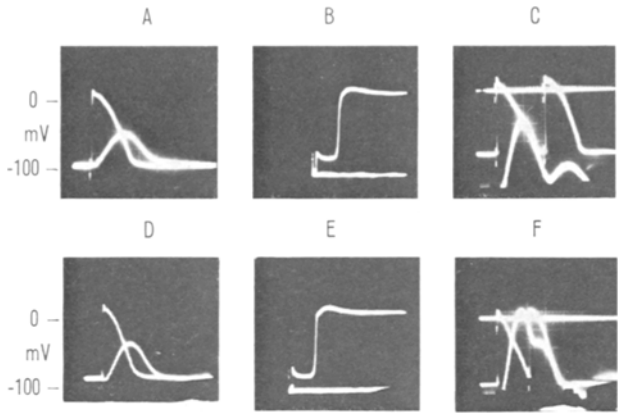
Investigated parameters in control conditions and after QTA administration

	Resting potential	Action potential			Effective	Mechanograms	
	(mV)	Amplitude (mV)	Duration of phase 0 (msec)	Duration of AP (msec)	refractory period period (msec)	Amplitude (%)	Duration (msec)
Control	87 ± 6.3	123 ± 8.5	1.9 ± 0.08	220 ± 16.7	170 ± 12.5	100	300 ± 10.6
QTA (5 mg/l	90 ± 4.1	121 ± 5.5	1.9 ± 0.1	310 ± 21.2	280 ± 17.2	98 ± 11.8	380 ± 15.5



Effect of QTA on the rabbit papillary muscle. Lower row, control records; upper row, 10 min after QTA administration. A, D, action potential and mechanogram; B and E, rapid upstroke of the action potential; C and F, effective refractory period. Time calibration: A, C, D, F: 500 msec; B, E: 10 msec.

quinidine[9,10] and QTA administration is similar. Furthermore, QTA has practically no negative inotropic effect, while quinidine alone causes a significant decrease of the contractility.

Theoretical explanation of the action of QTA is at present impossible, because the essential mechanisms of quinidine action are so far unknown. Theophylline has been found to increase the cellular level of the cyclic-AMP as a result of the inhibition of phophodiesterase activity[6]. It is possible that the action of QTA is due to the interference with the properties of quinidine and cyclic-AMP.

Regardless of the theoretical considerations, it seems important that chemical combinations of some antiarrhythmic drugs with theophylline have better properties than those substances by themselves. Evaluation of the action of some other combinations of the antiarrhythmic drugs with theophylline or other inhibitors of phosphodiesterase may be useful.

Zusammenfassung. Untersuchungen über die Aktion des Chinidin *bis*-(7-theophyllin acetat) auf den isolierten Pappilarmuskel beweisen, dass die Substanz die Verlängerung der Repolarisation, der Refraktärphase, als auch der Kontraktionsdauer bewirkt. Amplitude des Ruhe- und Aktionspotentials, Verlauf der Depolarization und die Kontraktionskraft bleiben praktisch unbeeinflusst.

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Interaction of Cocaine and Iproniazid on the H^3-Norepinephrine Uptake Mechanism on Isolated Strip Ventricle of Frog Heart

The catecholamines uptake mechanism by sympathetic nerves of isolated frog ventricle differs in some aspects with the catecholamines uptake mechanism by adrenergic nerves of isolated atrium of guinea-pig[1,2]. In a previous paper[3] we have reported that the potentiation by cocaine of the inotropic response to epinephrine and norepinephrine on isolated frog ventricle was 2,5-fold, while on isolated guinea-pig left atrium it was 30-fold. This fact prompted us to think of a different ability of the blockade by cocaine of catecholamines uptake on the isolated frog ventricle with respect to the isolated atrium of the guinea-pig. In the present work we have studied the blockade by cocaine of the H^3-norepinephrine (H^3-NE) uptake on the isolated ventricle of the frog.

On the other hand, it is established that iproniazid (IPN) inhibits monoamineoxidase and avoids the intraneuronal deamination of catecholamines by these enzymes; so that the norepinephrine and epinephrine uptake and retention by isolated atrium of the guinea-pig is greatly increased[4,5]. In this paper the behavior of the IPN with relation to the H^3-NE uptake and retention by the isolated frog ventricle has also been studied.

Methods. Ventricles of frog (*Rana pipiens*) were prepared and mounted as previously described by FURCHGOTT et al.[6] for isolated atrium of guinea-pig. Ventricles were suspended in an organ bath containing 20 ml of regular Ringer solution of the following composition (expressed in m*M*): NaCl, 103.4; KCl, 1.013; $CaCl_2$, 0.9009; CO_3HNa, 1.851, containing 10^{-5} g/ml of ethylene diaminetetraacetic acid (EDTA). A mixture of 95% O_2 and 5% CO_2 was bubbled through the bathing solution. All preparations were electrically driven at a frequency of 30 beats min. Ventricles were attached to force-displacement transducer (Grass model FT 03), and mechanical activity was recorded by means of a Grass polygraph. Each ventricle was subjected to a resting tension of 1 g. Under their respective conditions, halves were then incubated with 5 ng/ml of D, L-H^3NE for 5 min, and then thoroughly washed. 4 additional washes were given over the subsequent 40 min period, at the end of which the halves were removed for analysis of radioactivity. All preparations were performed at room temperature.

The catecholamine extraction was performed according to the method of ANTON and SAYRE[7] and radioactivity was counted in a Nuclear Chicago Liquid Scintillation Spectrometer model 725. All samples were corrected for quenching with an automatic external reference standard. Under our working conditions, the radioactivity present

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