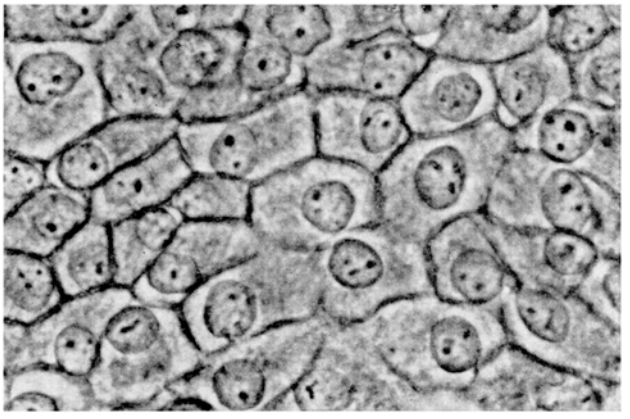

Cells from Ka Le strain magn. 450× fix. col. $AgNO_3$. Phase contrast.

Zusammenfassung. Die Isolierung einer Zell-Linie aus fötaler Kalbsleber wird beschrieben. Die Zellen wachsen in epithelialer Schicht und sind durch Kittsubstanz miteinander verklebt. Nach der fünfzigsten Passage scheinen noch immer spezifische Leberenzyme anwesend zu sein, so dass die Zell-Linie morphologisch und biochemisch als Leberepithel betrachtet werden kann.

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Physical Stress and Emetine Cardiotoxicity

In our previous papers we have reported the toxic patterns and the electrocardiographic changes observed in rabbits subjected to emetine acute intoxication[1], in guinea pigs subjected to emetine subacute intoxication[2], and in guinea pigs receiving courses of emetine chronic treatment similar to those used in human therapy[3]. A case of Wolff-Parkinson-White syndrome was observed in one guinea pig during such a course of treatment[4]. Degenerative and necrotic changes have been found in the myocardium of guinea pigs subjected to emetine subacute poisoning[5]. Emetine has shown inhibitory effects on the frog isolated heart[6], on the guinea pig isolated atria[7] and upon the respiration *in vitro* of guinea pig heart homogenates[8]. From these studies we have concluded that emetine is a drug with specific cardiotoxicity. This conclusion, beside having obvious repercussions in human therapy, provides also a useful basis for producing a pathological condition of the experimental animal heart which may be used in evaluating the cardiac effects of various drugs. So far we have studied the protective effect of fifteen drugs on the mortality, toxic patterns and EKG changes shown by guinea pigs during emetine subacute poisoning. Such an effect was not shown by methionine[2], γ-thyomethyl-α-hydroxybutyric acid[2], potassium chloride[9], diphosphopyridine-nucleotide[10–12], pyridoxine[13], inositol[13], adenosine-triphosphate[11,12], lipoid retina extract[6] or lipoid brain extract[6].

Protection was shown, however, by rybo-flavin-phosphate[11,12], pyridoxine-phosphate[11,12], cocarboxylase[11,12], lipoid diencephalon extract[6], lipoid heart extract[6] and embryonic heart extract[11,12], in increasing order of potency. The negative findings on the protective effect of methionine and γ-thyomethil-α-hydroxybutyric acid were confirmed by our histological studies[5]. Lipoid heart extract also showed its protective effect against emetine cardiotoxicity on the frog isolated heart[6], as did cocarboxylase on the guinea pig isolated atria[7] and embryonic heart extract on the respiration *in vitro* of guinea pig heart homogenates[8]. Emetine subacute poisoning may be useful also in the experimental study of the cardiac effects of various factors, such as physical and psychological stress. In the present paper we report the results of our research on the interactions between emetine cardiotoxicity and swimming exercise[14].

Three groups of guinea pigs were used. One group received 5 mg of emetine/kg/day, subcutaneously[2]. The second group was subjected to swimming exercise without emetine. The third group was subjected to swimming and emetine. In the second group the duration of the daily swimming sessions was 10 min on the first two days, 30 min from the third to the sixth day and 60 min from the seventh to the sixteenth day, as the animals' swimming ability increased. In the third group, from the eleventh day onwards the swimming sessions were followed by the daily injections of emetine (5 mg/kg/s.c., as in the first group). As a first consequence of emetine toxicity, the swimming ability decreased progressively in the third group. Guinea pigs swam in an ordinary bath tub. Water temperature was maintained constant at 30°C. The results are shown in Table I and II.

The combination of heart weight increase and EKG signs of Right Ventricular Strain with compensatory bradycardia, shown by the animals receiving swimming without emetine, is due to the cardiac hypertrophy already described in the rat subjected to swimming[15,16].

The typical effects of emetine subacute poisoning, such as loss of body weight, diarrhea, depression of spontaneous behaviour and EKG changes, appeared earlier and were more pronounced in the animals receiving swimming and emetine than in those receiving only emetine. The former survived a remarkably shorter time than the latter. Moreover, the third group showed EKG signs of coronary insufficiency.

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Tab. I

Experimental group	Animals no. used	Animals no. dead	Survival time in h (mean)	Heart weight (mean) mg	Heart weight (mean) mg/100 of body weight	EKG Sequential changes
1. Emetine	4	4	120	1200	240	Depressed or inverted T – Tachycardia – PR prolongation – QRS widening – Bradycardia – Blocks
2. Swimming	4	0	—	1550	323	Bradycardia – Right ventricular strain
3. Swimming + emetine	4	4	60[a]	1950	375	Coronary T – PR prolongation – QRS widening – Bradycardia – Blocks

[a] Test indicates that survival times of groups 1 and 3 differ significantly at 0.01 level.

Tab. II. Percentage of animals showing EKG changes

EKG changes	Treatment	Hours of emetine treatment 30	58	90	118
T	E	75	100	100	100
	E+S	100	100	D	D
ST	E	25	50	50	50
	E+S	75	75	D	D
T coronary	E	0	0	0	0
	E+S	75	75	D	D
Tachycardia	E	50	0	0	0
	E+S	0	0	D	D
Bradycardia	E	0	0	75	100
	E+S	75	100	D	D
PR prolongation	E	0	50	75	75
	E+S	100	100	D	D
QRS widening	E	0	25	50	75
	E+S	75	100	D	D
Blocks	E	0	0	0	75
	E+S	0	75	D	D
Deaths	E	0	0	25	100
	E+S	0	75	100	100

E = Emetine alone
E+S = Emetine and swimming

The T changes, sometimes accompanied by ST depression, are typical of subacute emetine poisoning, as we have observed them in more than 200 guinea pigs so treated in our previous research. They have been attributed to a generalized myocardial damage caused by emetine, which, in the terminal stages of treatment, spreads to the conduction tissue, determining the changes of intra- and atrioventricular conduction mentioned in Table I and II. In the present and previous research we never observed EKG signs of coronary insufficiency in guinea pigs receiving only emetine. This negative datum was observed not only in guinea pigs subjected to emetine subacute poisoning, but also in those subjected to emetine chronic treatment, in rabbits receiving emetine acute poisoning and recently in dogs[17] receiving intracoronary or intravenous injections of the drug, in which the coronary flow or the coronary debt was controlled together with the EKG and blood pressure. The EKG signs of coronary insufficiency, however, were evident in the group of animals subjected to swimming and emetine. This may be dependent upon the fact that the heart hypertrophy by exercise would require more nutrition of the myocardium not realizable because of myocardial damage caused by emetine. Finally, the increase of spontaneous behaviour depression by emetine, shown by the third group, confirms the myocardial origin of the emetine depression as we have suggested in other research[18], in which emetine did not show any effect on the conditioning, while the cardiac effects and the spontaneous behaviour depression were evident.

From the present studies we would conclude that: 1. swimming exercise causes very strong potentiation of emetine cardiotoxicity; 2. there are mutual interactions between EKG changes by emetine and EKG changes by swimming exercise; 3. swimming exercise evokes the appearance of coronary signs never observed with emetine alone; 4. the combination of swimming exercise and emetine subacute poisoning may form a basis for pharmacological production of experimental coronary insufficiency; 5. this combination may also serve as a model for the experimental study of the clinical problem of the interactions between physical stress and coronary disease.

Résumé. Nous rapportons ici des expériences sur le cobaye se rapportant à la toxicité de l'émétine pour le cœur, en particulier après potentialisations par de exercices de nage.

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Psychological Stress and Emetine Cardiotoxicity

The influence exerted by mental and especially emotional factors on the symptoms, course and prognosis of cardiac disease, is an observation as old as medicine. Very often, as also in our personal experience[1], emotional stress played the role of precipitating factor in the pathogenesis of the myocardium infarction and other cardiac diseases[1]. More recently, a direct role played by brain mechanisms in the origin of coronary disease was also suggested and supported by clinical and statistical evaluations[2]. Increase in

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