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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[17] A. BIANCHI and A. MARINO, to be published.
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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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serum cholesterol levels and decrease in serum phospholipid levels were recently reported in students under examination stress, in an attempt to study relationship between emotional stress, cholesterol-lipid-lipoprotein metabolism and coronary arteriosclerosis[3]. However, up till now, there has not been definitive experimental evidence of an association between cardiac disease and psychological factors. At present, there are two major experimental approaches to this problem. One approach is the study of the cardiovascular repercussions following ablation or stimulation of certain areas of the central nervous system, expecially of those which are supposed to have a role in the elaboration and regulation of emotions[4]. The second approach is the study of the cardiac reactions to experimental procedures, such as emotional stress, conditioning and conflict situations[5]. Since PAVLOV first demonstrated conditioned reflexes, cardiac and vascular conditioned responses have been investigated, particularly in the U. S. A.[5]. However, with both of these approaches, the peripheral responses to the neurological or psychological artificial conditions were elicited by a normal heart in basal condition or subjected to spontaneous physiological exertions. A third approach, in our view, may be attempted by producing a pathological condition of the heart and then evaluating the cardiac influences of psychological stress. In this way, the experimental approach may be closer to the clinical observation, which does admit a cardiac predisposition in the cases of psychogenic cardiac diseases, in order to explain the selective choice by the psychological factor of the heart as the organ involved. We have thought that emetine could be used in order to produce this predisposition in the experimental animal, since in our previous research[6] this drug has been shown to be a specific cardiotoxic agent. Emetine subacute poisoning has provided a useful method for producing a pathological condition of the heart of the guinea pig, which is similar to the interstitial myocarditis of human pathology and may be used in evaluating the cardiac effects of drugs and other factors[6]. Therefore, in the present research[7], the interactions between emetine cardiotoxicity and psychological stress have been investigated in the guinea pig.

Three groups of guinea pigs were used. *One group (controls) received only emetine.* The animals were given 5 mg of emetine hydrochloride/kg of body weight/day, subcutaneously, as described in our previous papers[6]. The treatment was continued until the death of the animals. *The second group was subjected to conditioning and emetine.* These animals were previously conditioned to an avoidance situation, according to the method described by MOWRER in the rat[8]. The unconditioned stimulus was a mild electroshock. The conditioned stimulus was a combination of a steady light and a noise. The animals were conditioned to avoid the shock by crossing a barrier from a lighted into a dark compartment of the experimental cage. They reached the maximum percentage of positive responses, i.e., Conditioned Avoidance (C.A.), between 7 and 11 training sessions, each session being comprised of 20 presentations of the conditioned stimulus. After this maximum had been maintained for more than three sequential sessions, the emetine treatment was begun and continued until the death of the animals, as described before, while the animals were regularly subjected to the daily training sessions. In our previous research emetine itself did not show any influence on the conditioning[6]. During the period in which the animals were subjected only to the conditioning, neither loss of body weight nor any adverse symptoms were observed. EKG records, performed 15 min after the training sessions, showed only a slight tachycardia. *The third group was subjected to conflict and emetine.* These animals were previously conditioned to the avoidance situation, as were the animals of the second group. They reached the maximum C.A. between 5 and 25 training sessions. After this maximum had been maintained for more than three consecutive sessions, the animals were forced into the conflict situation by alternating the training sessions with sessions in which the punishing stimulus was given even when the conditioned response was correctly performed. As a consequence of this procedure, a progressive reduction of C.A. resulted, together with typical symptoms of anxiety and tachycardia. No other significant EKG changes or reduction of body weight were observed during this period. When the

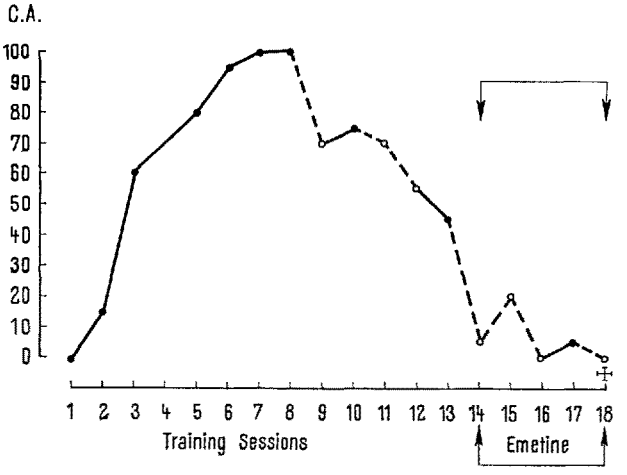

Fig. 1. Guinea pig, previously conditioned to the avoidance situation, then forced into the conflict situation and subjected to the emetine subacute poisoning. C.A. = Conditioned Avoidance or percentage of positive responses for each training session. The continuous lines indicate normal sessions, the broken lines the sessions in which the punishing stimulus was given even when the conditioned response was correctly performed.

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[6] For the references on our studies on *Emetine Cardiotoxicity*, see our previous paper on this Journal *17*, 116 (1961).

[7] This study was performed in the Lab. of Neuropharmacology, Dept. of Anatomy, University of California Medical Center at Los Angeles, during the period spent there by the author, on a Riker Fellowship, 1959–1960, through the International Union of Pharmacologists. The author wishes to thank the Department of Anatomy for the facilities generously provided, Dr. A. J. HANCE for his help and 'Horton & Converse, Los Angeles' for the Emetine used in this study. Part of the research was communicated to the Fall Meeting of the Amer. Soc. for Pharmacol. and exp. Therap., Seattle, Washington, Aug. 21–25 (1960).

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Experiment group	No. animals	Hours of emetine treatment and percentage of deaths 72 84 96 108 120 132 144 156 168 180 192	Survival time mean in h	σ_m	t	P	% change	Body weight % change at 5th day (mean)
E	11	0 0 9 9 27 36 63 63 72 72 100	144.6	± 9.4	—	—	—	−21.5
Condit. + E	6	0 0 0 33 66 66 66 66 66 100	131.0	± 12.9	0.6	0.05	− 9	−23.0
Conflict + E	9	0 11 11 88 88 100	102.2	± 3.1	3.74	< 0.01 > 0.001	−30	−26.0

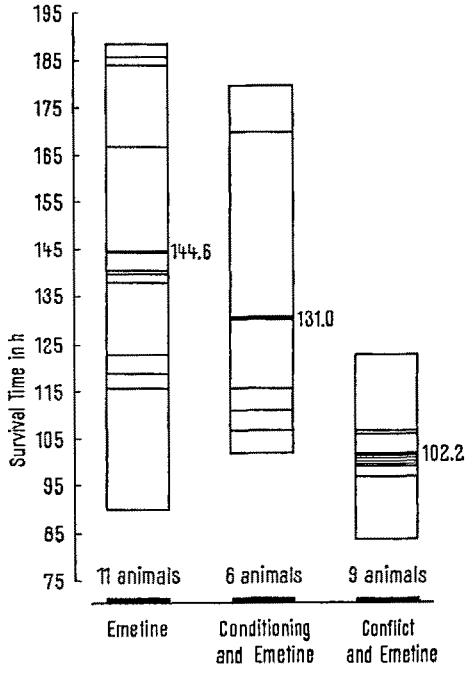

Fig. 2. Survival times in h after the beginning of emetine subacute poisoning. The heavy lines indicate the means of each group, the thin lines represent the individual values. Note the following: 1. the animals receiving emetine and conflict (third group) died remarkably earlier than the animals receiving emetine alone (first group) and those receiving emetine and conditioning (second group); 2. the maximum survival time in the third group is less than the means of the second and first one; 3. the survival times of the guinea pigs of the third group are closely concentrated around the mean, as compared to those of the other two groups, in which the individual values are more dispersed.

conflict had developed, the emetine treatment was begun and continued until the death of the animals, as described before. During the treatment, the animals were regularly subjected to the conflict sessions. In Figure 1 the behaviour of a typical animal of the third group is reported.

Comparisons of the survival times, percentage of deaths and body weight reduction in the three groups of animals are tabulated in Figure 2 and the Table.

The typical EKG changes associated with the emetine treatment, as described in our previous papers[6], appeared earlier and were more pronounced in the third group than in the second and in the first one. Also, from the comparison between the survival time after emetine and the conflict behaviour of each individual guinea pig of the third group, it would seem that there was a correlation between intensity of conflict and degree of mortality in the animals subjected to both conflict and emetine.

On the basis of these results, we would conclude that: 1. conditioning alone causes only a slight and non-significant potentiation of emetine cardiotoxicity; 2. conflict exerts an evident and significant potentiation of emetine cardiotoxicity; 3. since the conflict is a specific kind of psychological stress and, on the other hand, emetine has toxic effect specifically on the heart, the combination of psychological and pharmacological methods we have used in the present research, may form a basis for the experimental study of the association between psychological factors and cardiac disease.

While there is no question about the validity of these results, there is ambiguity about their cause. Thus, we do not know how the conflict potentiates the cardiotoxicity of emetine. It is supposed that emotions are able to cause changes in the visceral functions, as a result of their disturbing action on the autonomic or hormonal balance of the organism. In particular, a state of sympathicotonia and a release of hormones, such as adrenaline, cortisone or ACTH, have been suggested in the interpretation of these changes[2–5]. Therefore, the observed phenomenon could be connected with an interaction between the effect of these neurovegetative factors or hormones and the effect of emetine on the heart. In this way, it could be included in the patterns of the general adaptation syndrome according to SELYE[9], supposing conflict to play the role of the stressing factor and emetine that of the cardiac vector. Alternatively, the conflict may be supposed to activate the higher brain mechanisms suggested by ISCHLONDSKY[2] in the interpretation of the pathogenesis of some cardiac disease, in which case the brain mechanism could find an easy receptor in the heart damaged by emetine. These and other hypotheses are possible and further research is necessary to clarify the results reported above.

Riassunto. L'autore riporta i risultati di alcune ricerche sulle interferenze fra cardiotossicità dell'emetina, condizionamento e conflitto nella cavia. Il conditionamento esercita un lieve e non significativo potenziamento sulla cardiotossicità emetinica, mentre tale potenziamento è risultato evidente ed altamente significativo con il conflitto. I risultati vengono discussi e l'associazione di metodiche farmacologica e psicologica, usata nelle presenti ricerche, viene proposta come base di lavoro sperimentale per lo studio delle interferenze fra stress emotivi e cardiopatie.

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