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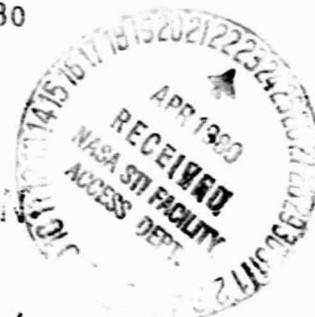
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EFFECT OF TRANQUILIZERS ON ANIMAL RESISTANCE TO  
THE ADEQUATE STIMULI OF THE VESTIBULAR APPARATUS

By

Ya. E. Maksimovich and N. V. Khinchikashvili\*

The sharp increase in migration of the population has entailed an improvement /606\*\*  
in the means of movement. Modern rapid transportation creates considerable  
rectilinear, radial and complex accelerations that are adequate stimuli of the  
vestibular apparatus. The vestibulosomatic and vestibulo-autonomic reactions that  
occur here are subjectively distressing and reduce the performance capacity of  
both the drivers and the passengers. This determines the urgency of a search  
for substances that alleviate the manifestations of these reactions. It is  
known that neuroleptics to a certain measure possess such properties (V. Ye.  
Motovilov, 1964; I. A. Yarosh, 1966; Wood et al., 1966; Deane et al., 1967;  
Johnson et al., 1976), however the depressing effect of these substances on the  
mental and psychomotor reactions makes them not very suitable for the indicated  
purpose (V. V. Zakusov, 1964). Isolated works make it possible to hypothesize that  
tranquilizers will be effective for preventing the negative consequences of ves-  
tibular stimuli (I. I. Voinova et al., 1975; Franks et al., 1962), the more so  
since the directed effect on the emotional sphere by means of prescribing tran- /607  
quilizers can increase the performance capacity of man (O. S. Lobastov et al.,  
1968; G. D. Glod et al., 1972; Hurst, et al., 1970). On the other hand, it is  
known that the emotional factor is one of the components that plays a role in  
the pathogenesis of motion sickness.

The tasks of this study were to establish in an experiment whether tranqui-  
lizers possess a group property to increase the resistance to the effect of

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adequate stimuli of the vestibular apparatus and in the case of obtaining a positive result to select a preparation with the most explicit effect of protection against accelerations.

#### Methods of Study

Work was done on 900 albino mice. For adequate stimulation of the labyrinth the fairly widespread method of centrifuging was used (A. V. Bogatskiy et al, 1978; L. D. Klimovskaya and L. S. Ivanenko, 1978) which according to K. L. Khilov (1969) excites the receptors and the otolithic instrument, and the semicircular canals. Taking into account the applied nature of the study it was necessary to obtain acceleration close to the transportation. For this purpose a centrifuge was made with synchronous motor with power 128 rpm with rotation radius 11 cm. The radial acceleration that thus developed was 2 g and acted on the animals in the direction back-chest. It is known that one of the frequent disorders occurring under the influence of acceleration is the set of motor-coordination disorders. Therefore in order to evaluate the effect of centrifuging on the motor activity of the animals the method of actometry was used that gives an objective numerical indicator. The simplest actometer equipped with an electromagnetic counter was used.

Five mice with the same body weight were placed in a drum of the centrifuge and exposed to 3-minute rotation clockwise. Directly after this an evaluation was made of the pronouncement and duration of reflexes (nystagmus of the torso, tail reflex) and the mice were moved to the chamber of the actometer, where they stayed for 1 h. At the 1st, 5th, 10th, etc. minutes the actometric counter was turned on. Thus, in 1 hour 13 measurements were made, the magnitude of each reflected the sum of movements of five animals in 1 min. The findings were statistically processed and from the 13 points curves were plotted for the motor activity of the animals under different experimental conditions.

The animals were divided into 5 groups of 180 individuals each. Since in the centrifuge and actometer 5 mice each were placed simultaneously, 36 experiments were conducted in each group; each animal was used only once in the experiment. The first group included intact mice not exposed to centrifuging, and from the data of these experiments a stable curve was derived for the spontaneous motor activity; the second group was the control--curve for the effect of

centrifuging on spontaneous motor activity; the animals of the 3,4 and 5th groups 15 minutes before the beginning of the rotation received tranquilizers--respectively meprobamate, elenium or nicolite.

The selected substances are the most widely used in practice and vary in chemical nature: meprobamate--derivative of propandiol, elenium--derivative of 1,4-benzodiazepine, nicolite--lithium salt of nicotinic acid (Ya. B. Maksimovich and V. I. Kresyun, 1973, 1974, 1976; Ya. B. Maksimovich et al., 1976; certificate of authorship No. 388555 of 2 April 1971). The substances were given in therapeutic doses (meprobamate--3 mg/kg, elenium--0.15 mg/kg, nicolite--10 mg/kg) in the same volume of physiological solution (0.4 ml) intraperitoneally once. At the end of the acute experiment the animals were observed for 1 month. The integral indices were considered: body weight, behavior, mortality rate.

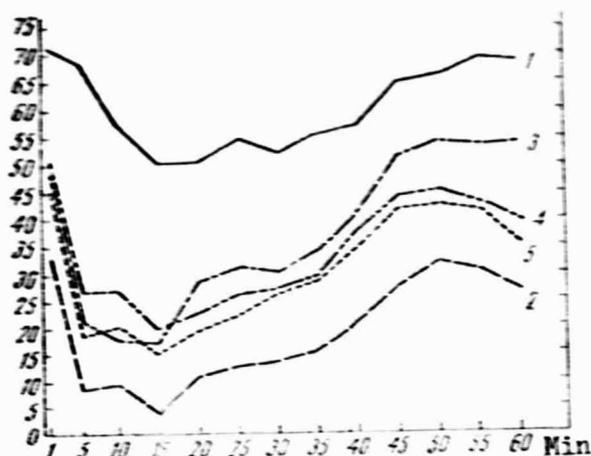
### Results

Spontaneous motor activity of the intact mice was not stable for 1 h: already from the 10th minute of observation it was reduced and for about  $\frac{1}{2}$  an hour fluctuated in the lowest limits, and then returned smoothly to the initial amounts.

The results of the control series of experiments indicated that the adequate stimulus of the vestibular apparatus sharply disrupts the motor system of the animals. Directly after centrifuging of mice they were rotated 2-3 times to the right around the longitudinal axis; torsal and eye nystagmus were clearly manifest (reaction of semicircular canals); the otolite reflex was observed (straightening of tail) and tremor of the extremities. Further attention was drawn to the sharp disruption in the coordination of movements and reduction in the general motor activity linked to the action of accelerations. A highly reliable reduction in the number of movements was noted during the entire experiment.

Under the influence of the tranquilizers the vestibulo-spinal reflexes were weakly pronounced, and often were missing (especially nystagmus of the torso and tail). At the same time in these animals the motor activity remained also diminished, although less than in the control. Further observations of the mice in all groups indicated the complete restoration of locomotor reactions in 24 h. No losses of body weight or increase in mortality of the animals were observed as compared to the intact mice in the 1 month from the conducting of the experiment.

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Dynamics of Motor Activity of Animals (Number of Movements in 1 min) under Different Conditions of Experiment  
 1--intact mice; 2--control; 3--meprobamate; 4--elenium; 5--nicolite.

Statistically processed results of the experiments on all five groups of animals are presented in table 1.

#### Discussion of Results

A comparison of the results of the conducted experiments outlined the following laws. First: powerful (2 g) stimulation of the vestibular analyzer by centrifuging leads to disruption of the vestibulo-spinal bonds. This is accompanied by the appearance of pathological reflexes interchanging with pronounced and stable hypokinesia. For 1 h after cessation of rotation the number of movements is reduced 2-4-fold as compared to the actometric index of intact animals and by the 60th minute of the experiment remains lower by more than double (-60.9%). Second: the tranquilizers regardless of their chemical nature sharply reduce the pathological hyper-reflex due to the centrifuging and noticeably diminish the subsequent hypokinesia. Thus, a unique effect that is common to all the tranquilizers of protecting the vestibulo-spinal bonds appears. It is possible that the effect of interruption of the interneural transmission that is inherent to tranquilizers is also spread on these paths. This would promote expansion of the extant ideas on the intracentral mechanisms for the effect of tranquilizers (I. P. Lapin and L. A. Allimets, 1967; Yu. N. Furman, 1974; Yu. A. Aleksandrovskiy, 1976; I. Temkov and K. Kirov, 1971; F. Shvets, 1971).

However, as is easy to see on the figure, although all the employed tranquilizers possess the protective properties, this effect is not expressed to the same

TABLE 1. MOTOR ACTIVITY OF ALBINO MICE ACCORDING TO DATA OF ACTOMETRY (NUMBER OF MOVEMENTS OF 5 MICE IN 1 MIN)

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Conditions of experiment	Stat. index	Period of observation, minutes												
		1	5	10	15	20	25	30	35	40	45	50	55	60
Intact animals	M	70.8	68.2	57.1	50.2	50.5	54.2	52.2	55.1	57.1	64.4	66.0	68.4	67.8
	±m	5.76	7.02	4.58	4.76	4.56	4.41	4.41	3.59	2.96	3.11	3.29	3.36	3.84
Control	M	32.9	7.9	8.6	3.0	10.6	12.6	12.9	15.0	20.0	27.1	31.8	30.3	26.5
	±m	3.21	1.68	1.86	0.84	1.17	1.23	1.17	1.35	1.31	1.86	2.20	2.54	2.54
Meprobamate	M	48.2	21.2	17.1	16.8	28.2	31.0	30.1	33.6	40.4	51.1	53.7	52.7	53.0
	±m	3.36	2.05	1.75	1.72	2.43	2.53	2.46	2.42	2.59	2.90	3.26	3.16	3.25
Elenium	P	<0.01	<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	±m	50.8	26.2	26.5	19.7	22.5	25.6	27.0	29.2	37.1	43.7	45.0	42.7	30.7
Nicolite	M	3.50	2.27	2.54	1.62	1.99	2.39	2.55	2.75	3.01	3.33	3.46	3.11	2.83
	±m	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.01	<0.01
Control	M	45.5	18.4	20.6	14.8	19.3	22.2	26.7	28.4	34.8	41.7	42.5	41.3	35.0
	±m	3.28	1.50	1.66	1.47	1.48	1.90	2.32	2.65	3.11	3.35	3.57	3.43	3.27
	P	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.05	<0.05	<0.05

Note: P is given in relation to the control

TABLE 2. DEGREE OF DECREASE (IN %) OF MOTOR ACTIVITY OF CENTRIFUGED ANIMALS (DYNAMICS IN 1 H)

Conditions of experiment	Stat. index	Period of observation, min												
		1	5	10	15	20	25	30	35	40	45	50	55	60
Meprobamate	P	31.9	68.9	69.7	66.5	44.2	42.8	42.3	39.0	28.2	20.7	18.6	23.0	21.8
	±m	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.05	<0.01	<0.01
Elenium	P	28.2	61.6	53.6	60.8	55.4	52.8	48.3	47.0	34.5	32.2	31.8	37.6	41.5
	±m	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Nicolite	P	35.7	73.0	65.0	70.5	61.8	59.0	48.9	48.5	39.1	35.3	35.6	29.6	48.4
	±m	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Control	P	53.5	88.4	84.9	94.0	79.0	76.8	75.3	72.8	65.0	57.9	51.8	55.7	60.9
	±m	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: The amounts of percentages and P are given in relation to the group of intact animals whose number of movements is taken as 100%.

degree. Mathematical analysis of the picture given in table 2 is convincing of this. It is apparent from it that in the first 10 min. the changes in the motor activity in all animals who took tranquilizers are of the same type regardless of the employed tranquilizer. However, already from the 15th minute individual peculiarities of the preparations begin to appear. At the same time in animals of the 4th and 5th group the second wave drop in motor activity begins, in mice who took meprobamate (third group) the motor system is stabilized, and from the 20th minute they begin to rapidly emerge from the state of hypokinesia. At the 50th minute the degree of suppression of the motor activity of the mice of the third group was almost two times lower than in the mice of the fourth and fifth groups (respectively -18.6% versus -31.8 and -35.6%).

There is yet another important detail. In the animals who took elenium and nicolite, starting from the 50th minute a third wave of drop in motor activity develops that is noticeable although not sharp. In the mice who received meprobamate there is no third wave of drop and the motor activity is generally stabilized on a level attained by the 50th minute and is fairly close to the amount of the actometric index of intact animals. The cited data force us to consider that in a comparative aspect meprobamate has the most pronounced effect in relation to increasing the resistance to accelerations and elimination of possible motor disorders. /610

### Conclusions

1. Tranquilizers increase the resistance of animals to the effect of adequate stimuli of the vestibular apparatus.
2. Meprobamate possesses the most pronounced protective properties.

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