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THE INFLUENCE OF PHYSIOLOGICALLY EFFECTIVE DOSES OF EPINEPHRINE ON VESTIBULARLY INDUCED NAUSEA

by

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LETTER OF TRANSMITTAL

November 14, 1942.

Dr. Dean R. Brimhall
Director of Research
Civil Aeronautics Administration
Washington, D. C.

Dear Dr. Brimhall:

The Committee on Selection and Training of Aircraft Pilots is pleased to transmit a report entitled "The Influence of Physiologically Effective Doses of Epinephrine on Vestibularly Induced Nausea," by Roy M. Dorcus.

The study was carried out by Dr. Dorcus at the University of California at Los Angeles. Dr. G. R. Wendt of Wesleyan University, Middletown, Connecticut, cooperated both in the development of the study and in the preparation of the attached report.

In presenting the report, it should be pointed out that the experiment was not designed to test the whole theory that fear increases the frequency of air sickness. Although many of the bodily changes in a natural state of fear can be traced to the influence of epinephrine, and although the injection of epinephrine in the laboratory reproduces many such changes, it is certain that many other factors enter into a full-fledged state of fear. While the results of the present study suggest that increased epinephrine with vestibular stimulation does not increase nausea, it is still quite possible that fear may increase nausea through the action of other mechanisms.

The results of the study do not lead to any positive proposals for action. The study serves a purpose, however, in testing one specific aspect of a hypothesis of the origin of air sickness, which has received considerable attention.

Very truly yours,

Morris S. Viteles, Chairman
Committee on Selection and
Training of Aircraft Pilots
National Research Council
Washington, D. C.

MSV:k

INTRODUCTION[1]

This report describes the results of an investigation of the effects of epinephrine[2] on the frequency of vomiting under conditions of vestibular stimulation. The purpose of the study was to test one aspect of a particular hypothesis of the mechanism of air sickness, i.e., the hypothesis that the nausea and vomiting of air sickness are the direct result of fear.[3] This view, widespread among flyers, has recently been endorsed by Armstrong: "The vomiting of airsickness is nothing more or less than the natural reaction of the body to a state of fear whereby it rids itself of all unnecessary impedimenta in prep-

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[1]This work was carried out with the cooperation and assistance of D. S. McKinnon, M. D., of the University Health Service, and George Mount, Graduate Teaching Assistant in Psychology. It was done in the Psychological Laboratory of the University of California at Los Angeles with the aid of a grant from the National Research Council Committee on Selection and Training of Aircraft Pilots from funds provided by the Civil Aeronautics Administration through the Committee's project at Wesleyan University, Middletown, Connecticut, concerned with air sickness, directed by G. R. Wendt.

[2]"Epinephrine is the active principle of the adrenal medulla.... In general the actions exhibited in the body by epinephrine resemble those obtained from stimulation of adrenergic nerves....Sweating and pilomotor reactions, however, are not elicited, and mydriasis is not obtained except under special circumstances. Particularly prominent are the actions of the drug on the heart, blood vessels and certain smooth muscles...." Quotations from pp. 396-401 of:

Goodman, L.,& Gilman, A. The pharmacological basis of therapeutics. New York: Macmillan, 1941.

[3]Editor's note. An association between fear and vomiting has been suggested by many observers of animal and human behavior in situations other than flying. In the case of flying, of course, the most obvious cause of air sickness is the experience of unusual motions, especially vertical accelerations. Such motion sickness is quite directly traced to the impulses from the vestibule and semicircular canals of the inner ear, with their sense organs which furnish cues of motion. When this sensory equipment is lacking, as it is in some deaf individuals, motion sickness does not occur. The vestibular equipment is not the only factor in motion sickness, however, as it is known that many other factors such as suggestion may increase the tendency to vomit. A state of fear might be one such factor.

aration for fight or flight."[4] The specific aspect of the hypothesis being tested is that the extra epinephrine released in the body in a state of fear might be the agent which would facilitate the nausea and vomiting induced by vestibular stimulation.[5] If this should be the case, injections of epinephrine should increase the frequency of nausea and vomiting under laboratory conditions of vestibular stimulation.

PROCEDURES

Two groups of male college students were selected on the basis of their response to a series of vestibular stimuli designed to produce nausea: 15 non-susceptibles and 15 who were strongly nauseated or vomited. Seven to ten days later, after the intramuscular injection of 1 cc. of 1:1000 solution of epinephrine hydrochloride, the procedures were repeated to determine whether there was a change in the frequency of nausea or vomiting.

Apparatus and method. Briefly described, the apparatus and general procedure were as follows:[6] On a rotating chair, head bent for-

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[4]Armstrong, H. G. Principles and practice of aviation medicine. Baltimore: Williams and Wilkins, 1939.

Editor's note. The quotation is from pp. 238-239. Armstrong's complete argument is much more complex than this quotation suggests. He feels that experiences of unusual motion and disorientation lead to an instinctive fear of falling, which need not be conscious.

[5]Editor's note. The question might be raised as to whether epinephrine alone produces vomiting and nausea. There is little evidence to suggest that it does. Vomiting may accompany hyperadrenia (a condition marked by excess epinephrine) and it sometimes occurs in experimental animals following massive doses. In these cases, however, the relationship is probably indirect. Doses of the size used in this experiment do not produce nausea independently of rotation.

[6]Apparatus and procedures, including the questionnaire mentioned below, are more fully discussed in:

Dorcus, R. M. Report on study of air sickness. (Unpublished.) Washington: National Research Council, Committee on Selection and Training of Aircraft Pilots, September 1941.

ward and eyes closed, the subject was rotated clockwise for 25 turns, during which he was four times momentarily slowed and then again accelerated (Rotation I). This was followed by ten counter-clockwise turns, head forward with eyes open, and watching a six-inch wide spiral line painted on the floor (Rotation II). This was followed by ten clockwise turns under the same conditions (Rotation III). He was then placed in the horizontal, prone position on a tilt table. Water at a temperature of 8° C. was injected into the ear for a period of three minutes, after which the subject was tilted to the vertical position (Caloric Stimulation).

The above procedure was applied to 38 individuals who had been selected from 350 cases on the basis of a questionnaire directed at susceptibility to motion sickness. Eighteen of these seemed from the questionnaire to have low susceptibility, and 20 to have high susceptibility. On the basis of the laboratory procedure, 30 subjects were retained for the full experiment: 15 of them showed no distress or only slight nausea, 15 vomited or were very strongly nauseated. (See Tables III and IV, Appendix.) All were male college students, aged 19 to 23. All were given a physical examination and found to be normal individuals.

Seven to ten days later each subject received an intramuscular injection of 1 cc. of 1:1000 solution of epinephrine hydrochloride. Blood pressure and pulse rate were taken at three-minute intervals until the maximum physiological effect appeared to have been reached. This time ranged from 4 to 16 minutes with an average of about 10½ minutes. The subject was then again put through the stimulation procedures described above. The total testing time was about 15 minutes with a variation of two minutes more or less. Observations were made of the degree of nausea and the occurrence of vomiting, and subjective judgments were solicited.

Relevance of procedures to air sickness. Earlier studies have given the following data on the relation of these laboratory procedures to air sickness:[7]

Ten aviators were tested who had been eliminated at flying centers because of air sickness. Nine of them became sick in Rotation II. All ten became sick when subjected to the three rotations and caloric stimulation.

A group of 117 primary and secondary aviators with no history of air sickness was tested. Four became nauseated in the rotation tests.

Of the preceding 117 men, 31 were put through the combined procedure. Eight of them became sick. (Of these eight cases, five were secondary and three were primary flyers. Whether any of these will subsequently be eliminated in combat training cannot be stated.)

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[7]Dorcus, op. cit., pp. 10-11.

RESULTS

1. Effects of vestibular stimulation without epinephrine. The results of this experiment are summarized in Figure 1 and in Tables I and II. Detailed results for each subject are presented in Tables III and IV (Appendix). Let us examine first the results of the first experimental session. Of the fifteen subjects we have called non-susceptibles (Group A) only three reported slight nausea symptoms on any of the four tests prior to the injection of adrenalin, two of these indicating the symptom following Rotation III and the other one following caloric stimulation.

In the susceptible group (Group B) before injection of epinephrine three subjects reported slight nausea following Rotation I. Seven reported slight nausea following Rotation II; one reported that he was very nauseated; and one vomited. Following Rotation III, two reported slight nausea; eight reported extreme nausea; and three vomited. Following caloric stimulation, one reported slight nausea; one reported extreme nausea; and thirteen vomited. It is fairly obvious from these results that there is a cumulative effect of the stimulation insofar as it influences vomiting.

2. Combined effects of vestibular stimulation and epinephrine. The results after injection of epinephrine were very similar to those before epinephrine. If epinephrine is a causative agent in inducing nausea, we might expect individuals in Group A to become nauseated after the injection or we might expect that individuals in Group B would become nauseated earlier in the experimental procedure. In Group A only one subject who had not previously reported symptoms became slightly nauseated from the caloric stimulation after the injection. The three who had reported slight nausea in the first session reported it again. One of them (subject 8) vomited when given caloric stimulation, which may mean that he was affected to some extent by the drug.

The situation in regard to Group B appears in Table I and Figure 1. There is no higher incidence of nausea in any part of the procedure. If any effect was produced by the epinephrine it was of an inhibitory nature, since following Rotation III, eight subjects who had previously reported severe nausea reported only slight nausea. Most of the subjects who had vomited before the injection, said that after the injection of the epinephrine they did not feel as badly as they felt without epinephrine, even though they were nauseated and vomited. What this means we are unable to state.

FIGURE 1

A comparison of the effects of vestibular stimulation before and after the injection of epinephrine (data from the 15 subjects of Group B).

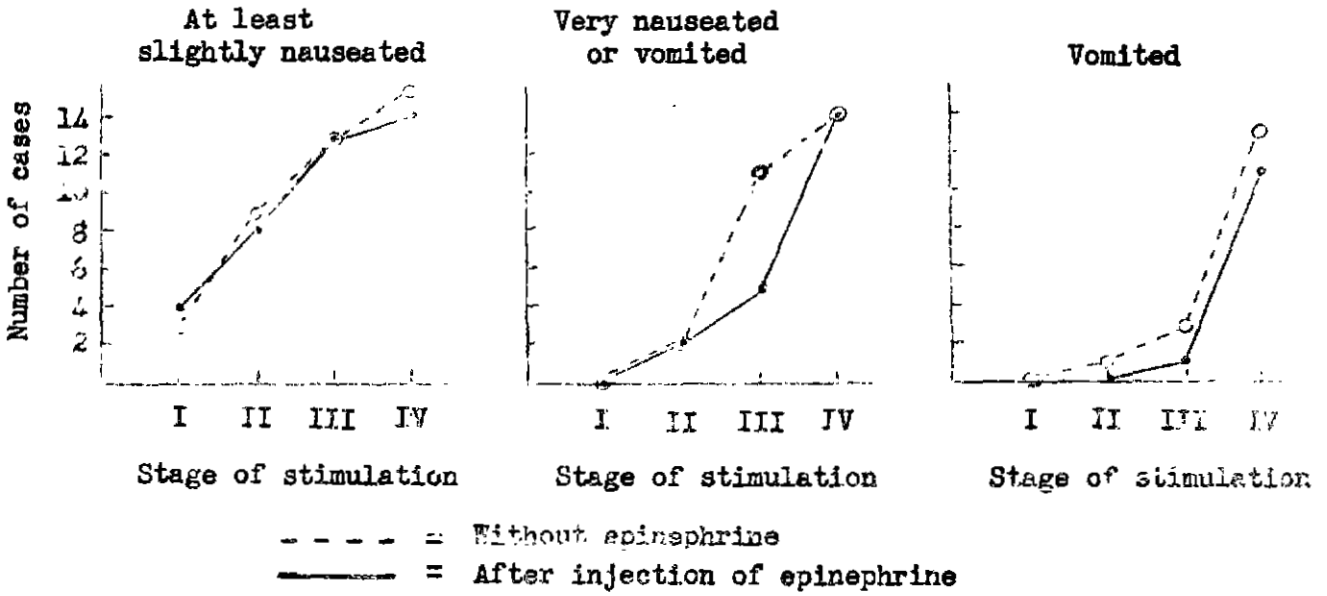

TABLE I

Summary of the effects of vestibular stimulation before and after the injection of epinephrine

		ROTATION I				ROTATION II				ROTATION III				CALORIC IV			
	Condition reported	0	*	**	V	0	*	**	V	0	*	**	V	0	*	**	V
GROUP A	Number of cases before Epinephrine	15	0	0	0	15	0	0	0	13	2	0	0	13	2	0	0
	Number of cases after Epinephrine	15	0	0	0	14	1	0	0	13	2	0	0	11	3	0	1
GROUP B	Number of cases before Epinephrine	12	3	0	0	6	7	1	1	2	2	8	3	0	1	1	13
	Number of cases after Epinephrine	11	4	0	0	7	6	2	0	2	8	4	1	1	0	3	11#

#Including one case that would not go through Part IV who in our opinion would have vomited.

Symbols: 0 no symptoms
* slightly nauseated
** very nauseated but did not vomit
V vomited

3. Relative physiological effects of epinephrine on vomiters and non-susceptibles. Calculations from Tables III and IV give the results shown in Table II. A moment's inspection of this table will show that, so far as these subjects were concerned, there were no significant differences in resting pulse rates or blood pressures. Furthermore, there were no differences in their reactivity to the autonomic drug, epinephrine, insofar as these are revealed by pulse rate or blood pressure changes.

TABLE II

Average Blood Pressures and Pulse Rates

	Susceptibles		Non-susceptibles	
	Normal	After drug	Normal	After drug
Systolic	123.3	136.6	122.8	135.3
Diastolic	69.3	64.2	69.3	64.4
Pulse Rate	81.0	87.6	81.1	85.5

(Averages are based on 15 cases except for the blood pressures of non-susceptibles which are based on 14 cases.)

DISCUSSION

The amount of nausea in the second part of the experiment (with epinephrine) was about the same as in the first part (without epinephrine). The results suggest quite strongly that epinephrine is without effect in these experiments.

Such variations in effects as appeared might well be due to uncontrolled or unknown factors. If there is any faint hint of a trend, it is that symptoms were slightly more evident in the non-susceptible group after epinephrine, and slightly less evident in the susceptible group. This trend is just what would be expected in a retesting without epinephrine, however, if there are daily variations in "susceptibility," on the assumption that if a non-susceptible was feeling unusually well on his first test, he stands a chance, on the whole, of feeling not so well on the second test. The opposite situation would hold for the susceptibles.

A question might be raised about the possible effects of practice. If a group of subjects tested a second time <u>without</u> epinephrine should show increased vomiting (reverse conditioning), results like the present might mean that the drug has beneficial effects. If such a group should become less ill (habituation) then the effect of the drug would seem to be harmful. Since practice may result in habituation of those who do not become nauseated and in adverse conditioning of those who do, there is a possibility that the drug helped the susceptibles. To evaluate the relative effects of practice and of drugs completely would require a rather elaborate experimental design. The present results give an answer to the immediate question, and the more elaborate experiment would be justified only if it seemed important to prove or disprove a beneficial effect of epinephrine.

CONCLUSIONS

1. The obtained results are that epinephrine produces no changes in frequency of nausea or vomiting in response to vestibular stimulation under the conditions of this experiment.

2. This may safely be interpreted as demonstrating that under these conditions epinephrine does not facilitate nausea and vomiting.

3. It does not, however, exclude the possibility that epinephrine may tend to prevent or alleviate nausea.

4. It was found, incidentally to the main problem, that the normal resting blood pressures of those who were subsequently nauseated, were on the average equal to those of the non-susceptibles, and that their blood pressure changes from epinephrine were equal.

5. The results cast doubt on one aspect of the hypothesis that motion sickness is a consequence of fear. If fear actually increases the frequency of air sickness, the effect, insofar as it can be gauged from this experiment, does not seem to be a direct physiological result of the increased secretion of epinephrine, known to occur during fear.

APPENDIX

TABLE III Individual results for Group A (the non-susceptibles).

TABLE IV Individual results for Group B (the susceptibles).

G R O U P A

SUBJECT	Before Epin. Rot I	Rot II	Rot III	Col IV	After Injection 1 cc Epin. Rot I	Rot II	Rot III	Col IV	Blood Pressure Before Epin.	Before Rotation	Pulse Pressure Before Epin.	Before Rotation	Increase or decrease	Pulse Rate Before Epin.	Before Rotation
1	0	0	0	0	0	0	0	0	135/85	135/60	50	75	+25	60	60
2	0	0	0	0	0	0	0	0	125/70	130/90	55	40	-15	90	100
3	0	0	0	0	0	0	0	0	130/70	155/60	60	95	+35	92	94
4	0	0	0	0	0	0	0	0	132/70	130/65	62	65	+ 3	80	84
5	0	0	0	0	0	0	0	0	115/80	150/60	35	90	+55	80	88
6	0	0	0	*	0	0	0	*	120/75	140/70	45	70	+25	76	96
7	0	0	*	0	0	0	*	*	130/90	100/?	40			76	50
8	0	0	*	*	0	*	*	V	125/60	150/45	65	106	+41	112	98
9	0	0	0	0	0	0	0	0	135/70	130/62	55	58	+ 3	60	97
10	0	0	0	0	0	0	0	0	10 /80	125/60	20	65	+45	108	95
11	0	0	0	0	0	0	0	0	10 /50	105/60	50	45	- 5	88	88
12	0	0	0	0	0	0	0	0	140/65	150/65	75	85	+10	80	80
13	0	0	0	0	0	0	0	0	110/60	115/65	50	50	0	64	80
14	0	0	0	0	0	0	0	0	130/80	155/80	50	75	+25	73	78
15	0	0	0	0	0	0	0	*	132/55	135/60	77	79	+ 2	78	95

Symbols: - no symptoms ** - very nauseated but did not vomit
* - slightly nauseated V - vomited

TABLE B

Before Epin. Rot I	Rot II	Rot III	Cal IV	After Injection 1 cc Epin. Rot I	Rot II	Rot III	Cal IV	Blood Pressure Before Epin.	Blood Pressure Before Rotation	Pulse Pressure Before Epin.	Pulse Pressure Before Rotation	Pulse Pressure Increase or decrease	Pulse Rate Before Epin.	Pulse Rate Before Rotation
[illegible]	[illegible]	[illegible]	V	*	*	*	**	145/70	155/60	65	95	+30	80	[illegible]
[illegible]	[illegible]	**	V	0	*	*	V	125/70	150/63	55	87	+32	82	[illegible]
0	0	**	V	0	0	0	0	145/75	155/75	70	80	+10	104	[illegible]
[illegible]	*	**	V	0	*	* would not take		130/65	145/70	45	75	+30	84	[illegible]
[illegible]	*	**	V	0	*	**	V	120/70	135/60	50	75	+25	80	[illegible]
[illegible]	*	**	V	*	**	**	V	100/65	120/60	35	60	+25	85	[illegible]
[illegible]	*	**	V	0	0	*	V	125/70	135/80	55	55	0	75	[illegible]
[illegible]	*	**	V	0	0	*	V	132/50	155/90	72	65	- 7	92	[illegible]
*	V	V	V	0	0	V	V	140/80	150/70	60	80	+20	65	[illegible]
0	*	0	*	0	*	*	**	120/70	130/60	50	70	+20	76	90
0	0	V	V	0	0	*	**	110/65	130/40	45	90	+45	80	[illegible]
0	0	*	**	0	0	0	V	110/60	122/55	50	67	+17	80	[illegible]
0	0	0	V	0	0	*	V	110/60	115/60	50	55	+ 5	75	[illegible]
*	*	V	V	*	*	**	V	115/60	130/60	55	70	+15	105	[illegible]
*	**	**	V	*	**	**	V	122/70	122/60	52	62	+10	82	[illegible]

Symbols: 0 - no symptoms

* - slightly nauseated

** - very nauseated but did not vomit

V - vomited