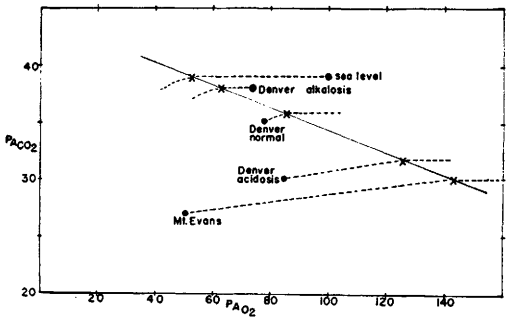

FIG. 1. Hypoxic threshold line is the solid line drawn between probable hypoxic thresholds of residents at sea level, Denver, Mt. Evans, and of Denver residents who are acidotic and alkalotic. Dashed lines indicate probable alveolar gas changes resulting from gradual decreases in alveolar oxygen tensions. When the threshold line is crossed, breathing increases and $^{P_A}CO_2$ decreases.

tilatory drive.

Summary. 1. Inspired oxygen tensions which produce the first discernible increases in ventilation (hypoxic thresholds) were measured in subjects acclimatized to Mt. Evans, Colo. (14,150 feet) and to Denver, Colo. (5300 feet). In addition thresholds were measured in subjects living in Denver who were in chronic metabolic acidosis (NH_4Cl) and in chronic metabolic alkalosis ($NaHCO_3$). 2. Mt. Evans subjects showed an average threshold of 179 mm tracheal $^{P}O_2$ and those at Denver 127 mm. Reports in the literature pinpoint the threshold for sea level dwellers at about 93 mm. Furthermore the threshold for Denverites ingesting NH_4Cl was 163 mm and for those ingesting $NaHCO_3$ was 107 mm. 3. Since NH_4Cl changed $^{P_A}O_2$ and pH in the opposite direction from altitude but changed the hypoxic threshold in the same direction, these agents were ruled out as threshold governors. It was suggested that probably the hypoxic threshold is a function of either the resting $^{P}CO_2$ or the bicarbonate level to which the individual had acclimatized.

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Prevention and Treatment of Motion Sickness by Intranasal Medication. (22131)

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Rapid absorption of hyoscine hydrobromide (scopolamine) after intranasal instillation has recently been reported(1,2). This route of administration combines simplicity of self-medication with rapid drug absorption. It has the further advantage of circumventing the oral route when nausea, psychic factors, or lack of cooperation make swallowing difficult. This technic should be especially valuable in prevention and treatment of motion sickness. Its effectiveness against swing- and airsickness is the subject of this report.

Experimental. Scopolamine Spray and Swing Sickness. Healthy, male adults ranging in age from 17 to 24 years (average 19 years) were used as subjects. The experimental group were given varying amounts of scopolamine in each nostril by a plastic spray bottle† and the remainder were given saline in a similar manner. Exact amount of fluid instilled was determined by loss in weight of spray bottle. Thirty minutes after spraying, the subject was placed in the carriage of a motor-driven swing and swung through an arc of 120° for 20 min-

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† We acknowledge a generous supply by the Doho Chemical Corp.

utes, unless vomiting occurred earlier. Radius of swing was 14 feet and frequency of swingings 14 per minute. Data on occurrence of side effects was obtained from questionnaires distributed upon completion of swinging. Scopolamine was dissolved in 0.9% NaCl solution immediately before use. Originally, it was planned to spray approximately 0.3 mg of scopolamine into each nostril. Therefore, a solution containing 3 mg/ml was prepared and approximately 0.1 ml sprayed into each nostril. The volume sprayed varied considerably and an occasional subject received 1 to 1.5 mg of scopolamine. Dosage level was, therefore, reduced to 2 mg/ml to provide a greater margin of safety. As evident from Table I significant protection was afforded although the average dose was only 0.43 mg ($\sigma = 0.22$) compared with 0.65 mg to 1 mg ordinarily given by mouth. At this dose level, the only side effects markedly increased were those of dizziness, which rose from 23% to over 45%, and dry mouth which was more than twice that of control group. There was no significant increase of drowsiness or blurred vision. Other side effects such as headache, fatigue, nervousness, and sweating were uniformly less than the incidence among the control group. The high percentage of mild dizziness after scopolamine (despite the relatively small dose administered) was disturbing. Therefore, to increase further the margin of safety, scopolamine was prepared in a concentration of 1 mg/ml and administered as before. With this solution, an average dose of 0.26 mg ($\sigma = 0.14$) of scopolamine was sprayed. The number vomiting was slightly less than in the control group but the difference was not statistically significant. Since the detergent sodium lauryl sulfate (Duponal C) increased the absorption of scopolamine in a nasal spray(1) it was added (0.01%) to the saline solution (0.9%) containing 1 mg/ml of scopolamine. As is evident from Table I this preparation sharply decreased the incidence of vomiting from 15.3 to 5.9%. Incidence of dry mouth was greater than normal, but no other significant increases in side effects were apparent. Incidence of headaches, sweating, and fatigue was reduced. The average dose of scopolamine administered was 0.31 mg ($\sigma =$ 0.12). This was slightly higher than the amount sprayed when Duponal was not employed at the 1-mg dose level.

TABLE I. Effectiveness of Scopolamine against Swing-Sickness when Administered as Nasal Spray.

	No. of subjects	Avg dose, mg	Vomit, %	Protection,† %
Saline control	47		14.9	71.8
2 mg S‡	47	.43	4.2*	
Saline control	94		13.8	23.2
1 mg S	94	.26	10.6	
Saline-Duponal control	85		15.3	61.5
1 mg S (0.9%)—Duponal (0.01%) sol.	85	.31	5.9*	

* $P = \leq 0.05$.

† $\frac{\%\text{ of vomiting placebo} - \%\text{ of vomit. medication}}{\%\text{ of vomiting placebo}}$.

‡ S = Scopolamine/ml in saline.

Scopolamine Spray and Airsickness. The effectiveness of intranasal administration in preventing swing sickness suggested that it be tried therapeutically as well. For this purpose, our subjects were exposed to an hour's flight of standardized turbulence in C-47 (DC-3-type) aircraft. Procedure was the same as previously reported(3) in which the route, altitude, and maneuvers were standardized as rigidly as possible to insure reproducible flights. Originally, the subjects were given the plastic spray bottles containing either control saline-Duponal solution or freshly prepared scopolamine (2 mg/ml) in this solution. Each person was instructed to use the spray as soon as he felt nauseated. It rapidly became apparent, that the subjects were reluctant to medicate themselves since to do so constituted an admission of nausea. Consequently, very few utilized the medication despite obvious distress and subsequent vomiting in many cases. To obviate this difficulty, observers sprayed each subject intranasally 15 minutes after take-off. This time was chosen since in scores of previous flights vomiting rarely occurred earlier, although vasomotor disturbances and nausea were already evident. The spray bottles were weighed before and after use to determine the quantity lost. The subjects were observed for remainder of test period and the incidence of side effects was obtained by questionnaire, as

TABLE II. Therapeutic Effectiveness of Nasal Administration of Scopolamine.*

Dose of scopolamine	No. of subjects	Vomit, %	P†	Protection, %
0 (saline)‡	79	44.3	—	—
.80 ($\sigma = 0.50$)‡	79	22.6	.01	48.6
0 (saline)§	89	28.1	—	—
.2 §	90	17.8	.10-.20	36.6
.4 §	90	15.6	.05	44.5
.6 §	90	10.0	<.01	65.0

* Administered 15 min. after take-off.
† Saline vs medication.
‡ Nasal spray.
§ Nose drops.

already described. The results are summarized in Table II. As can be seen, the scopolamine spray significantly reduced the incidence of vomiting. Since medication was not administered until 15 minutes after flight had begun and the average time of vomiting was 30 to 35 minutes, it is apparent that absorption and action of scopolamine by this route is extremely rapid. The incidence of blurred vision, drowsiness, and dry mouth was increased in the medicated group, although not to the significant level. Sweating was significantly reduced ($P = 0.01$) among those receiving scopolamine.

Scopolamine Nose Drops and Airsickness. Despite careful selection of the spray bottles and indoctrination in their use, the variation in amount of drug given was surprisingly great, ranging from less than 0.10 mg to more than 1.5 mg ($\sigma = 0.50$). To obtain more exact dosage response data, the experiment was repeated utilizing nose drops rather than the spray. Again, 15 minutes after take-off, 0.2 ml of solution was instilled into each nostril. Varying quantities of scopolamine were dissolved in 0.9% NaCl containing 0.01% Duponal so that total dose administered was 0.2, 0.4, or 0.6 mg, respectively. A control group received the Duponal-saline solution alone. The results are given in Table II. Marked protection was afforded by 0.4 and 0.6 mg of scopolamine and apparently some protection even by 0.2 mg. Significant side effects were confined to blurred vision, dry mouth, and sweating. No changes were observed with 0.2 mg of scopolamine, except for a decrease in incidence of sweating. At the 0.4 mg level, blurred vision was reported, and with 0.6 mg all 3 side effects were accentuated. A slight, but nonsignificant, increase in drowsiness was also reported.

Effectiveness of Scopolamine by Various Routes Against Airsickness. Another practical means for self-administration of drugs is by the sublingual route. Many drugs have been given in this fashion and absorption is known to be rapid. It was of interest, therefore, to compare effectiveness of scopolamine by this route with that after intranasal instillation. Volunteers were again subjected to a period of standardized turbulence in military aircraft before receiving medication. Eighteen minutes after take-off, subjects received a placebo capsule taken by mouth, or 0.65 mg of scopolamine by mouth, or as sublingual tablet. Two minutes later, a fourth group received the same amount of scopolamine in the saline-Duponal solution as nose drops. The 2-minute interval permitted dissolution of the sublingual tablet. Regular 0.01 grain hypodermic tablets were used for this purpose. These small tablets were placed under the tongue and the subject cautioned not to swallow. They were found to dissolve well within the 2-minute period. Exposure time prior to medication was lengthened (20 vs. 15 min) over that in earlier trials to provide a more rigorous test for the drug. As before, scopolamine nose drops markedly lowered the incidence of vomiting (Table III), whereas the drug was completely ineffective when given orally or sublingually. The rapidity of its absorption through the nasal mucosa is also reflected by side effects recorded in Table IV. Nose drops produced highly significant increases ($P = 0.01$) in dizziness, drowsiness, and dry mouth, as well as a significant decrease in incidence of headaches. The only other significant change from the control group was a moderate increase ($P = 0.05$) in

TABLE III. Route of Administration on Effectiveness against Airsickness.

	Dose, mg	Route	No. of subjects	No. of vomit	Vomit, %
Placebo	—	Oral	84	29	34.5
Scopolamine	.65	"	85	30	35.3
	.65	Sublingual	82	26	31.8
	.65	Intranasal	82	13	15.9

TABLE IV. Side Effects of Scopolamine by Various Routes.

Dose, mg	Route	Dizzy	Drowsy	Dry mouth	Headache
		%			
0	Oral	16.5	41.2	9.4	22.4
.65	"	23.5	47.1	12.9	16.5
.65	Sublingual	22.4	40.0	20.0*	18.8
.65	Intranasal	45.9†	69.4†	47.1†	8.2†

* P = .05. † P = .01.

dry mouth among those receiving scopolamine sublingually.

Discussion. It is apparent from these results that intranasal medication is feasible in the prevention and treatment of motion sickness. The rapid action of scopolamine by this route was the most striking feature. In the aircraft, vomiting was largely prevented despite the short period available for its action on an already nauseated individual. Since the drug was not given until 15-20 minutes after take-off and the test period was only 60 minutes, a maximum period of 40-45 minutes was available for absorption and action. As expected because of the short period allowed for absorption, scopolamine by mouth was completely ineffective. Ineffectiveness by sublingual route indicates that absorption here, too, is slower than from the nasal mucosa.

Administration as a spray would seem the simplest technic for intranasal instillation. The marked variation in the quantities nebulized, however, makes this procedure unreliable at present. Small, disposable spray bottles holding only a single dose would obviate this difficulty, if their production is feasible. For the present, nose drops, although slightly more difficult to administer are preferable since their dose can be more accurately controlled.

Summary. Scopolamine in small doses (0.3-0.4 mg) given intranasally by spray 30 minutes prior to exposure, exerted significant protection against swing sickness. During actual flight testing, addition of a surface active agent (sodium lauryl sulfate-Duponal C) increased its effectiveness. Nasal instillation to subjects 15-20 minutes after take-off sharply reduced the incidence of vomiting from airsickness during subsequent 40-45 minutes. Oral and sublingual administration under these conditions were ineffective. Considerable variations in the drug instilled resulted when given by spray. The use of nose drops allowed more accurate medication. The significance of this mode of administration for treating motion sickness is discussed.

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