# EFFECTS OF TWO ANTIHISTAMINE-CONTAINING COMPOUNDS UPON PERFORMANCE AT THREE ALTITUDES

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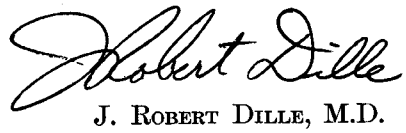

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## I. Introduction.

A number of antihistaminic compounds are available today for symptomatic treatment of common colds, hay fever, and allergies. Many of these can be obtained without prescription. Some of the antihistamines found in these compounds are known to have side-effects which might modify both psychomotor performance and physiological function.[1,2] Although these drugs may not impair performance while the individual using them is under no stress, the imposition of adverse environments may place the individual in a condition where decrements in both physiological function and psychomotor performance occur. It is the purpose of this study to test for synergistic effects of antihistamine-containing compounds and lowered atmospheric oxygen on psychomotor performance and physiological response.

## II. Methodology.

Forty-five healthy human male subjects (18 to 35 years old) were tested under nine experimental conditions (five subjects per condition), in combinations of three altitudes (ground level [1,274 ft.], 10,000 ft. and 14,000 ft.) and three drug compounds. Experiments were conducted with conditions presented in a random sequence.

Fasted subjects were examined by a medical monitor. Each subject was then trained on a modified Mashburn coordination task (Fig. 1). This task required repeated matchings of four banks of lights with four adjacent banks of lights. The controls for lighting the adjacent banks were manipulated by moving hand levers and foot pedals, with one bank each under the control of the right hand, the left hand, the right foot, and the left foot. Nine practice runs, each consisting of 28 sets of matchings, were completed to reduce learning effects. After training, each subject ingested two capsules of one of the compounds or the placebo. Compound A contained phenylephrine (5 mg.), phenindamine (10 mg.), aspirin (320 mg.), and caffeine (16 mg.). Compound B contained chlorpheniramine maleate (2 mg.), aspirin (390 mg.), and caffeine (30 mg.). Capsule C, the placebo, was filled with sucrose. The experimental phase was begun 1 hour after drug ingestion when the orally administered antihistamines reach peak blood levels. Neither the drug administered nor the chamber altitude was revealed to the subjects.

The experimental period consisted of 1 hour in an altitude chamber. After the prescribed altitude was attained, respiratory rate (RR) was measured with an impedance pneumograph across the chest connected to a low-level DC pre-amplifier; heart rate (HR) was measured with EKG leads to the EKG pre-amplifier; and rectal temperature ($T_r$) was measured by means of a thermistor probe inserted 10 centimeters beyond the anal sphincter with signals transferred through an appropriate bridge to a low-level DC pre-amplifier. All these responses were displayed on a Grass (Model 5C) polygraph. The oxygen saturation measurements were assessed with a Waters ear oximeter (Model XP–350) using the Waters earpiece (Model XE–350). All the above measurements were obtained each 10 minutes over the 1-hour period.

Venous blood samples were drawn immediately prior to ascent, at 25 to 28 minutes after ascent, and at the end of the experimental period prior to descent. From these samples determinations were made of blood pH and $Pco_2$[3] and plasma catecholamines.[4] Performance tests were conducted using the complex coordination task[5,6] immediately after each set of physiological measurements. Performance scores were the total time (in seconds) required to match preprogrammed 28 sets of lights.

## III. Results.

The data were treated by a three-way analysis

of variance for repeated measures.[7] The main effects were drug, altitude, and time. Student multiple-range tests were also employed to further test for differences.

*Respiratory Rate and Plasma Catecholamines*—These parameters showed no significant differences for main effects or interactions.

$P_{CO_2}$—This parameter showed a significant time effect (<.001 level) with $P_{CO_2}$ values decreasing through time. There was also a significant altitude-time interaction (<.001 level); the higher the altitude, the greater the decrease of $P_{CO_2}$ as a function of time.

*pH*—pH showed a significant increase with time (<.001 level). The altitude-time interaction was also significant (<.001 level); the higher the altitude, the greater the increase in pH with time.

*Heart Rate*—HR was significantly higher (<.05 level) at 14,000 feet than at the two lower altitudes. There was also a significant time effect (<.001 level) with HR increasing from the initial measurement through the successive measurement periods. Although the heart rates for drug A were higher than for drug B and placebo, statistical significance was not obtained.

*Oxygen Saturation*—This parameter was significantly different (<.001 level) for altitude effect; the lower the altitude the higher the $O_2$ saturation readings. There was also a significant time effect (<.01 level), the readings being lowest at 30 minutes and highest at the beginning and at the end of the experimental period. There was also a significant altitude-time interaction (<.001 level). The decline in oxygen saturation with time was greatest at 14,000 feet.

*Internal Temperature*—A significant altitude-time interaction (<.01 level) was obtained, with little change at ground level and an increase through time at the higher altitudes. Further, there was a significant drug-altitude interaction (<.05 level). Groups taking drugs A and B demonstrated an increase in $T_r$ with time, but the placebo groups demonstrated little change.

*Motor Coordination*—There was a significant time effect (<.001 level) with an improvement in performance scores through time. There was also a significant drug effect (<.10 level), when comparing drug B responses with placebo responses. Performance under drug B was poorer than under the placebo. Scores for those receiving drug A were also poorer than for those receiving the placebo, but not statistically so. Also, there was a significant altitude effect (<.05 level) with the performance scores lower for those at 14,000 feet than for those at ground level.

## IV. Discussion.

Where changes in catecholamines have been described with exposure to altitude,[8,9,10] the studies examined longer altitude exposures than those used here or involved acclimatization. There were no significant catecholamine responses seen for any effects in the short-term exposure used in this study.

Both blood pH and $P_{CO_2}$ showed significant changes with time (Fig. 2). These gave a consistent picture, indicating an increased hyperventilation; $P_{CO_2}$ decreased and pH increased with time. Although RR did not reflect hyperventilation, no assessments of minute-volume changes were made. The changes in pH and $P_{CO_2}$ were quite marked at 10,000 feet, and were even more produced at 14,000 feet. The data suggest that the effects would be even greater for higher altitudes. Von Muralt[11] states that one of the well-established facts of high altitude physiology is the development of acapnia leading to a respiratory alkalosis. This alkalosis, however, disappears with acclimatization.

There was a significant altitude effect for the $O_2$ saturation measurements (Fig. 3). This expected effect showed declines in oxygen saturation for each higher altitude. Oxygen saturation measurements with drug A compared to those with placebo demonstrated a drug effect (Fig. 4). Although no significant differences appeared at ground level, drug A responses declined less with exposure to the higher altitudes than did the responses with the placebo. Apparently drug A enhanced the oxygen saturation ability at these higher altitudes. It is possible that there was an increased cardiac output with drug A. The heart rate for drug A conditions was higher than the placebo conditions, although the differences were not statistically significant. There was also a significant change through time, with time period "30 minutes" showing the lowest $O_2$ saturation (Fig. 5). Satisfactory explanations for this finding are not presently apparent.

Our study shows no significant difference in $T_r$ due to altitude, although ground level read-

ings were slightly higher. Brendle[12] reports a lower $T_r$ at altitude. He attributed this effect, however, to a colder temperature at altitude and the fact that the subjects were well-insulated by protective clothing which prevented stimuli from skin receptors to increase heat production, while cooling was increased via the respiratory tract. However, Weihe[13] reports that body heat regulatory mechanisms are undisturbed at high altitudes. $T_r$ with placebo remained fairly constant throughout the experiments (Fig. 6). Both drug groups, however, showed an increase in $T_r$ through time which might be indicative of an increase in vasoconstriction, thereby conserving heat. Antihistamines have the ability to block the dilating action of histamine on vascular smooth muscle.[1] Initial $T_r$ readings for drug A subjects were higher, and for the drug B group were lower, than with the placebo, although compound B responses compared with placebo responses showed no significant effects. The cause for the higher readings for compound A could be due to increased metabolism or peripheral vasoconstriction greater than with placebo or compound B. The phenylephrine in compound A is an effective vasoconstrictor although its effects are transient unless the drug is repeatedly administered.[14] Phenindamine is known to increase metabolic rate in rats and to increase adrenaline responses in humans.[15] Although these measurements were not made, it appears to be consistent with the stimulatory effects of other parameters determined for compound A. Phenindamine in contradistinction to other antihistamines, which are sedatives, is an excitant to humans.[16]

On the performance test the total response with drug A was somewhat poorer than with the placebo, but not significantly so. Drug B, however, when compared with placebo produced significantly longer response-time scores (Fig. 7). The performance of subjects at higher altitudes was poorer than those at ground level, and the performance of those individuals using drug B was significantly poorer than the performance of those receiving the placebo. However, the decrement for the combined effects was greater than the sum of the decrement of the two (Fig. 7). There was, then, a synergistic effect, so that performance under both drug B and 14,000 foot altitude conditions was poorer than the sum of the two separate influences. Wagner,[17] in a study of the effects of 23 different antihistamines on performance, recommended that individuals taking pheniramine (a chemical compound closely related to chlorpheniramine found in drug B) should not drive a vehicle because of the impairment of performance caused by the drug. However, there were no objections to the use of phenindamine (found in drug A) in small doses since it did not show an impairment in performance. Although our study revealed no significant decrement of performance by those individuals who received the compound containing phenindamine, it did produce some undesirable side-effects. Three of the subjects who received compound A experienced a short-term loss of consciousness, and several others reported symptoms such as feeling "uneasy," "jumpy," or "jittery."

## V. Summary.

In a study of 45 human subjects it was determined that a compound drug containing the antihistamine phenindamine did not statistically impair performance on a modified Mashburn coordinator. Another compound, containing the antihistamine chlorpheniramine, did impair performance. Performance also was impaired by increasing altitudes. The combined effects of chlorpheniramine compound and increased altitude proved more detrimental to performance than the sum of the decrements that each influence caused when encountered separately. Although no performance change was demonstrated as a result of administering the phenindamine compound, undesirable side-effects were noted.

## BIBLIOGRAPHY


1. DiPalma, J. R., Ed.: *Drill's Pharmacology in Medicine*, pp. 763–782, McGraw-Hill, New York, 1965.
2. Modell, W., Ed.: *Drugs of Choice*, pp. 487–491, C. V. Mosley Co., St. Louis, 1966.
3. Gambino, S. R. and H. Schreiber: A Two Minute Assay Technique for pH and $Pco_2$ Utilizing an Ultramicro pH/$Pco_2$ Electrode. *Am. J. Clin. Path.*, 45(6): 772–774, 1966.
4. Fiorica, *V.*: An Improved Semi-Automated Procedure for Fluorometric Determination of Plasma Catecholamines. *Clin. Chem. Act.*, 12: 191–197, 1965.
5. Melton, A. W.: The Selection of Pilots by Means of Psychomotor Tests. *Aviation Med.*, 15: 116–123, 1944.
6. O'Connor, W. F., J. Scow and G. Pendergrass: Hypoxia and Performance Decrement. *OAM Report No. AM 66–15*, 1966.
7. Winer, B. J.: *Statistical Principles in Experimental Design.* McGraw-Hill, New York, 1962.
8. Cunningham, W. L., E. J. Becker, and F. Kreuzer: Catecholamines in Plasma and Urine at High Altitude. *J. Appl. Physiol.*, 20: 607–610, 1965.
9. Moncloa, F., M. Gomez and A. Hurtado: Plasma Catecholamines at High Altitude. *J. Appl. Physiol.*, 20: 1329–1331, 1965.
10. Ulvedal, F., W. R. Smith and B. E. Welch: Steroid and Catecholamine Studies on Pilots During Prolonged Experiments in a Space Cabin Simulator. *J. Appl. Physiol.*, 18: 1257–1263, 1963.
11. Von Muralt, A.: "Introduction" in *The Physiological Effects of High Altitude*, Edited by W. H. Weihe, p. xix, The MacMillan Co., New York, 1964.
12. Brendel, W.: Ampassung von Atmung, Hämoglobin, Körpertemperatur und Kreislauf bei langfristigem Aufenthalt in grossen Höhen (Himalaya). *Pflügers Archiv.*, 263: 227–252, 1956.
13. Weihe, W. H.: "Some Examples of Endocrine and Metabolic Functions in Rats During Acclimatization to High Altitude" in *The Physiological Effects of High Altitude*, Edited by W. H. Weihe, p. 35, The MacMillan Co., New York, 1964.
14. Grollman, A., Ed.: *Pharmacology and Therapeutics*, p. 425, Lea and Febiger, Philadelphia, 1962.
15. Kassila, O. J. and M. Paarsoren: Chlorprophenpyridamine and Phenindamine—Effect on Increased Oxygen Consumption Produced by Adrenaline. *Ann. Med. Exper. et Biol. Fenniae.*, 32: 230–234, 1954.
16. Cohen, M. B., H. B. Davies and W. A. Mowery: Thephorin in Allergy—A Study of 292 Cases. *Am. J. Med.*, 5: 44–47, 1948.
17. Wagner, H. J.: Review of Performance Under the Effects of Various Antihistamines. *Arzneimittelforschung*, 12: 1065–1070, 1962.

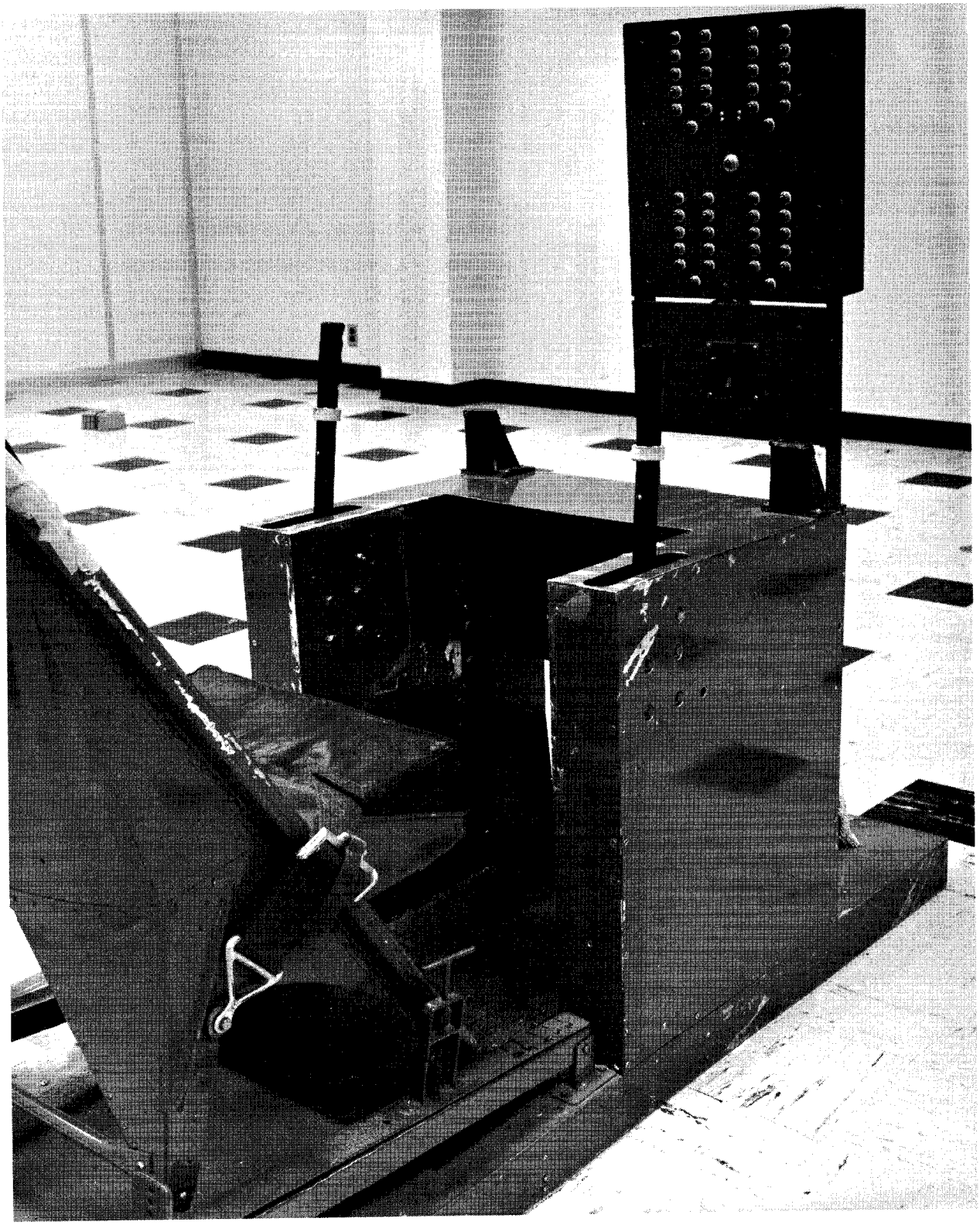

FIGURE 1. Modified Mashburn Coordinator.

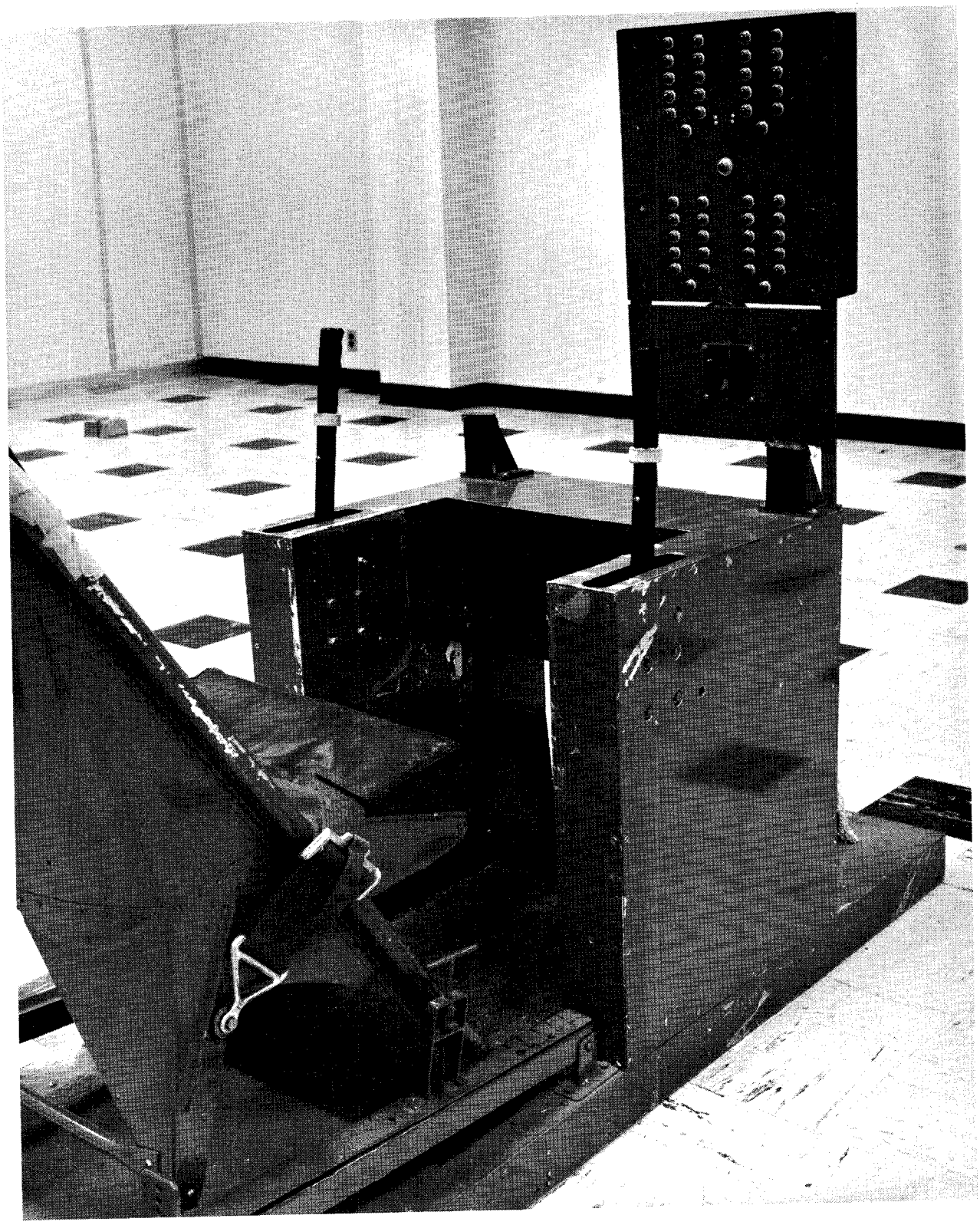

FIGURE 1. Modified Mashburn Coordinator.

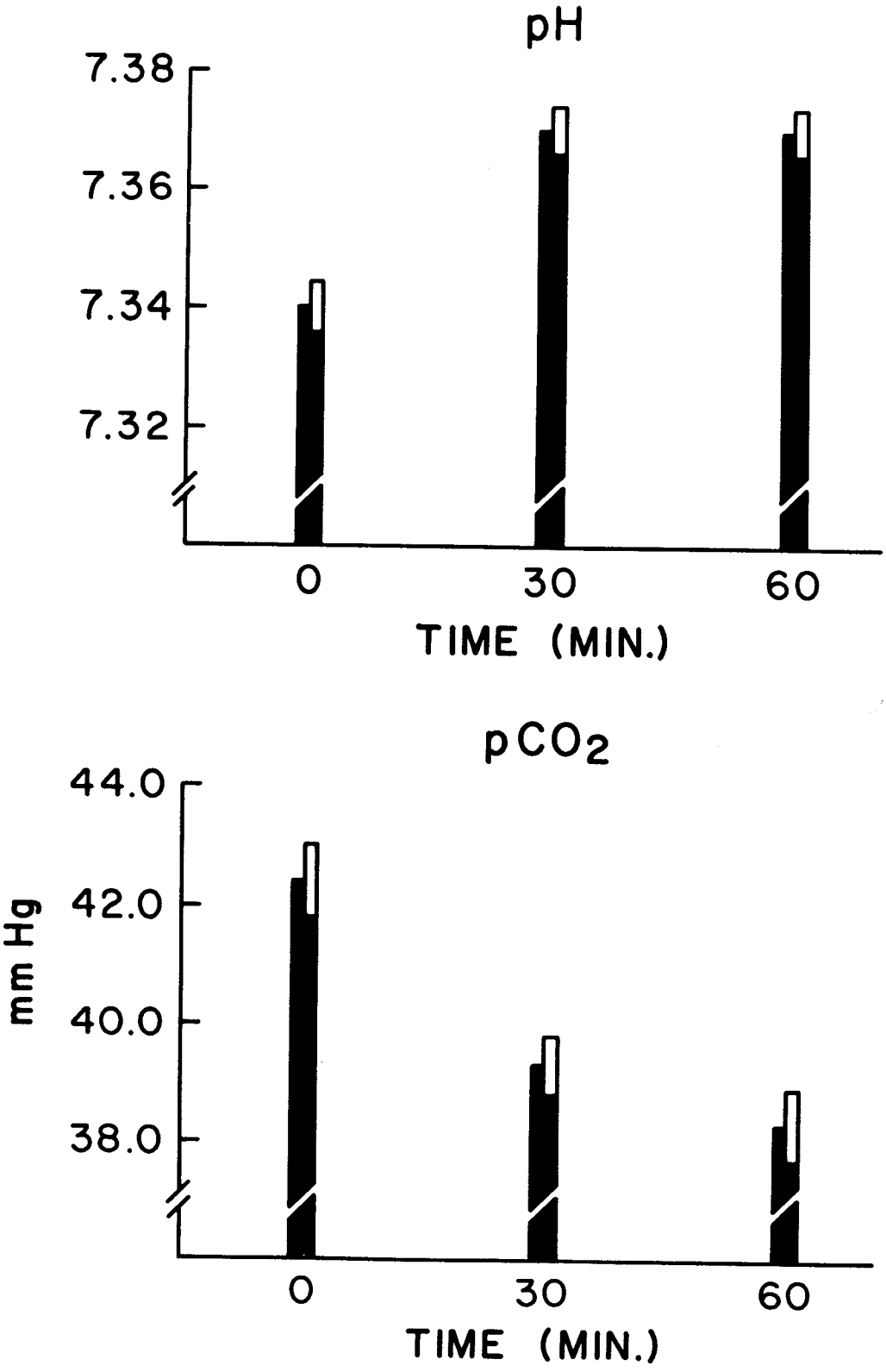


FIGURE 2. pH and $P_{CO_2}$ expressed as a function of time. Reported as means plus or minus standard error.

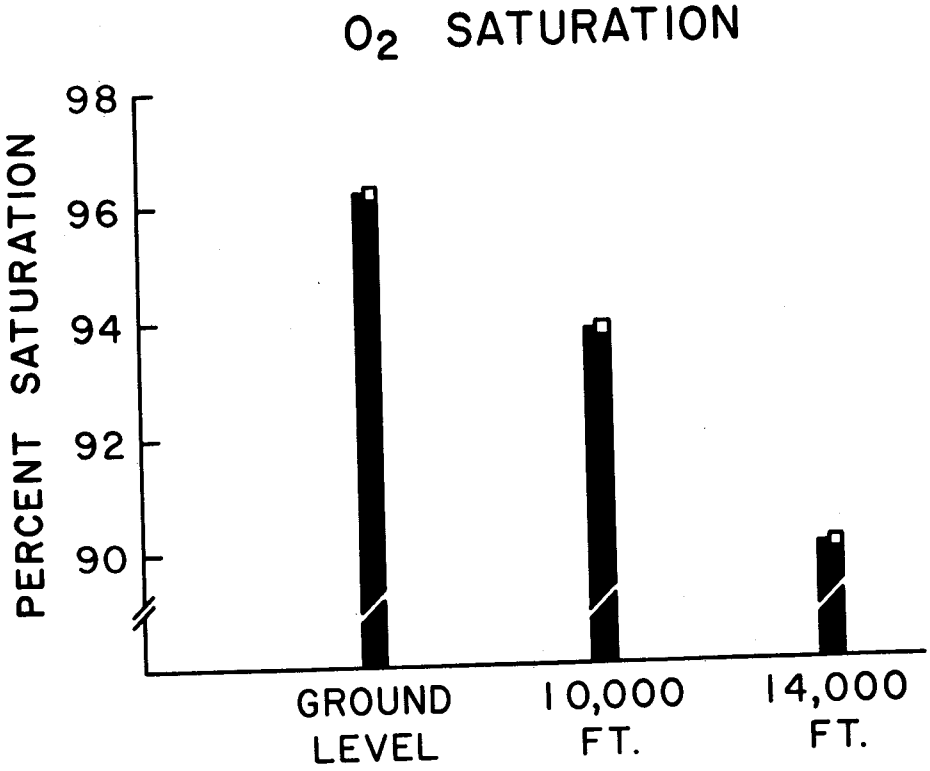


FIGURE 3. Oxygen saturation expressed as percentage saturation for three altitudes. Reported as means plus or minus standard error.

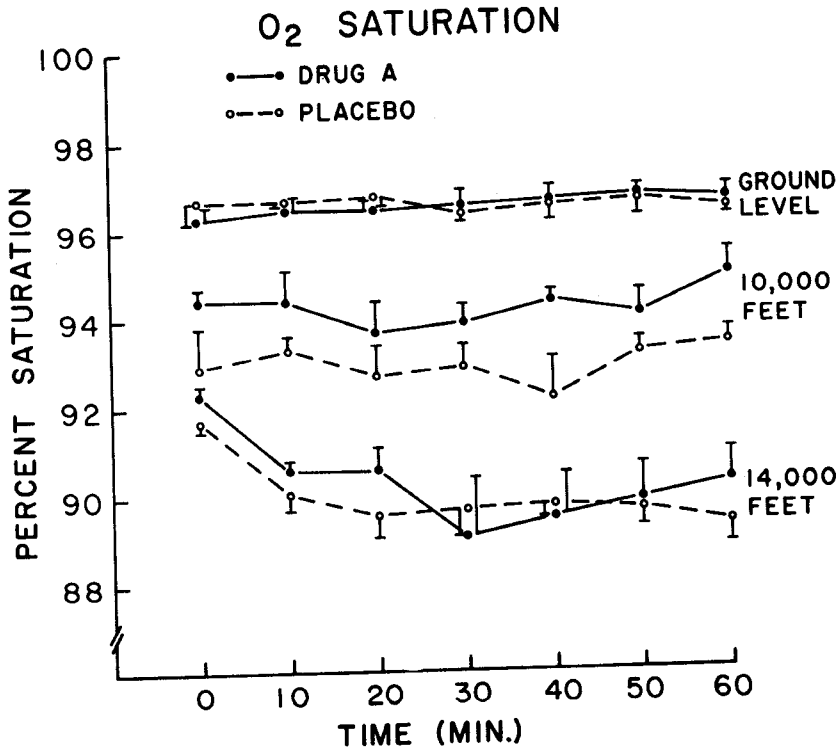


FIGURE 4. Oxygen saturation for drug A and placebo expressed as percentage saturation for three altitudes. Reported as means plus or minus standard error.

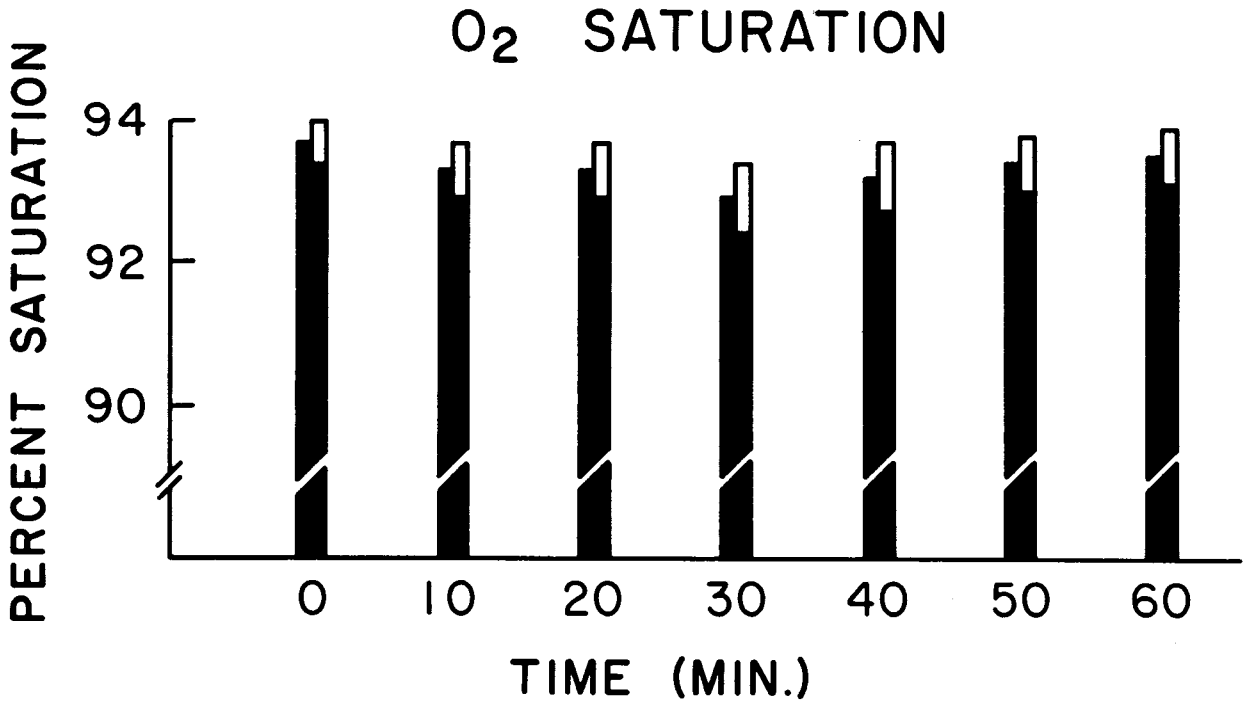


FIGURE 5. Oxygen saturation expressed as percentage saturation as a function of time. Reported as means plus or minus standard error.

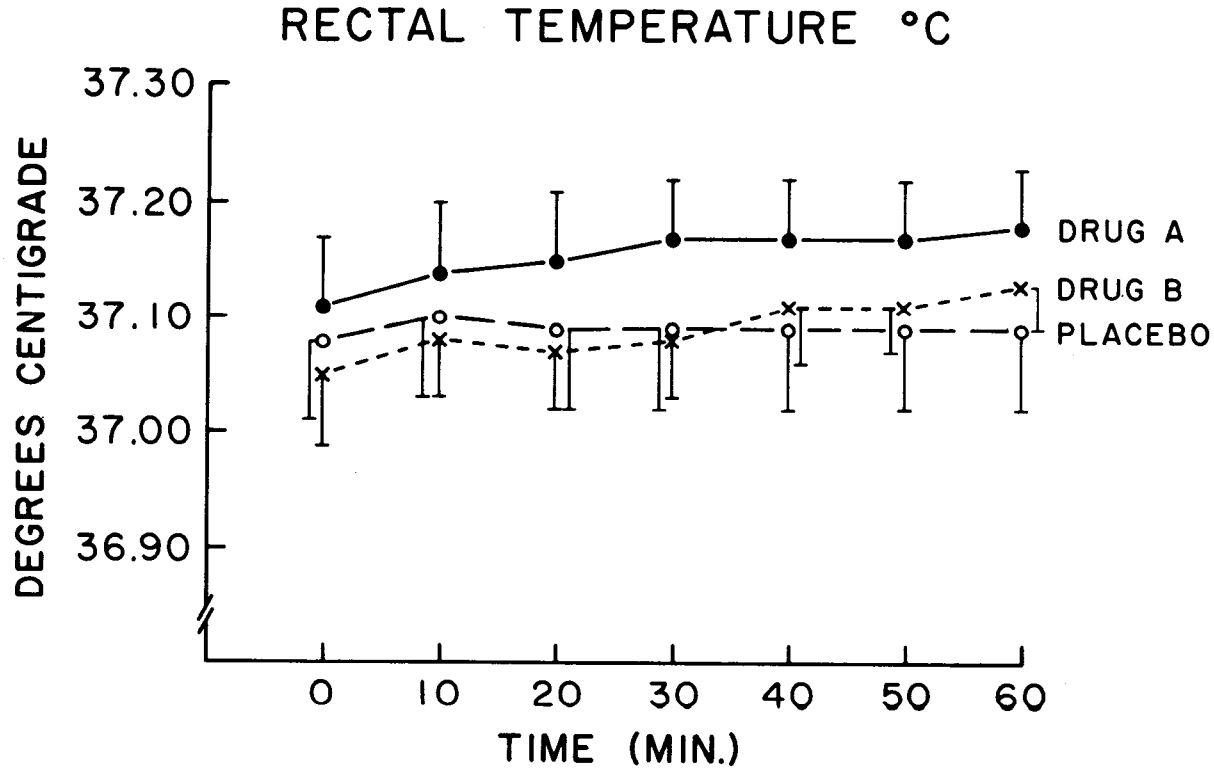


FIGURE 6. Rectal temperature in degrees Centigrade expressed as a function of time for the two drugs and placebo. Reported as means plus or minus standard error.

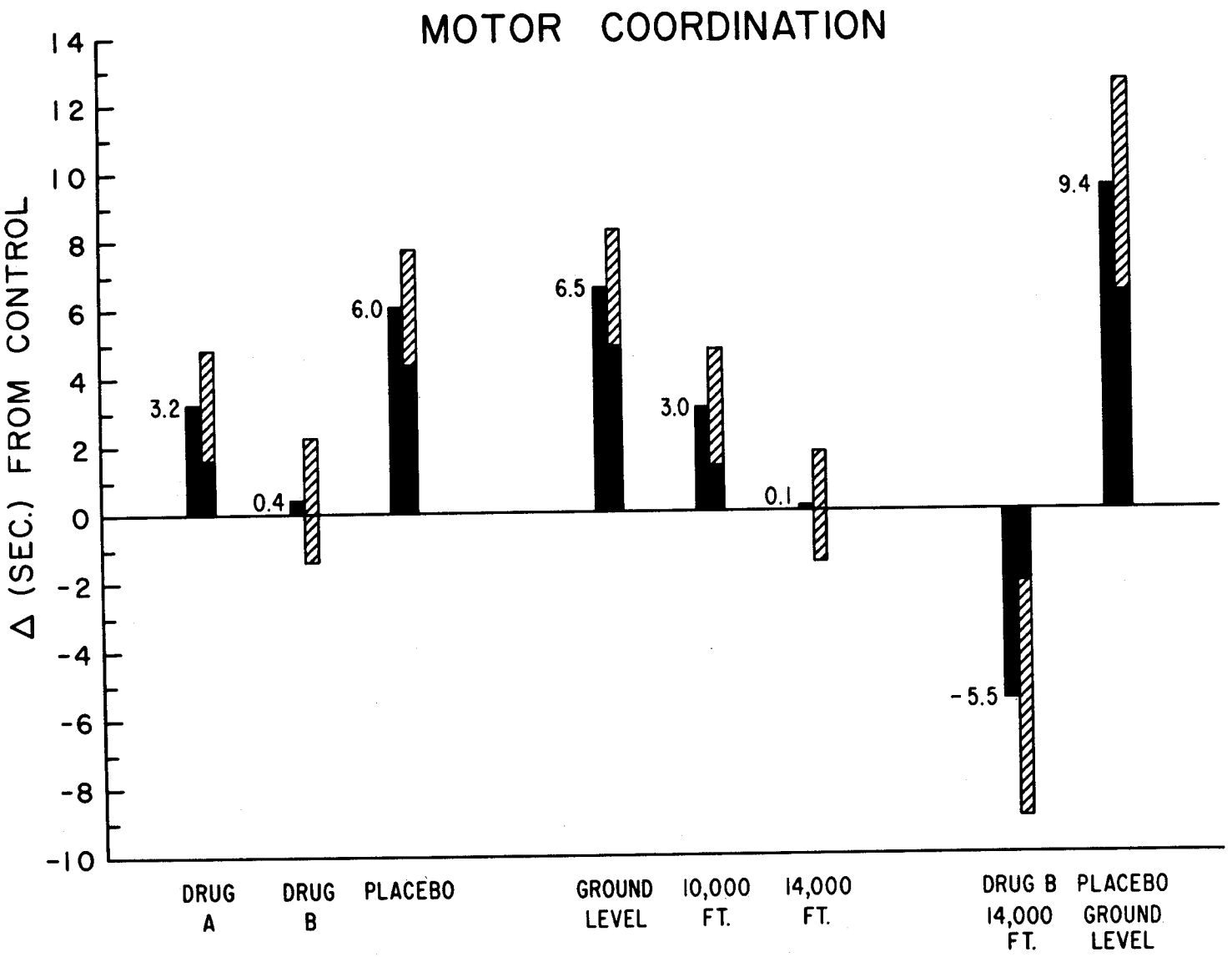


FIGURE 7. Performance scores (total time to complete task) expressed as the change in seconds from the control period for the two drugs and placebo, the three altitudes, and drug B at 14,000 feet and placebo at ground level. Reported as means plus or minus standard error.