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EFFECT OF DRUGS ON OCULAR COUNTERROLLING

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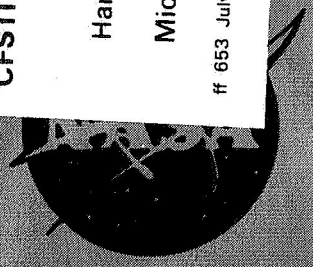

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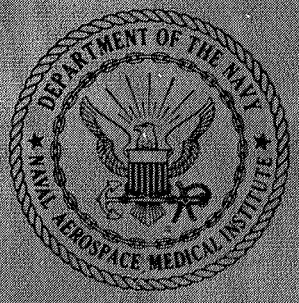

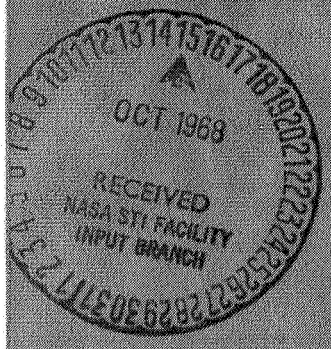

NAVAL AEROSPACE MEDICAL INSTITUTE

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

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EFFECT OF DRUGS ON OCULAR COUNTERROLLING*

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SUMMARY PAGE

THE PROBLEM

To determine the temporal effect of each of several selected drugs and a placebo upon ocular counterrolling, a specific indicator of otolith activity.

FINDINGS

Counterrolling under controlled conditions was measured before and at various times after the oral administration of the drug or placebo. A pool of nine normal subjects participated, and from four to six were used in each experimental trial. Alcohol, 1 cc/lb body weight, had a marked and progressive depressant effect on the amount of eye roll during the intoxication period; complete recovery was recorded six hours after its ingestion. Scopolamine, meclizine, acetylsalicylic acid, meprobamate, chlordiazepoxide hydrochloride, d-amphetamine, and diphenidol, given in twice the usually recommended doses, had little or no effect.

INTRODUCTION

The site of action of antimotion sickness drugs and others which affect responses subserved by the labyrinth is unknown or incompletely understood. Evidence has been introduced (1) which indicates that certain of these drugs may selectively affect the vestibular apparatus or its pathways while others appear to act indirectly through CNS mechanisms, e.g., to suppress the vegetative symptoms of motion sickness generated by vestibular stimulation. The effect of drugs upon labyrinthine activity has been studied by observation and measurement of nystagmic type eye movements in response to angular and linear accelerations (1-5) or of neurovegetative changes as indicated by motion sickness symptoms (6-9).

The purpose of the present study was to explore in a preliminary way the specific effect upon otolith activity of several drugs, including those which have been found to be effective in reducing motion sickness symptoms (7-9). Objective determination of otolith organ activity in man can be accomplished by the measurement of ocular counterrolling which has been well established as a specific indicator of otolith function when certain experimental procedures are followed (10, 11). Developments in technique (10,12) have greatly improved the accuracy of the measurements and have made the use of this reflex for studying the function of the otolith organs more practical.

A reflex change in ocular counterrolling normally correlates with a change in direction or magnitude of linear acceleration including gravity acting upon man (13,14). If the gravitoinertial stimulus is kept constant, such as was done in the present study by holding the subject in a given tilt position, the effect of factors other than this stimulus upon otolith activity can be studied. The parameter used in this investigation was acute alteration in the internal bodily environment as effected by drugs. A significant increase or decrease in ocular counterrolling which might occur following the administration of a specific drug and correlate with its known temporal mode of action would be evidence of the extent and type of effect upon the otolitho-ocular reflex arc. In selecting drugs for the present study, several categories were chosen, but emphasis was placed on those drugs which were known to influence general or specific response to vestibular stimulation (1,8,9).

PROCEDURE

SUBJECTS

The subjects were nine young healthy Navy men ranging in age from 18 to 20 years. Special tests of the labyrinthine organs made on each of these men had demonstrated that semicircular canal response as elicited by thermal stimulation (15) and otolith organ activity as determined by the standard test (12) of ocular counterrolling were within normal limits. Four of the subjects were tested with each of the drugs and the placebo used in this study, while the others, due primarily to military obligations, were unavailable for testing with the entire drug list shown in Table I.

Table I

Experimental Schedule Used for Investigating the Effect of the Oral Administration of Each of Several Drugs and a Placebo Upon Ocular Counterrolling Response

Drugs	Dosage*	Time of CR Test After Drug Admin. (in min.)	Subjects Receiving Drugs
Placebo (lactose), mg	750	60-180-240-300	BU, CH, HA, WI
Alcohol (vodka 80 proof), cc/lb	1	30-60-90-150-360	CH, HA, WH, WI
Scopolamine (Hyoscine), mg.....	1.2	30-60-420	BU, CH, HA, LA, WI
Chlordiazepoxide hydrochloride (Librium), mg.	50	4th day	CH, GL, LA, WH
Meprobamate (Miltown), mg.....	400	60-90-120-420	BU, CH, GL, HA, WI
Meclizine (Bonamine), mg.....	100	30-60-90-420	BU, CH, CO, HA, LA, WI
Acetylsalicylic Acid (aspirin), grains	25	30-60-120-360	BU, CH, HA, WH, WI
d-Amphetamine (Dexedrine), mg.....	20	30-60-90-420	BC, BU, CH, GL, HA, WI
Diphenidol (Vontrol), mg.....	100	60-90-120-420	BU, CH, HA, LA, WI

* Each subject listed for each drug received only one dosage except for that of chlordiazepoxide hydrochloride which was given to each of four subjects once for 3 consecutive days.

METHOD

Each subject was tested according to the standard method of measuring counter-rolling used in this laboratory, which involves photographically recording the natural iris landmarks of a subject positioned upright, and tilted laterally to one of four positions: ±25 degrees and ±50 degrees. The subject's eye when properly fixating the center of a ring of light was photographed as a rule six times at each of the five body positions. The counterrolling tilt apparatus and specific procedures for its use have been described in detail in other communications (10, 12). Three standard tests were made prior to the day on which the experimental trials began to provide baseline counterrolling data for comparison with the results obtained at the time of testing when the subject was under the influence of a drug. Table I lists the particular subjects tested with each of the drugs (including a placebo), the drug dosage, and the times at which the standard counterrolling test was started following oral administration of the drug.

Alcohol (80 proof vodka) was administered in the proportion of 1 cc/lb body weight; in all other drugs the dosage was twice that usually recommended. When it could be determined from standard pharmacological manuals, the absorption and excretion or destruction rates of a given drug formed the general basis for the test schedule. A period of at least thirty minutes separated test sessions to allow adequate time for conducting the ocular counterrolling test as well as for resting the subject.

Immediately prior to administration of the drug and also at the time of predicted termination of its effect (shown in Table I), the subject was tested twice in succession by the standard counterrolling method; during interim times, only one such test was given. The subject was removed from the tilt device and allowed to rest following each of the single or double counterrolling tests of a given time period. This general procedure was followed for the placebo and all drugs except in the case of the drug chlordiazepoxide hydrochloride which was administered on three consecutive days to take advantage of its cumulative action and several standard counterrolling tests were made on the fourth day without regard to time.

On the day of the drug or placebo test, the subject did not eat breakfast but was fed approximately two hours after administration of the drug. A period of from 48 to 72 hours elapsed between drug tests for any one subject.

RESULTS

The mean counterrolling values of the nine subjects which were determined for upright and the four body tilt positions (±25°, ±50°) in the baseline test series are portrayed in Figure 1.* By definition, the mean value obtained with the subject in

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*In order not to break the continuity of the report, all figures appear after the text.

the upright position represents zero counterrolling as shown in this figure. Each subject exhibited substantial counterrolling relative to his basic eye position, a valid indication that he had normal otolith organ function. The subject's over-all response patterns were qualitatively and in most cases quantitatively similar to each other and to those of previously tested subjects (11).

In an attempt to present the counterrolling data of this study in a more graphic form than the one depicted in Figure 1 and one which would allow ready visual comparisons among the results, measurements at each of the two magnitudes of tilt (25° and 50°) were averaged without respect to the clockwise (+) or counterclockwise (-) direction (or algebraic sign) of the counterrolling response. This data reduction procedure also decreases the amount of artifact introduced by spontaneous physiological changes in eye roll position, changes which are frequently found among successive recordings of counterrolling in the same subject as well as between tests conducted under apparently identical experimental conditions. Although such variations in roll position of the eye for a given angle of body tilt usually are small, amounting only to several minutes of arc, they occasionally may exceed one or two degrees. The influence of these physiological changes in counterrolling upon the results of the present study is by no means eliminated by averaging the measurements, since substantial variance is still quite evident among the composite results of the placebo trials of four subjects (Figure 2) and certain of the baseline and predrug trials (Figures 3-10). Each curve shown in Figures 2 through 10 is derived from the measurement of several hundred photographic recordings and represents the mean counterrolling data of four to six subjects tilted 25 and 50 degrees. Shown are the data collected in the baseline tests, and in those tests conducted just prior to and following the administration of each drug.

For technical reasons the counterrolling recordings of one baseline trial of certain subjects were unusable; this accounts for the fact that for the placebo, d-amphetamine, and diphenidol (Figures 2, 9, 10), only two baseline trials are plotted. Where there are differences in magnitude of counterrolling, the predrug trial data probably serve better than the baseline values obtained days and weeks in advance as a standard against which postdrug values may be compared. Spontaneous day-to-day variability of other compensatory eye movements have been reported and recognized as a complication in the demonstration of a pharmacological effect (1).

DISCUSSION

In interpreting the results, it was necessary to differentiate between a measured change in ocular counterrolling which was the result of the experimental variable, in this case drug action, and the change due to spontaneous variability or "noise" of the system caused by many other factors which contribute to the tonicity of the extraocular muscles. Differentiation was made possible by imposing three main requirements that had to be satisfied before a change in magnitude of counterrolling was accepted as a specific indication of drug action upon this reflex mechanism: 1) the magnitude of the change had to differ significantly from that found in the predrug test made on the same day, 2) the response had to correlate in some fashion with the known temporal aspects

of drug effectivity, and 3) the responses for the 25- and 50-degree body tilts had to be essentially in parallel.

Physiological variability of counterrolling, as of other biological system responses, occurs at random, under a given set of conditions, and within certain limits. This fact and the fact that the three requirements set forth above were not met are illustrated by the experimental trials in which a placebo was substituted for a drug (Figure 2). Among the five placebo-test sessions distributed similarly in time to the test schedules of the various drugs, the amount of counterrolling tended to rise and fall several minutes of arc at random. The average deviation of the response for 25- and 50-degree body tilts equalled 18 and 9 minutes of arc, respectively. No longitudinal trend with regard to change in counterrolling or correspondence between the 25- and 50-degree body tilt values was apparent.

Similarly, for several of the drugs used, namely, scopolamine, chlordiazepoxide hydrochloride, meprobamate, meclizine, d-amphetamine, and acetylsalicylic acid, no clear-cut effect upon the average counterrolling response was found. Further study is required to determine why meclizine, although structurally related to Cinnarazine, had no depressant effect upon the otoliths, as has been reported for the latter drug (1,4). It would seem that these particular drugs in this study were not specific for the otolitho-ocular system, and the well-recognized beneficial effects against motion sickness provided by scopolamine and meclizine cannot be attributed to any direct action upon the otolithic receptor organs or nervous pathways leading ultimately to the extraocular muscles. Jongkees and Philipszoon have reported that scopolamine had no effect on otolithic type compensatory eye movements of rabbits (1).

In the case of the antihistamine-type drug diphenidol, a small but definite decrease in counterrolling was recorded one hour after the drug was taken (Figure 10). Within the next hour the magnitude of the response at 50-degree tilt had returned to, and at 25-degree tilt was slightly higher than, the baseline values. The final measurements were essentially the same as those of the predrug trials.

Among all drugs tested in this study, alcohol had the most marked effect upon counterrolling. It can be seen from Figure 3 that a progressive and rather rapid fall in counterrolling was measured in all subjects at both angles of tilt after they ingested alcohol. The lowest level was reached at about 90 minutes into the intoxication period. This rather rapid reduction in the magnitude of counterrolling was followed by a slower return to base level and perhaps slightly above it after about six hours. It is interesting to note that this sequence is not unlike the characteristic temporal changes in blood alcohol concentrations (16) as well as the concomitant manifestation of positional alcohol nystagmus (PAN, phase 1) (16) and ataxia (17), although no direct comparisons with these factors can be made since they were not tested concurrently.

Alcohol, by some unknown mechanism, acts to release positional nystagmus, and from the evidence of this study also suppresses otolith organ activity. Whether or not these findings are physiologically related must await further investigation. From the

substantial evidence that otolith organs play a predominate role in PAN (16, 18), the possibility exists that a change in the modulating influence of the otolith organs may be involved.

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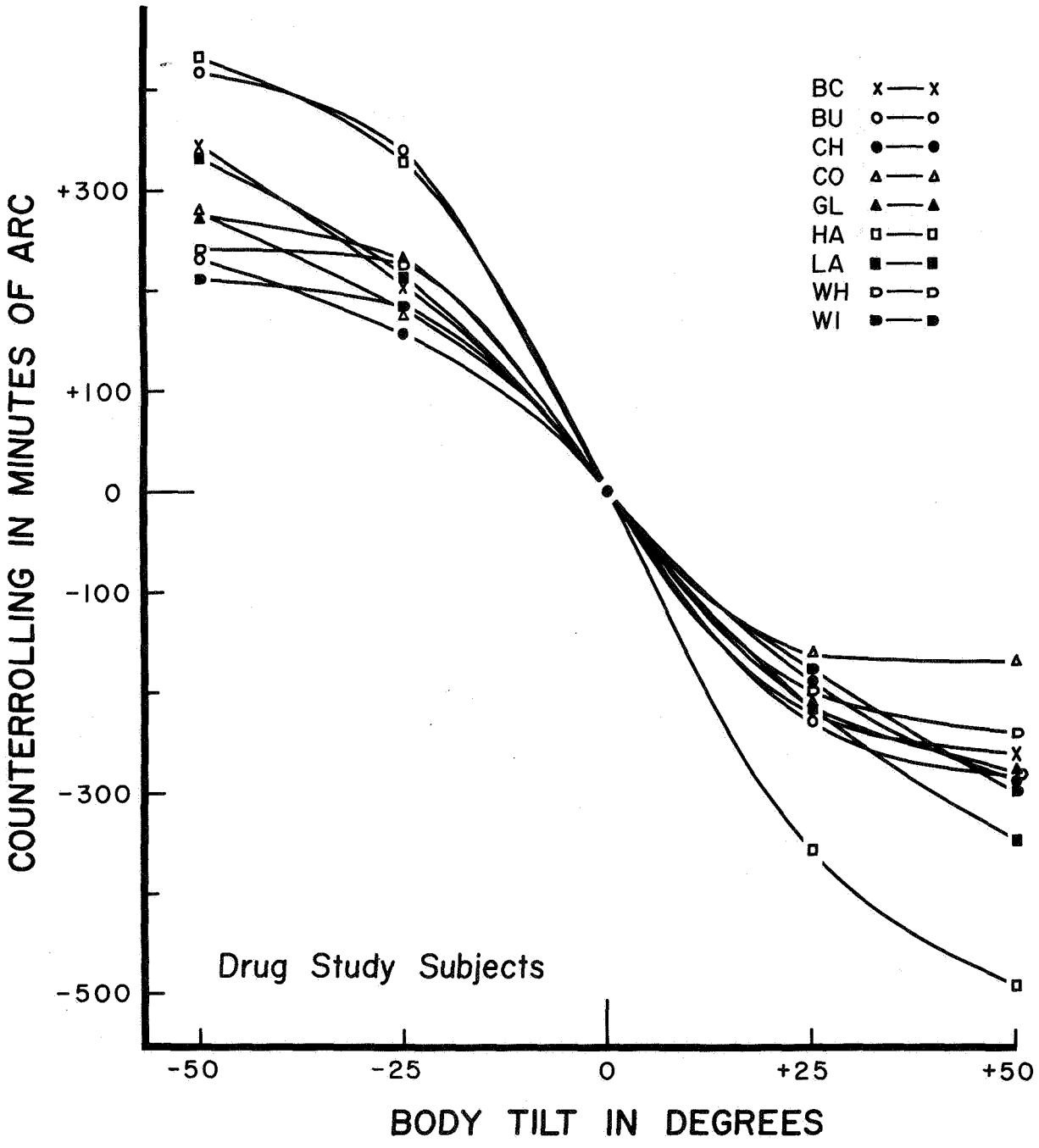

Figure 1

Baseline Mean Counterrolling Response of Each of the Nine Subjects

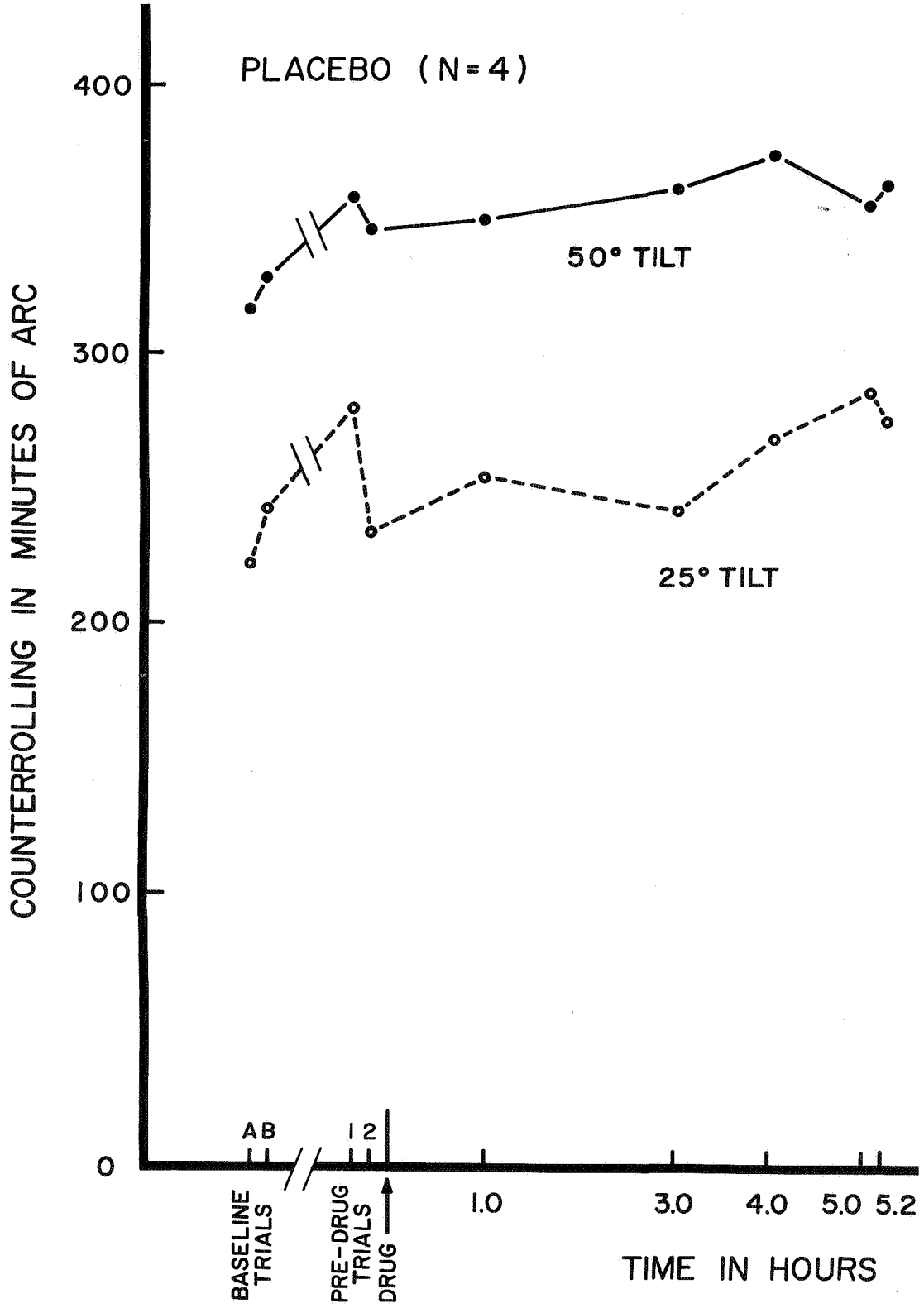

Figure 2

Effect of a Placebo Upon Ocular Counterrolling Response of Four of the Subjects

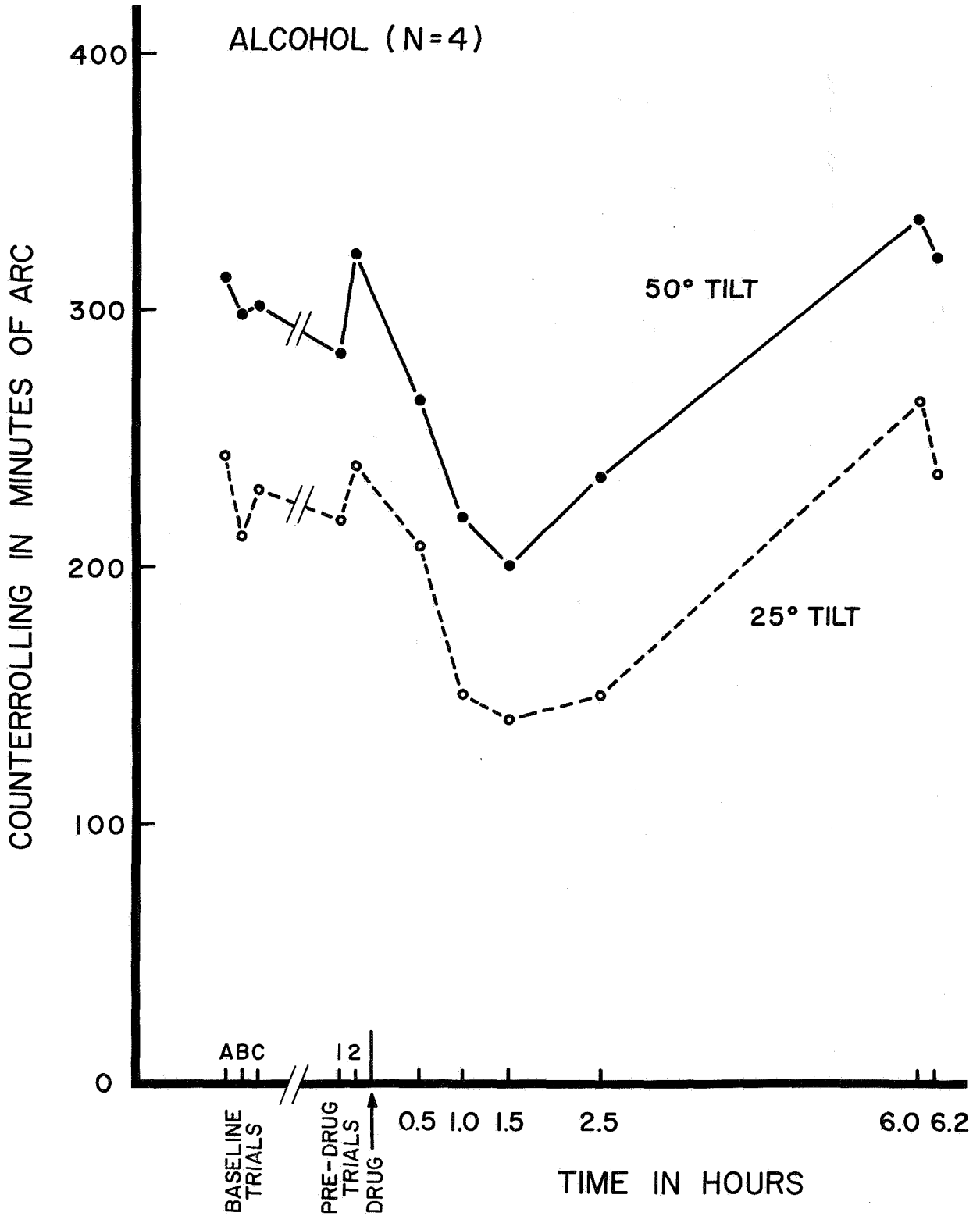

Figure 3

Effect of Alcohol Upon Ocular Counterrolling Response of Four of the Subjects

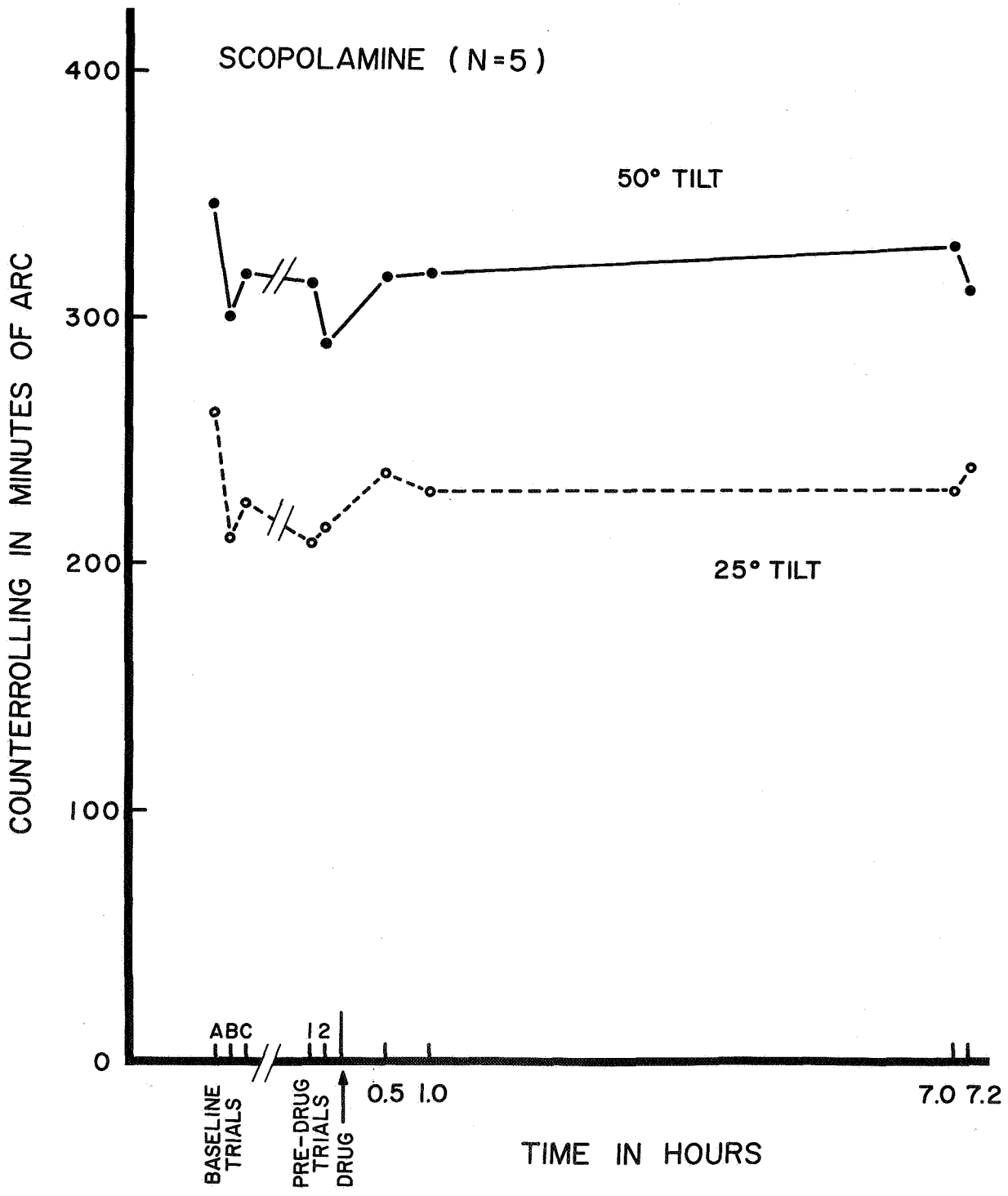

Figure 4

Effect of Scopolamine Upon Ocular Counterrolling Response of Five of the Subjects

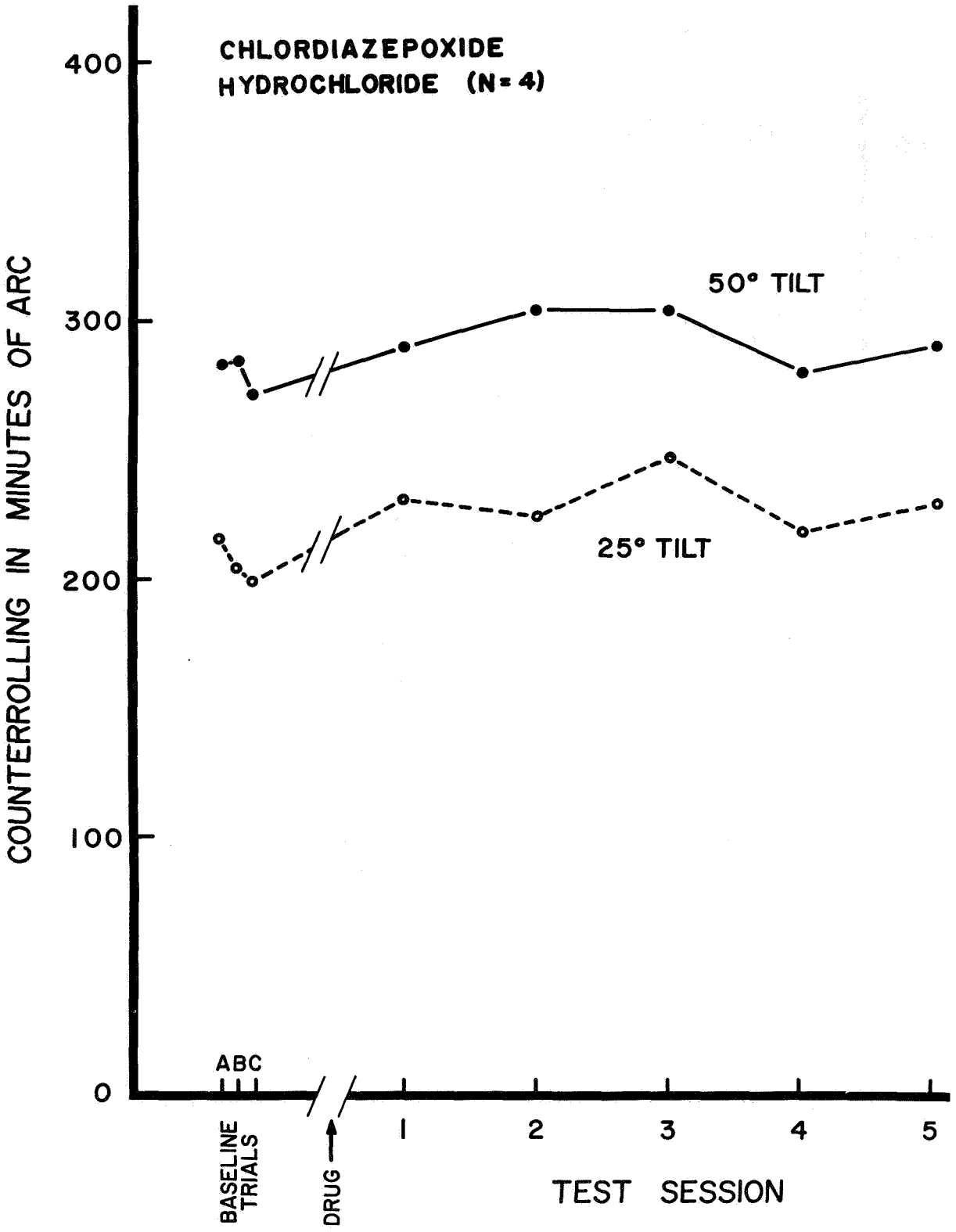

Figure 5

Effect of Chlordiazepoxide Hydrochloride Upon Ocular Counterrolling Response of Four of the Subjects

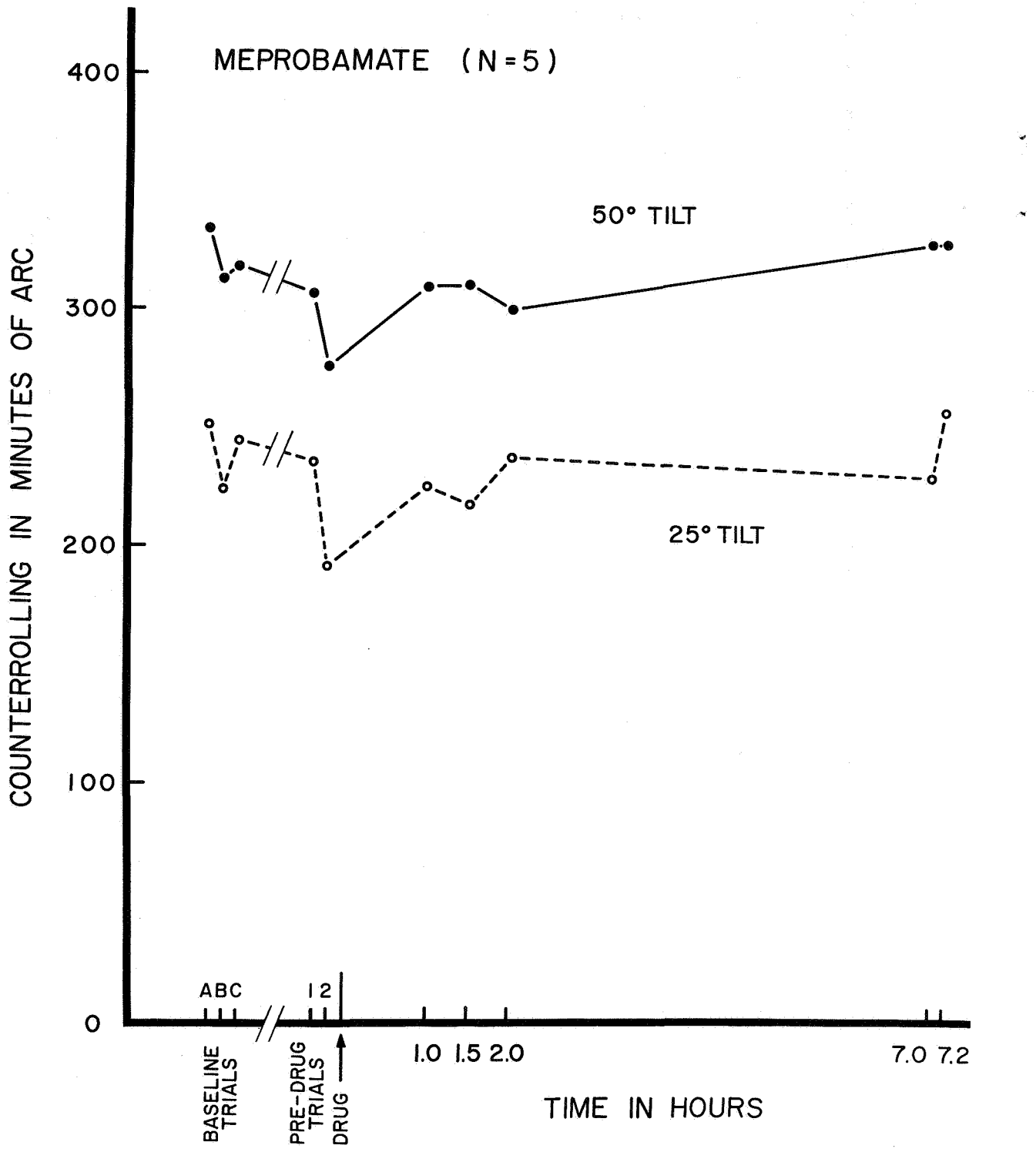

Figure 6

Effect of Meprobamate Upon Ocular Counterrolling Response of Five of the Subjects

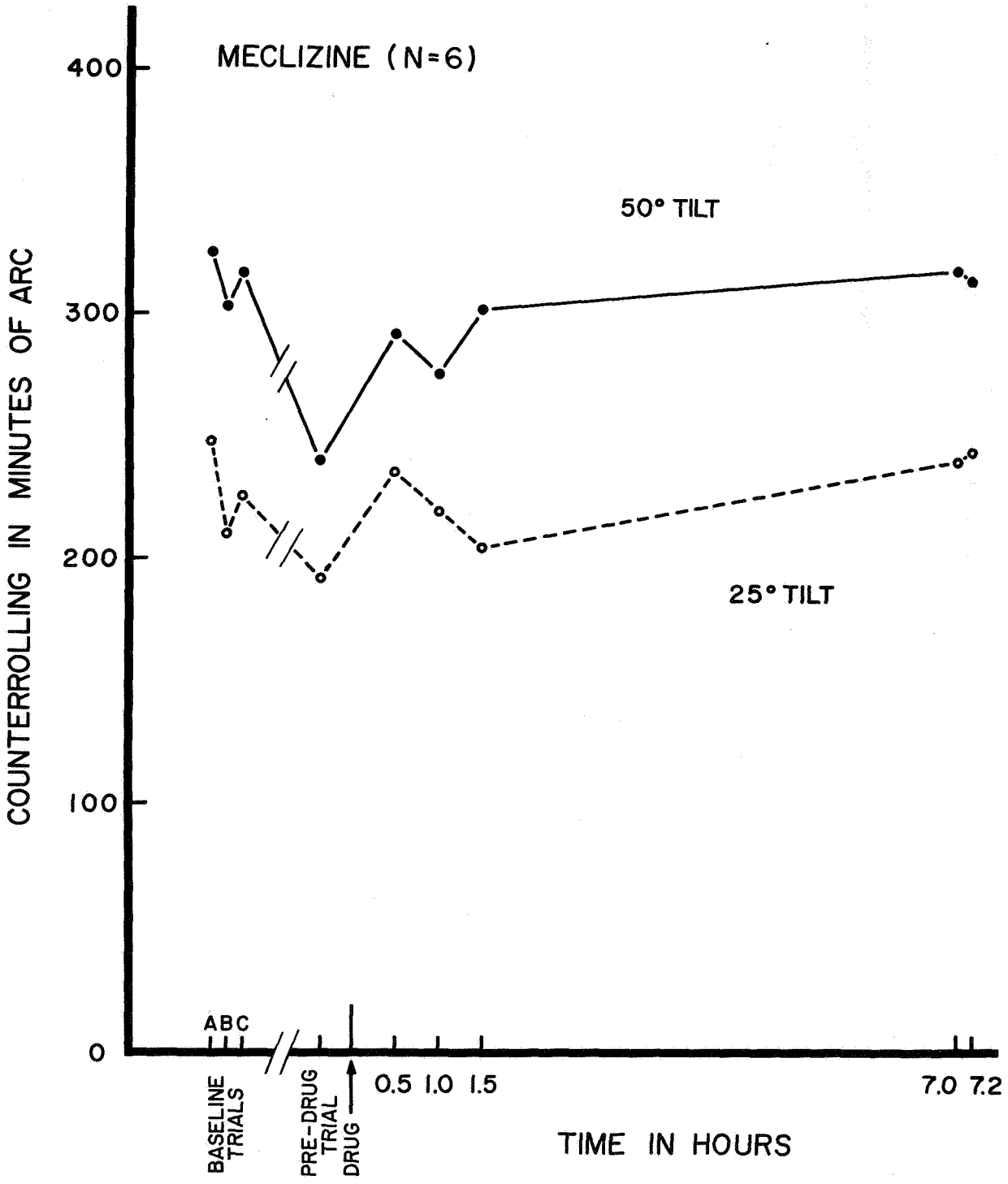

Figure 7

Effect of Meclizine Upon Ocular Counterrolling Response of Six of the Subjects

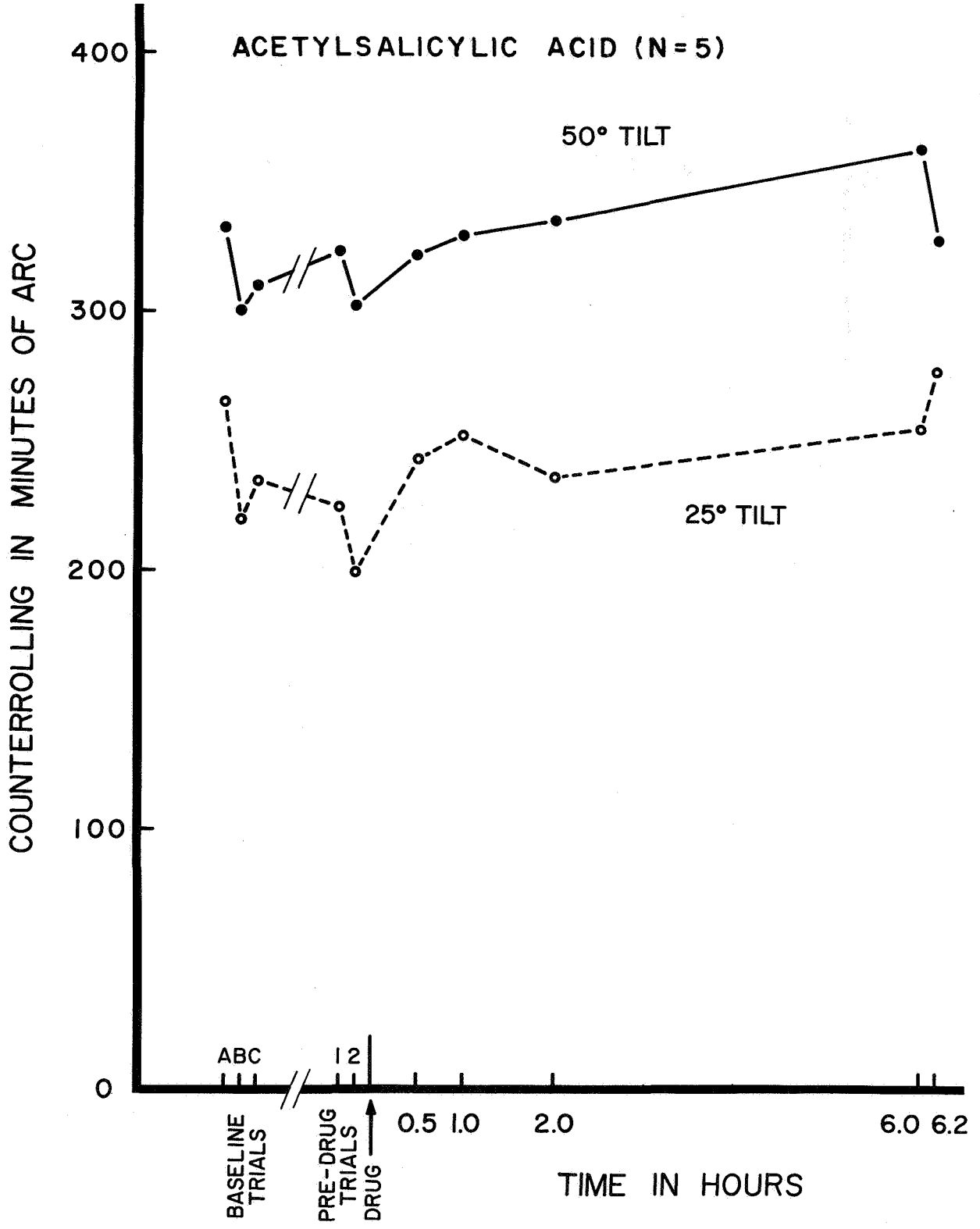

Figure 8

Effect of Acetylsalicylic Acid Upon Ocular Counter-rolling Response of Five of the Subjects

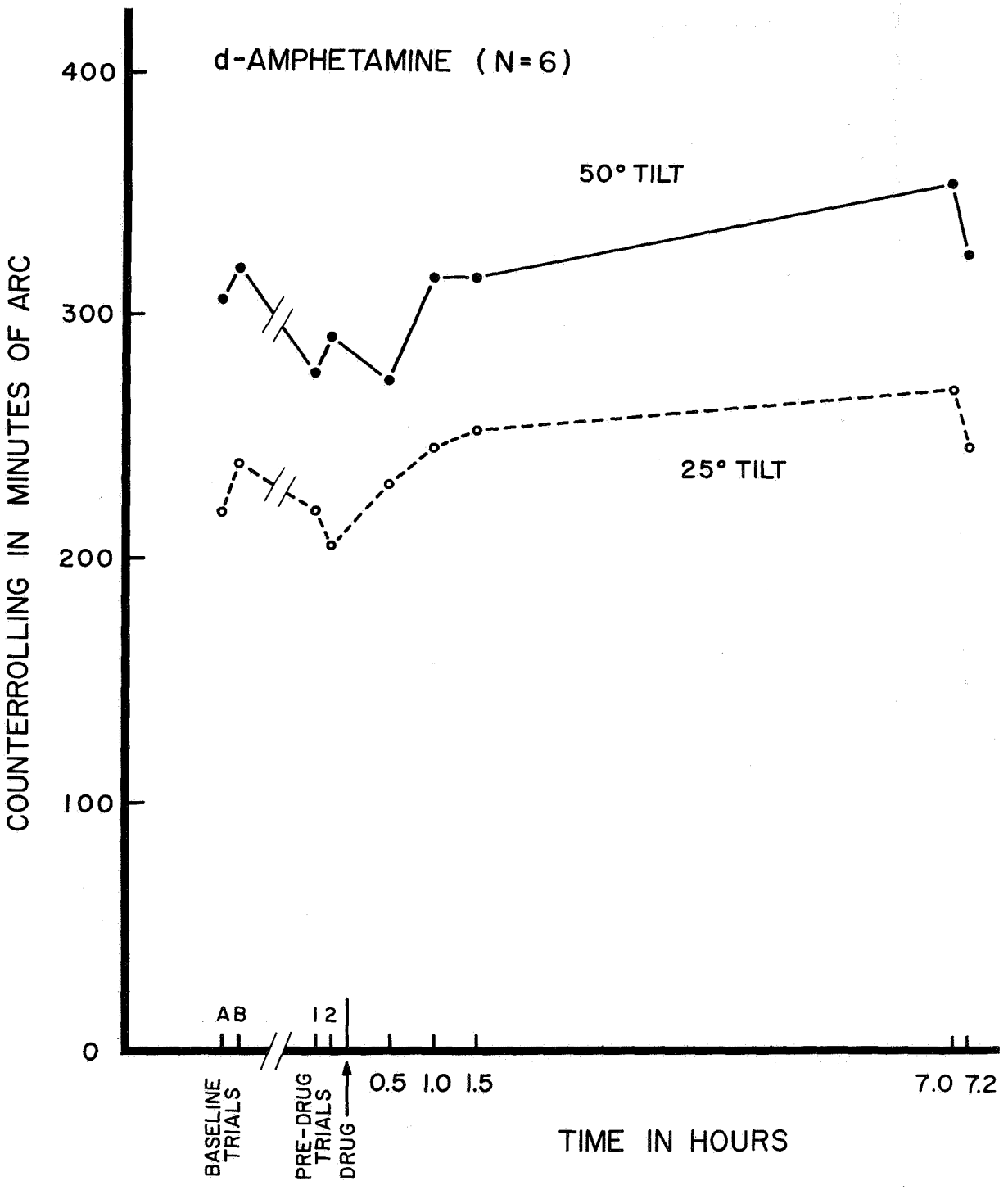

Figure 9

Effect of d-Amphetamine Upon Ocular Counter-rolling Response of Six of the Subjects

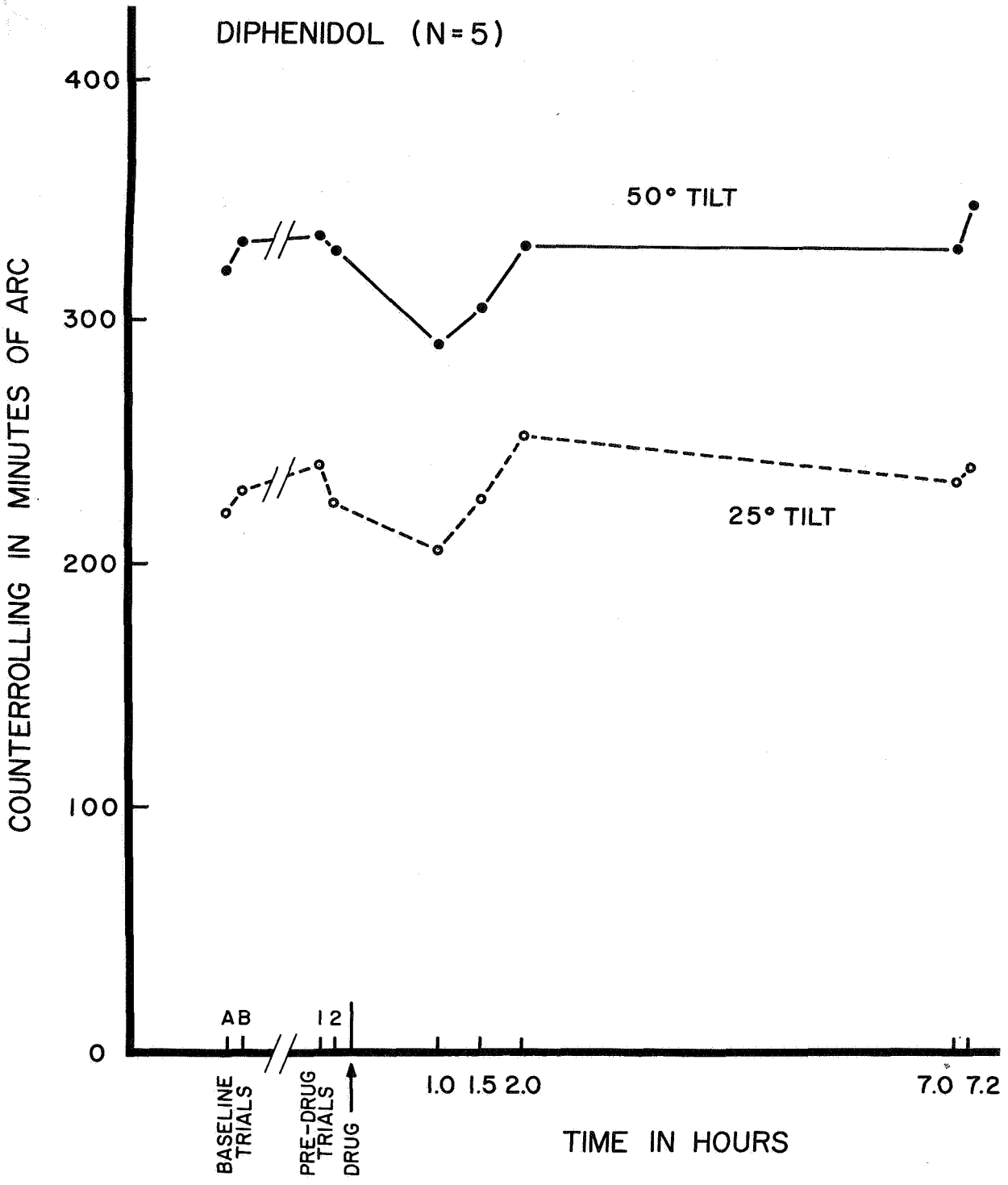

Figure 10

Effect of Diphenidol Upon Ocular Counterrolling Response of Five of the Subjects

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13. ABSTRACT

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
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Motion Sickness						
Counterrolling						
Drugs						
Eye movement						
Otolith apparatus						
Vestibular function						