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**ASSESSMENT OF NEUROLOGICAL EFFECTS OF DRUGS
ON OCULOMOTOR AND VISUAL FUNCTION IN THE PRIMATE**

Annual Report

E. Gregory Keating, Ph.D.

December 15, 1983

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20. Continued

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The eye movements of cynomolgous monkeys (Macaca fascicularis) were recorded with the magnetic search coil technique while they searched for camouflaged targets or tracked moving targets. A preliminary analysis was completed of the effects of atropine on performance of the Visual Search and Target Tracking test as well as on the effects on the Visual Search test of atropine/pralidoxime and pyridostigmine. (A. J. ...)

Atropine at all levels tested (.014 - .25 mg/K) caused mydriasis and some drift in eye fixations. Performance on visual search and tracking of targets was consistently disrupted only at the highest dose. The decrements in search were not drastic but atropine more substantially interfered with the gain, phase and continuity of tracking eye movements.

Atropine/pralidoxime (.014/1.0 - .25/8.0 mg/K) caused mydriasis, excessive eye blinks, some drift in fixations but had little effect on performance of visual search.

Pyridostigmine (14 mg/K daily for 2 weeks, orally) had no detectable effect on the monkey's neurological status or its performance of visual search.

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Summary

A number of cholinergic agents are deemed useful as prophylactics or antidotes to organophosphate poisoning yet have their own toxic effects. Dosages of these agents which are known to not grossly disrupt behavior may nonetheless degrade performance of sophisticated tasks required of the personnel of a modern mechanized army.

The contract uses an animal model (primate) to assess the effects of cholinergic drugs on the performance of visual search and tracking tasks which mimic skills generally used in the field.

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Foreword

In conducting the research described in this report, the investigator adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978.

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Methods of Research

The following annual progress report is submitted in compliance with the terms of our contract "Assessment of Neurological Effects of Drugs on Oculomotor and Visual Function in the Primate." The report covers data collected during the second year of the contract from August, 1982, through September, 1983.

The purpose of the contract is to develop an animal model (primate) for visual search and target tracking performance so as to assess the behavioral effects of cholinergic drugs (e.g., atropine, 2-PAM Cl, physostigmine, pyridostigmine). Two tasks have been developed to mimic the visual search and tracking skills required of military personnel in the field. A search task requires the monkey to find and fixate a target spot embedded in a field of distractors. A second tracking task requires the monkey to track and predict the trajectory of a moving target. We use the magnetic search coil technique to record their eye movements during the tasks. The data provide indices of basic visual and oculomotor competence as well as measures of more cerebral or attentional decrements caused by cholinergic agents.

During the past year, drug trials with the visual search test continued with cynomolgus monkeys (Macaca fascicularis). The schedule of drug trials completed up the end of the report period is shown in Table 1.

Table 1

VISUAL SEARCH TEST

Pralidoxime (A = 1; B = 2; C = 4; D = Saline; E = 8; F = 16 mg/K)

Subject 1	B D C C C B D D A E E A* A
Subject 2	D C C E E B D A B* A B
Subject 3	A* A D B D B C E C E F F
Subject 4	C* A D B C A E B E D F F

Physostigmine (A = .025; B = .050; C = .075 mg/K)

Subject 1 D A B B A D C C
Subject 2 B D B C D A C A
Subject 3 D C B A A D C B* B
Subject 5 D D C C* A A B B

Atropine (A = .014; B = .045; C = .14; D = Saline; E = .25 mg/K)

Subject 1 D C A E D E C B B A
Subject 2 C C B A E B E A D D
Subject 3 E A C D A C B E B B
Subject 6 D D C A E A B E B C

Atropine-Pralidoxime (combination of doses shown above for individual drugs)

Subject 1 A D E A B C E B C D
Subject 2 D B E C B D A E A C
Subject 3 D D C A E A* B E B C

Pyridostigmine (7 mg/K twice daily for 14 days)

Subject 1 Completed trial
Subject 2 Completed trial
Subject 3 Completed trial

TARGET TRACKING TEST

Atropine (A = .014; B = .045; C = .14; D = Saline; E = .25 mg/K)

Subject 1 C E A E A B C D B
Subject 2 E C B A A C D B
Subject 3 A B
Subject 6 D E C C A B

*Technical imperfections invalidate data.

Results on the effects of pralidoxime and physostigmine on Visual Search have been presented previously (cf. first annual report). The present report provides a preliminary analysis of the effects of atropine on both the Visual Search and the Target Tracking test and the results on the Visual Search test from the atropine-pralidoxime and pyridostigmine trials. The report includes for each of these drugs a summary of any observed neurological effects, description of oculomotor changes as characterized by unanalyzed strip-chart recordings of the eye movement traces, and finally, graphs of performance on the Visual Search and Tracking tests. Performance on these tests is expressed as "Z scores" in which the monkeys' behavior under the influence of the drug is normalized to the mean and variation of its baseline behavior. Specifically, $Z = \frac{X_D - M_B}{\sigma_B}$, where

σ_B

X_D = average performance over the trials of Visual Search or Target Tracking on the day of the drug

M_B = mean performance over all blocks of trials on the baseline days (20-30 days of testing)

σ_B = standard deviation of the baseline blocks

Data were collected during an Early (15-25 minutes; Atropine = 45-65 minutes) and a Late (40-50 minutes; Atropine = 65-85 minutes) session after drug administration. Under the assumption that the "Z scores" distribute normally, performance within $Z < \pm 1.96$ is considered to represent the limits of normal behavior. In practice, our previous experience with this measure and the Visual Search test is that reliable drug decrements are signalled by Z scores falling well outside their limits.

Visual Search: Graphs show the results for 3 measures: percent of trials on which the monkey successfully fixated the target and, on successful trials, the time and the number of fixations needed to find (fixate) the target.

Target Tracking: The graphs plot over time the positions of the target and the monkey's gaze. Targets moved horizontally and we collected only the horizontal eye movement made in response. A good informal idea of tracking performance can be gleaned from examining by eye the degree of fit between eye and target position traces. We've developed three measures to characterize performance more formally. Target and eye position signals were sampled every 3 msec., digitized, then differentiated into velocity traces. Failure to track a target with smooth pursuit movements forces the monkey to catch up to it with saccadic eye movements. A velocity criterion was used to detect saccades and arrive at the first measure: percent of time spent in saccades rather than smooth pursuit movements. To examine the dynamics of just the pursuit epochs the saccades were then removed from the record and a cross-correlation analysis of the "cleaned" eye velocity trace was carried out, in general outline according to the method described by Cassell (Med. Biol. Eng., 1973, p. 755). The target velocity trace was first correlated with itself and the first positive peak of the autocorrelation function was taken as a measure of target velocity (V_T). The autocorrelated target trace was cross-correlated

with the monkey's "cleaned" velocity trace. The first positive peak of the cross-correlation was considered an index of the monkey's best tracking performance (V_E) and expressed as a second measure:

$$\text{Gain} = \frac{V_E}{V_T}$$

The third index was a measure of phase or the average tendency of the monkey to lead or lag behind the target:

$$\text{Phase (in msec)} = T_{V_E} - T_{V_T}$$

T_{V_E} is the time of occurrence of the monkey's best performance relative to a target time (T_{V_T}) = 0.

During each session monkeys were tested under four target conditions. The target could travel at one of two velocities and through either a predictable or unpredictable trajectory. The Predictable condition was a regular sinusoidal function of 9° amplitude. With such a function, the subject can predict that whenever the target slows to zero velocity it will reverse direction. The Unpredictable condition was a "random walk" of sinusoids. Each time the target sinusoid crossed zero velocity, a random number table was consulted to see if the next half-cycle of the target function would reverse direction and complete the sinusoidal cycle or instead continue on with a sinusoidal velocity in the same direction. This left the monkey uncertain of the exact trajectory and less able to generate a predetermined ballistic program of movement to it. The two conditions were run at either 0.4 or a faster 1.4 HZ.

Only results from the two conditions using the faster velocity target are reported here. As with Visual Search, the formal measure on pursuit collected during drug trials were converted to Z scores of performance relative to baseline scores. However, the plots of eye trajectories provide some absolute gain, phase, and percent-of-saccades scores achieved during some drug trials to give some feeling for typical actual scores achieved under these testing conditions.

Atropine Summary

.014 mg/K

Slight pupillary mydriasis appeared; the monkeys were otherwise neurologically normal. Eye records were for the most part normal, but with excessive eye blinks and the suggestion of slight drift of fixations in 2 subjects.

Visual Search: Performance normal with occasional borderline performance in 2 subjects.

Target Tracking: Normal.

.045 mg/K

Moderate mydriasis and continual lip movements indicative of a dry mouth occurred in all subjects, but with no other symptoms of muscle weakness. Oculomotor record was mostly normal but contained excessive eye blinks and the hint of shorter and perhaps slightly drifting fixations.

Visual Search: Normal.

Target Tracking: Normal.

.14 mg/K

Mydriasis and dry mouth was variable and ranged from moderate to severe. Slight ptosis occurred in one monkey, but limb movement and posture did not indicate general muscle weakness. The oculomotor record at this dose displayed obvious drift in fixations and the saccadic traces were sloped (slowed). Fixations were shorter than normal -- interrupted more frequently by small shifts of gaze. There was slight dysmetria which included both over- and undershooting of the target.

Visual Search: Largely normal, but with some variability between subjects and between first and second testing of this dose. Two subjects (1,2) required slightly more fixations to find the target on the first but not the second testing. This dose did not appear to disrupt the monkey's willingness to search for targets.

Target Tracking: Results were similar to those on the Visual Search test. In general the gain and phase of pursuit were normal but with exceptions. Subject 1's tracking was abnormal in one session, that of Subject 2's faulty in both sessions of this dose.

.25 mg/K

Mydriasis was quite pronounced although the pupils were not dilated to their limits. Dry mouth and ptosis were seen but no obvious skeletal weakness. The oculomotor record was markedly disfigured by eye blinks, drifting and fractured fixations.

Visual Search: Testing of two subjects proceeded smoothly. The other two appeared less motivated and paused occasionally between trials. The effect on performance is reflected in fewer targets acquired and an increase in time and number of fixations to find the target. However, these changes did not show up consistently and at their worst were not drastic decrements.

Target Tracking: Decrements in formal measures of this task were clearer and more consistent than on the Visual Search test and were reflected in lowered gains, a greater phase lag behind the target, and an increase in the amount of time spent making corrective saccades to catch up to the target.

ATROPINE

EYE MOVEMENTS DURING SEARCH

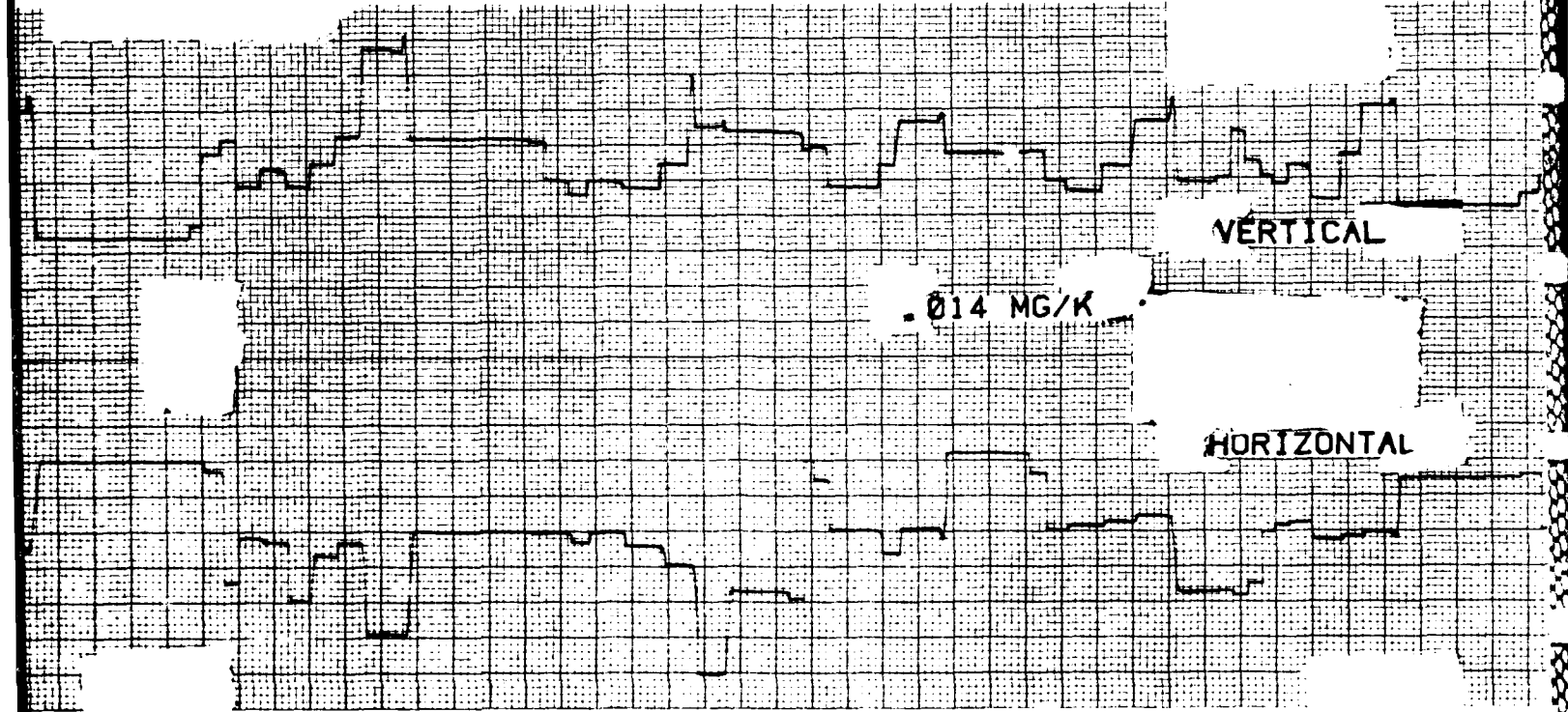
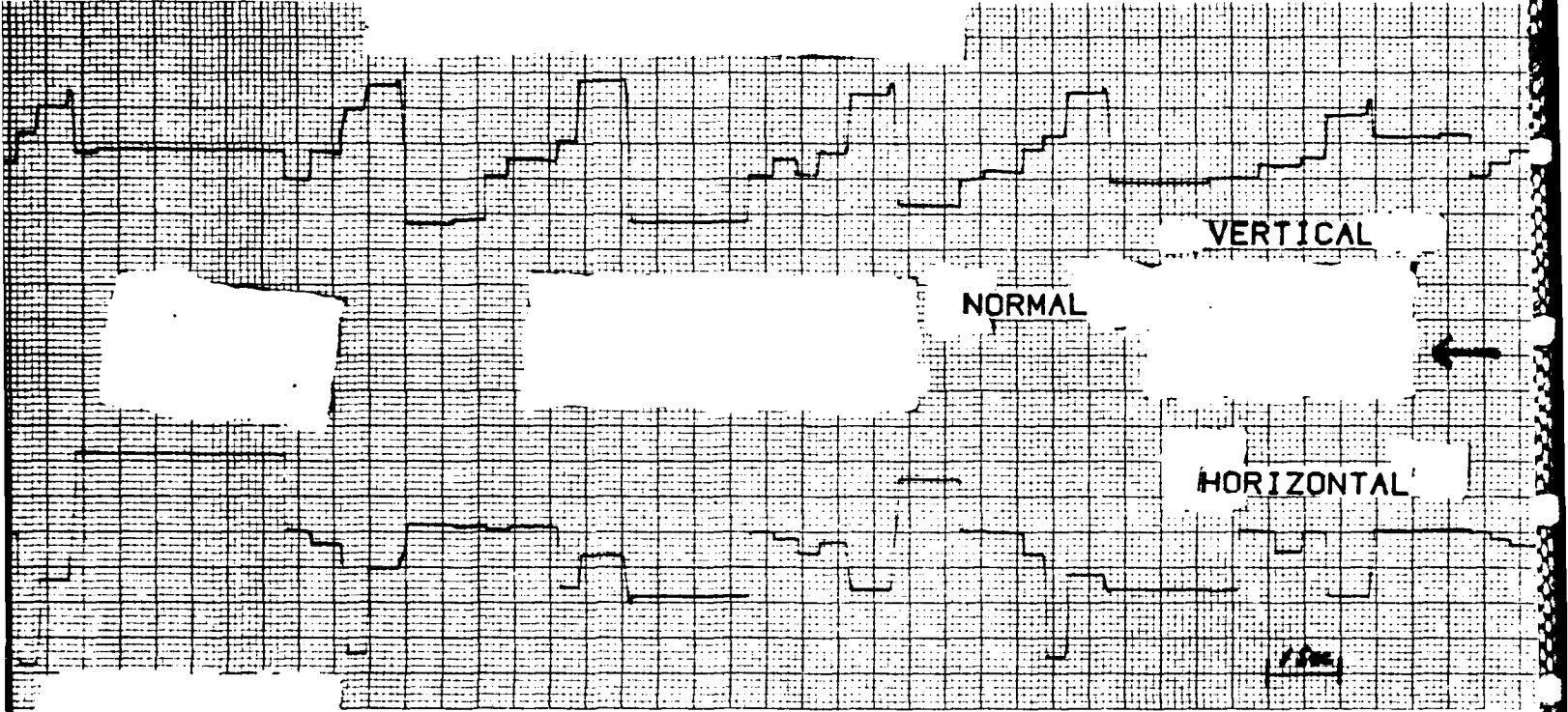
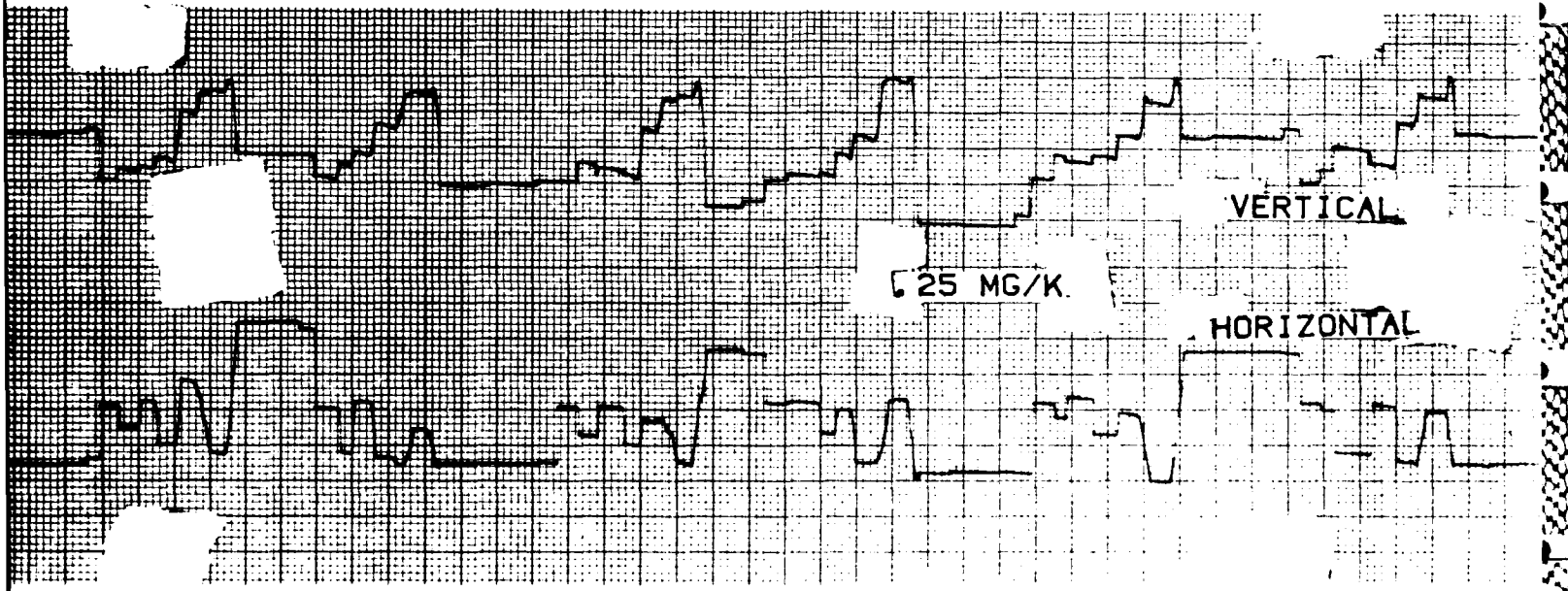
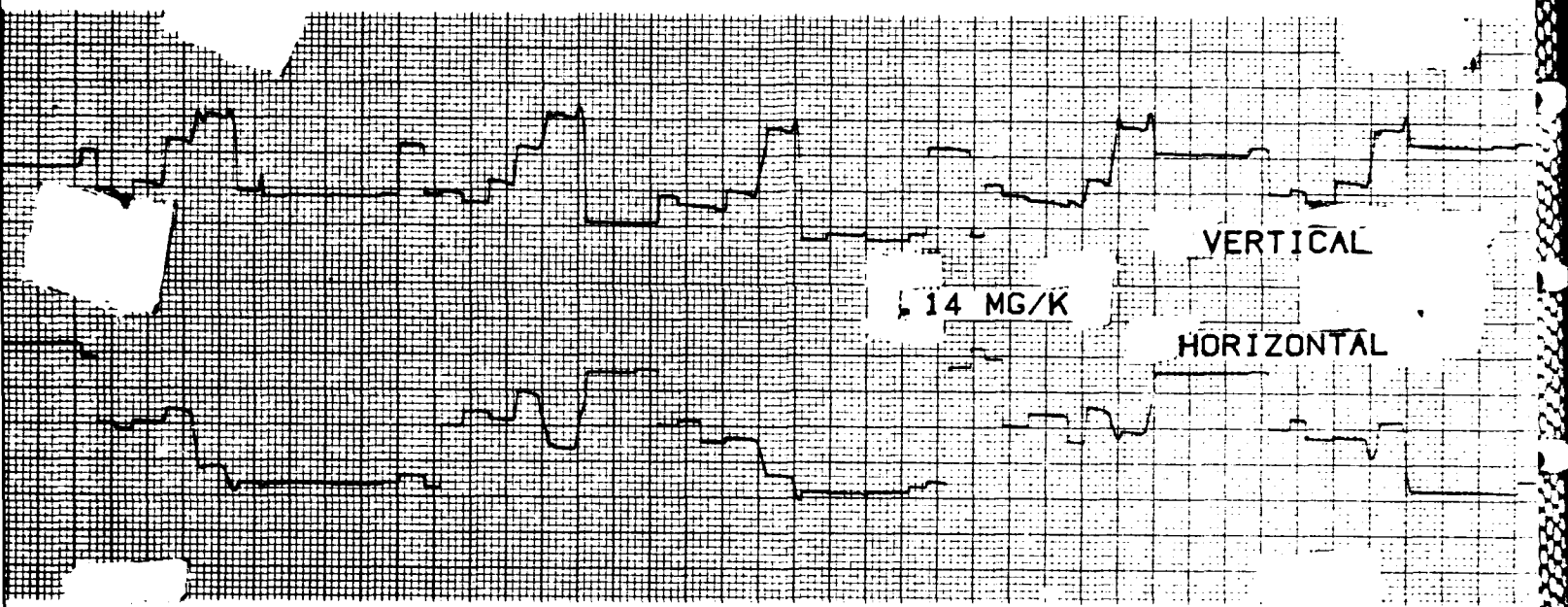
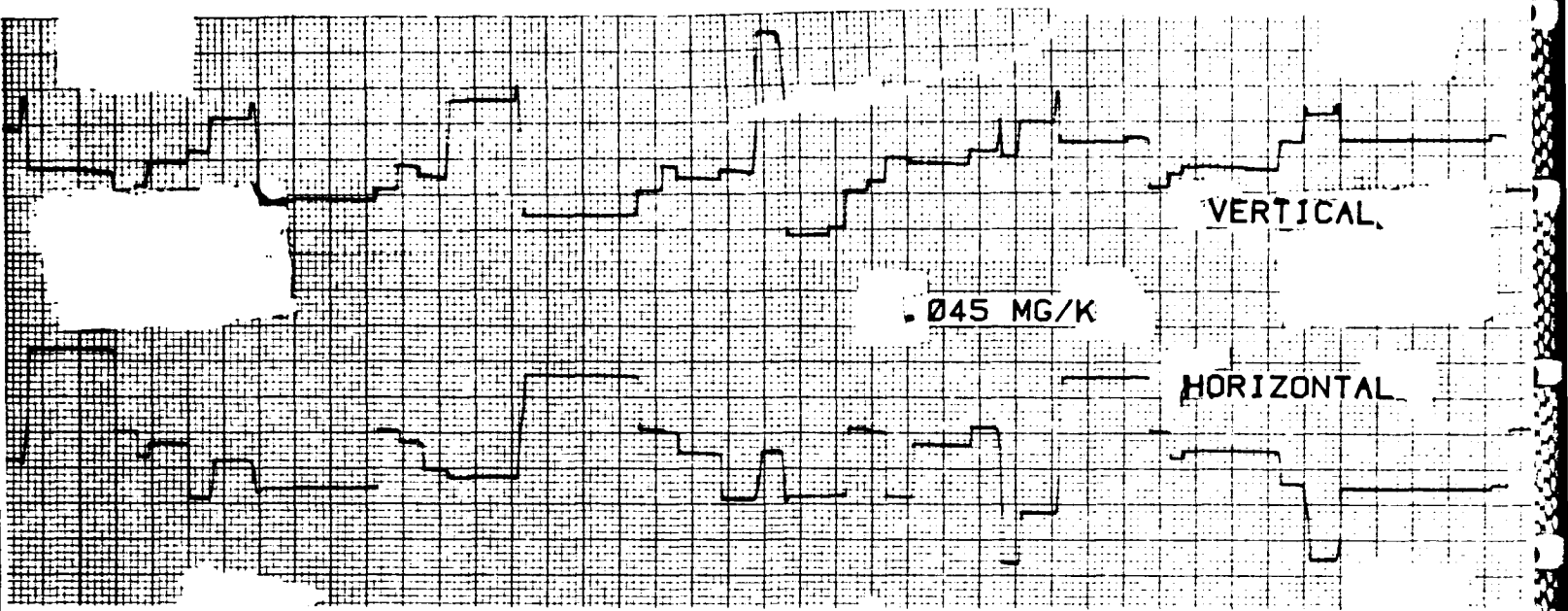
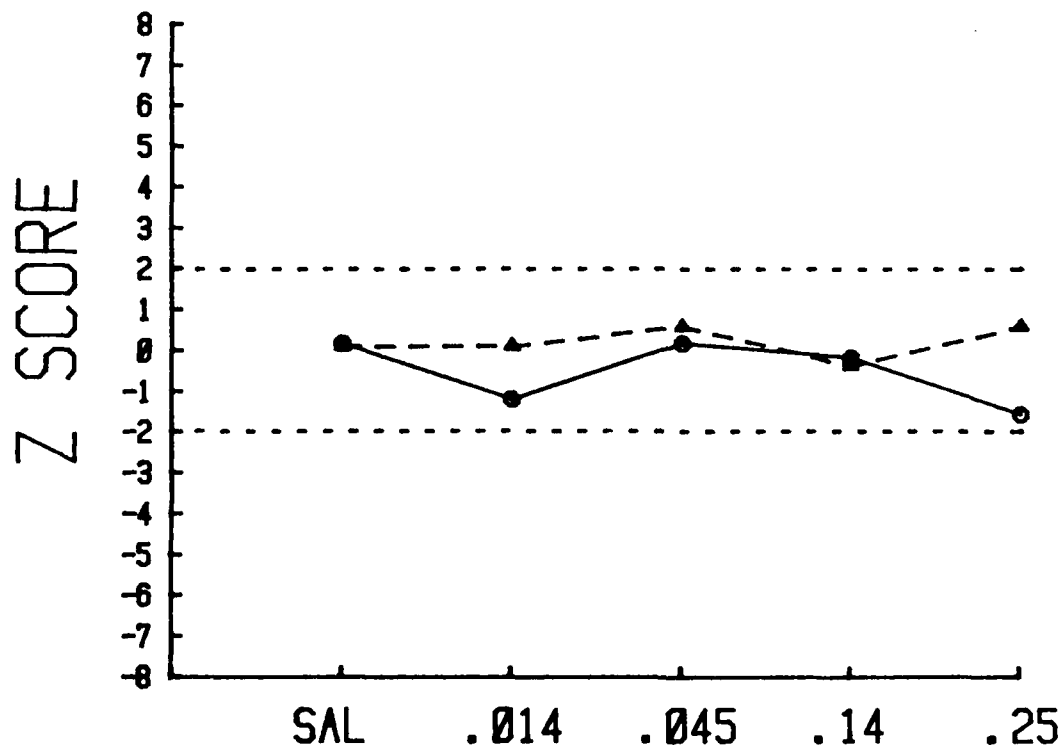
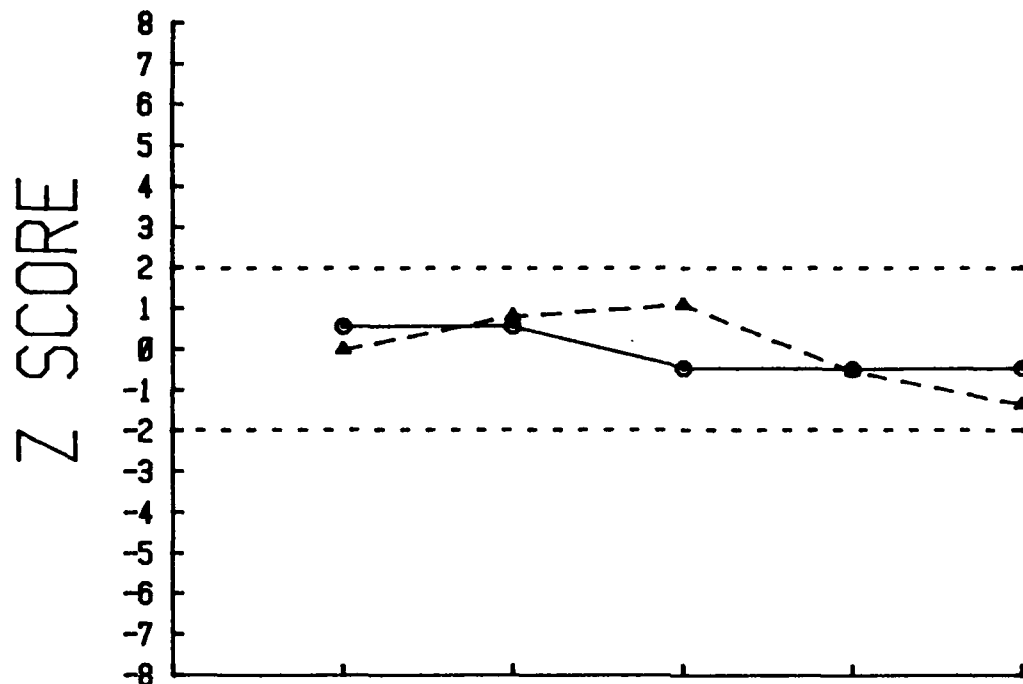


Figure 1



ATROPINE PERCENT OF TARGETS FIXATED

▲ - - - ▲ EARLY
○ - - - ○ LATE



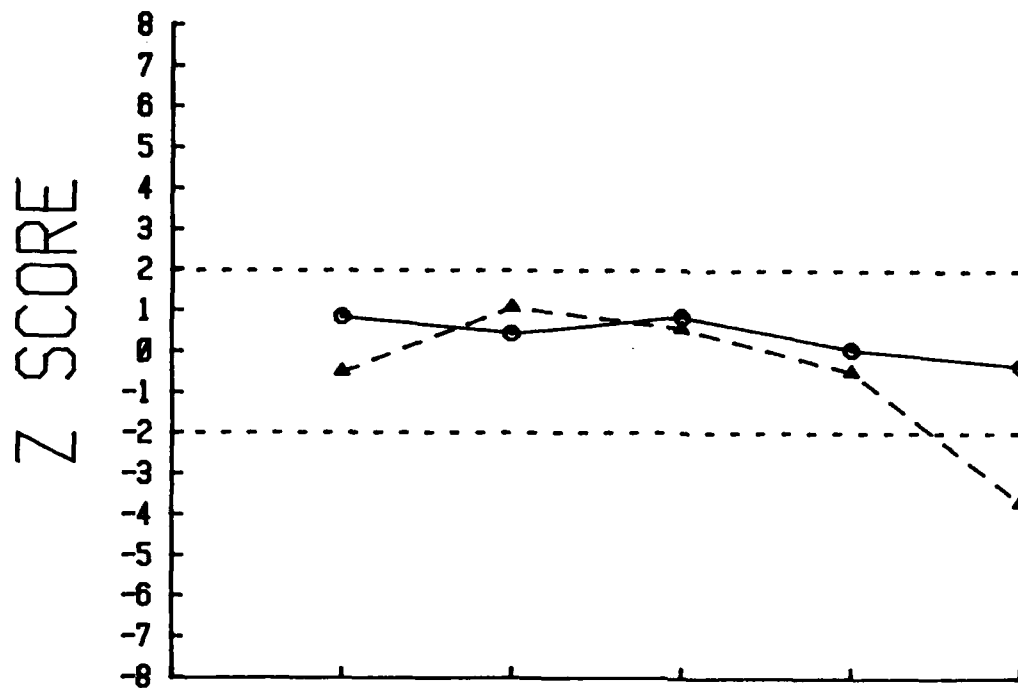
MG/K

Figure 2

ATROPINE PERCENT OF TARGETS FIXATED

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

SUBJECT 3



SUBJECT 6

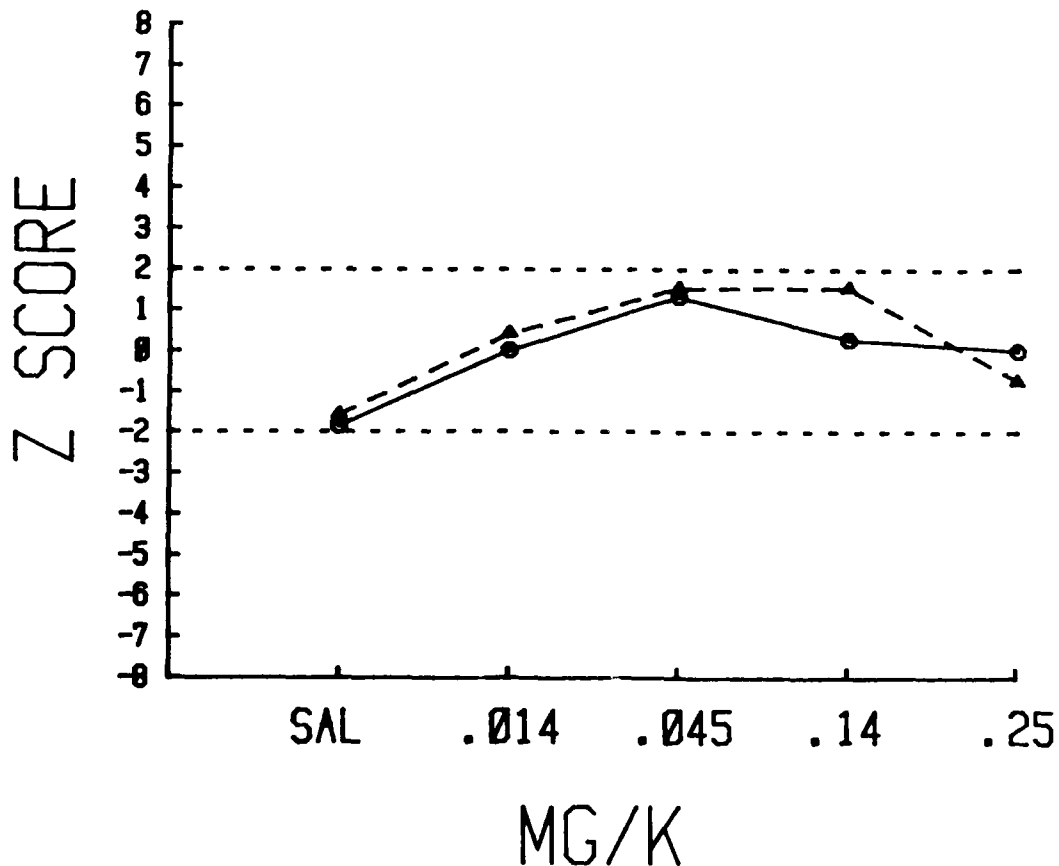
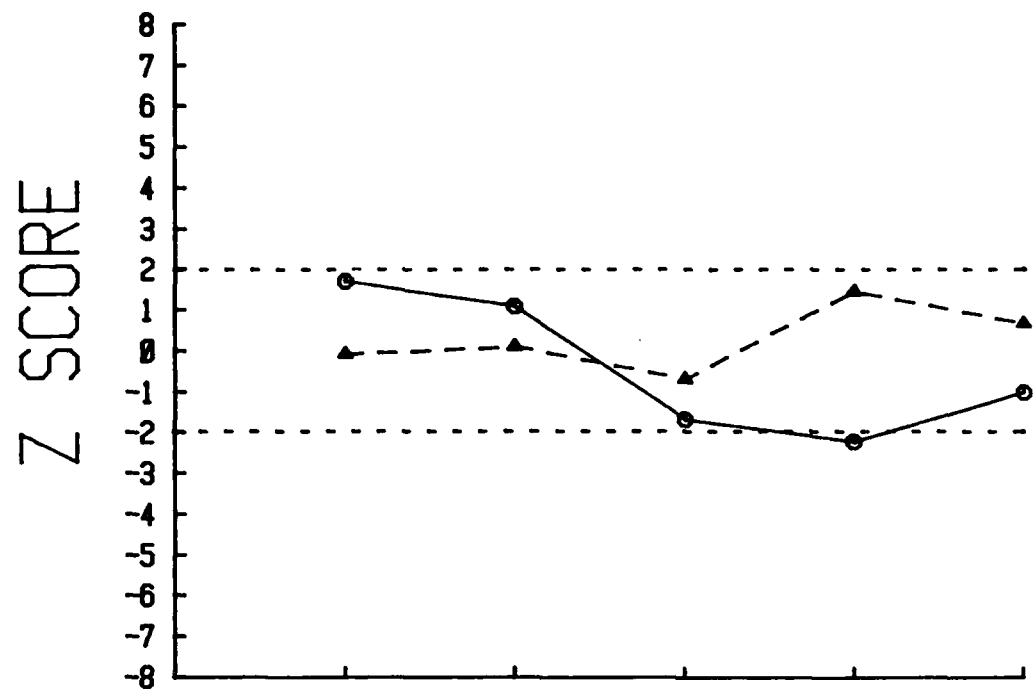


figure 3

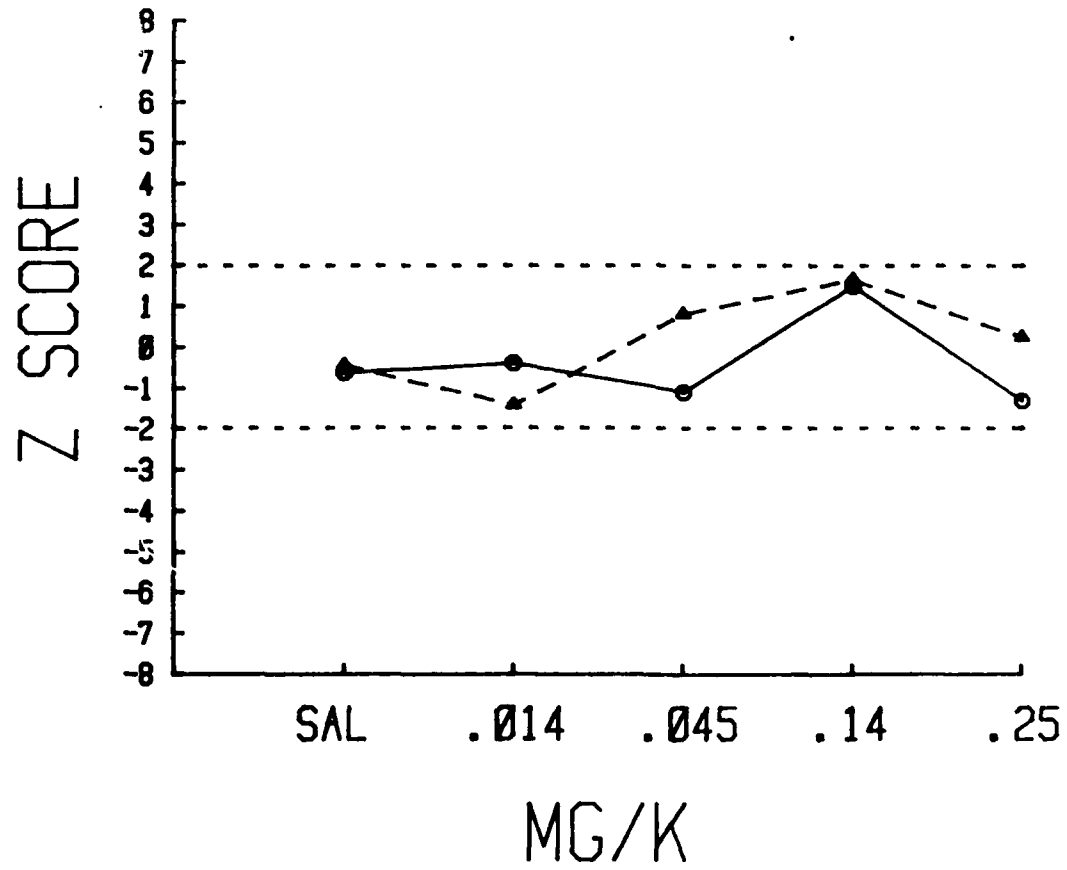
ATROPINE TIME TO FIND TARGET

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

SUBJECT 1



SUBJECT 2



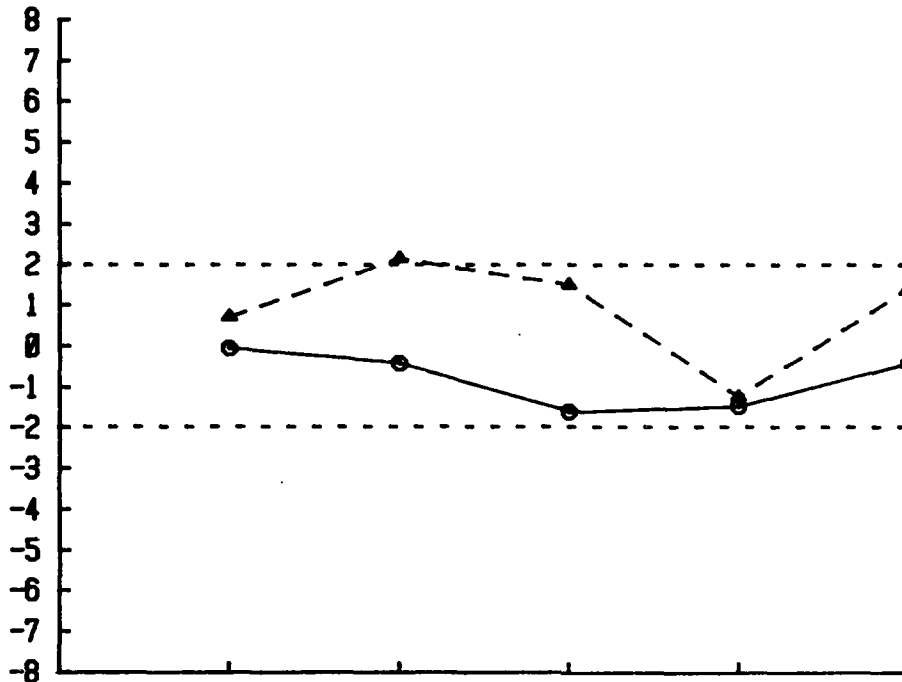
MG/K
Figure 4

ATROPINE TIME TO FIND TARGET

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

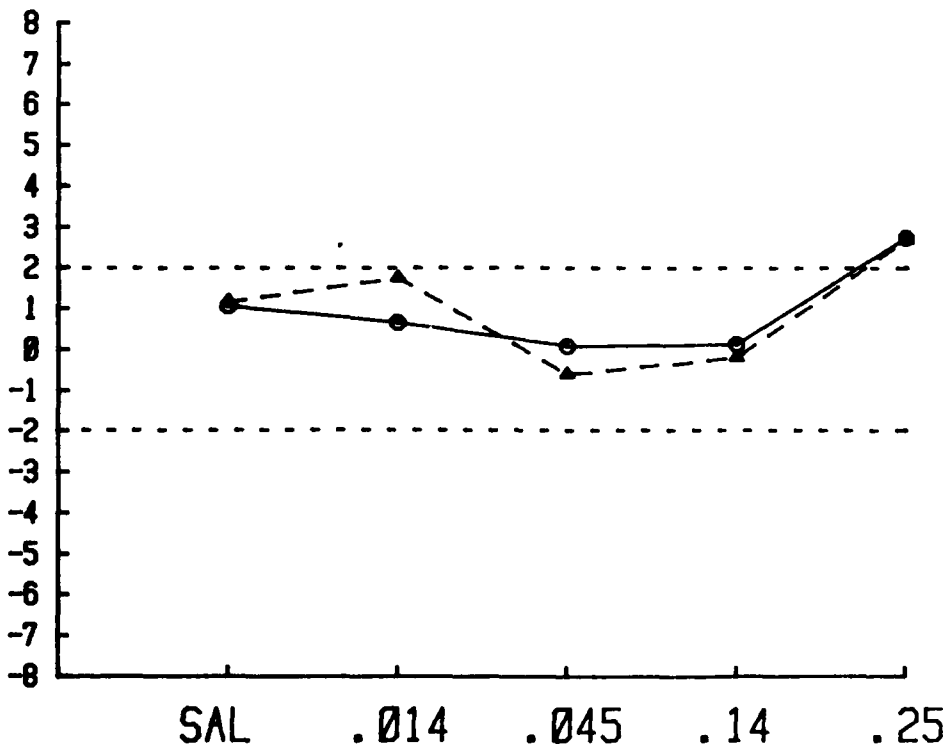
SUBJECT 3

Z SCORE



SUBJECT 6

Z SCORE



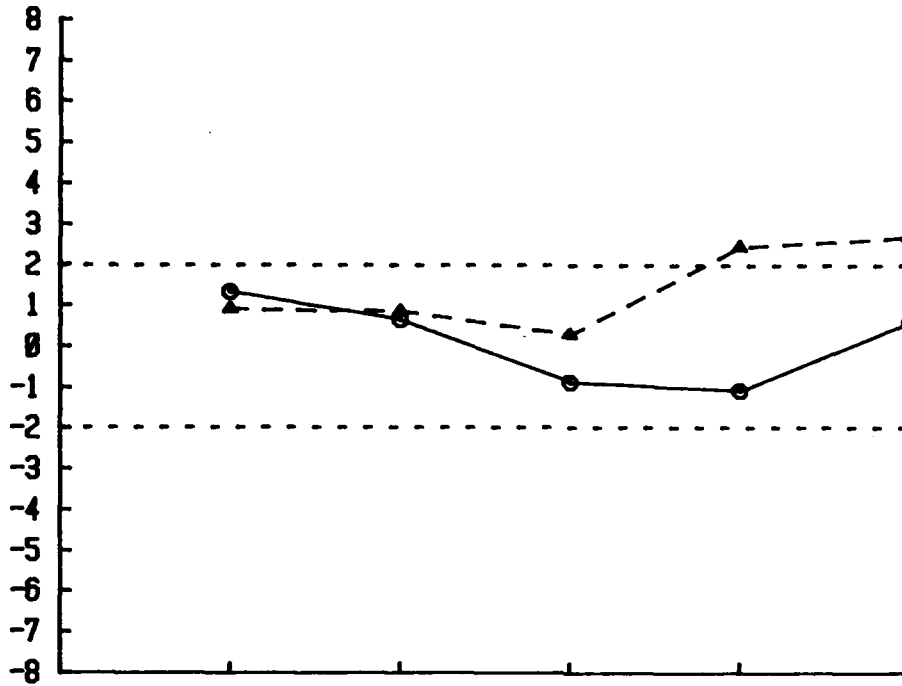
MG/K
figure 5

ATROPINE
NUMBER OF FIXATIONS TO FIND TARGET

▲ - - - ▲ EARLY
○ - - - ○ LATE

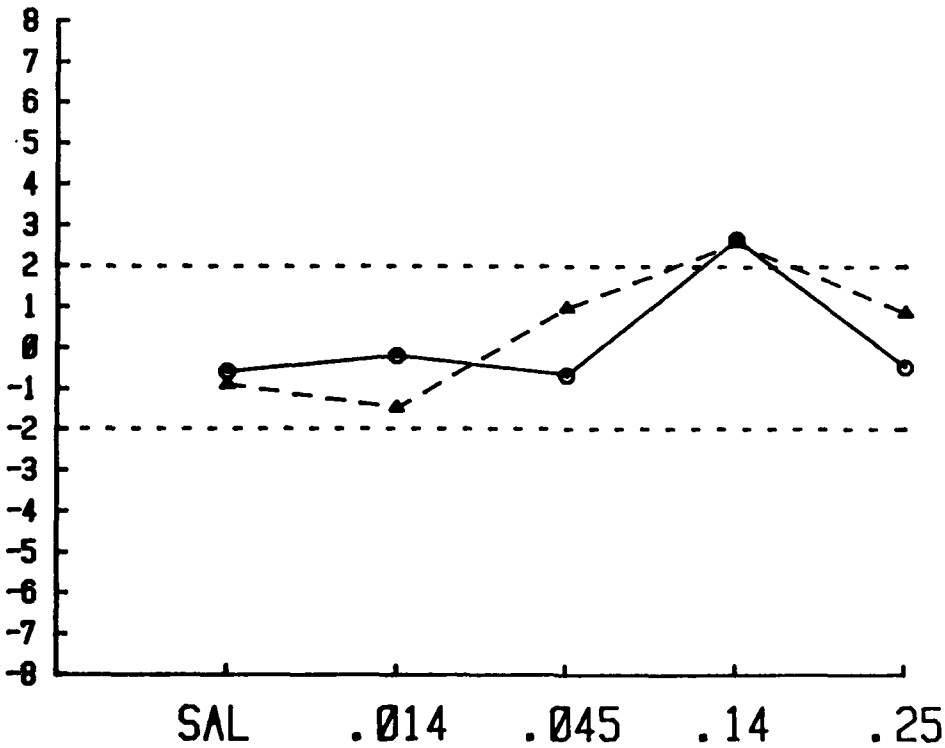
SUBJECT 1

Z SCORE



SUBJECT 2

Z SCORE



MG/K

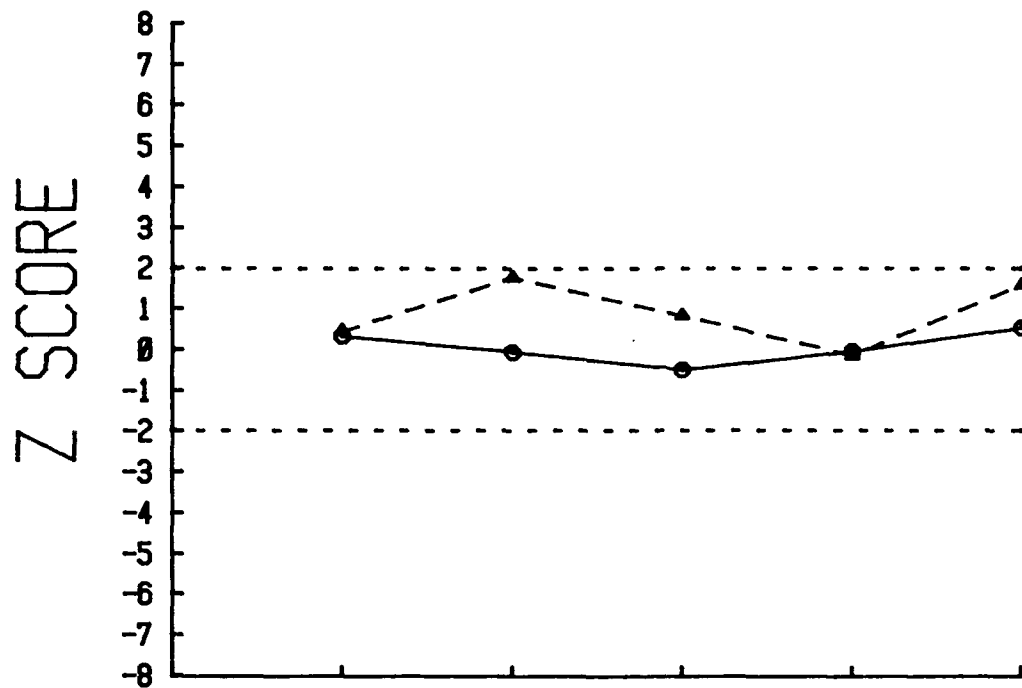
Figure 6

ATROPINE

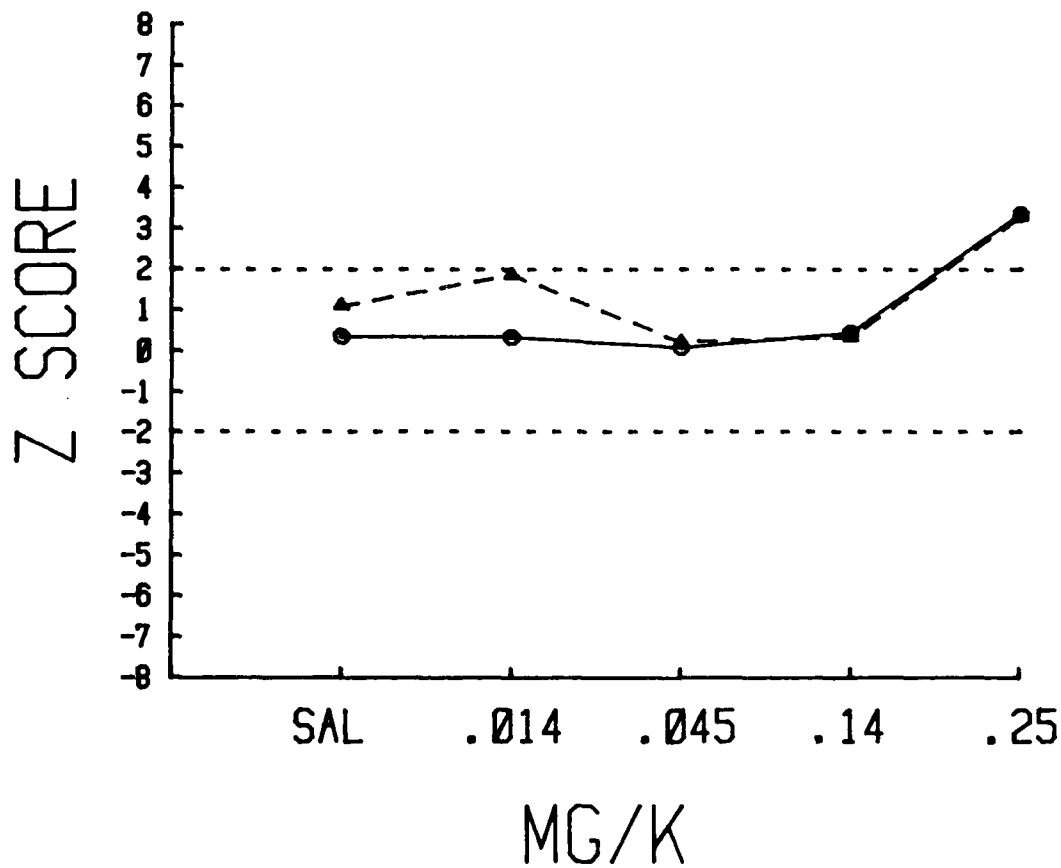
NUMBER OF FIXATIONS TO FIND TARGET

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

SUBJECT 3



SUBJECT 6



MG/K

figure 7

Atropine "Worst Case" Block Scores on Visual Search

Subject 1; .25 mg/K; Early

	<u>Baseline Avg.</u>	<u>Baseline STD</u>	<u>Drug Avg.</u>
Percent of targets fixated	97.3	2.6	90.3
On successful trials:			
Time to find target (msec.)	298	13	330
Number of fixations to find target	1.16	.04	1.37
Oculomotor:			
Saccadic velocity (deg./sec.)	291	5.4	284
Fixation drift (degrees)	.34	.02	.47
Fixation duration (msec.)	597	55	411
Error in fixating target (deg.)	.37	.04	.51

ATROPINE - EYE MOVEMENTS DURING TARGET TRACKING

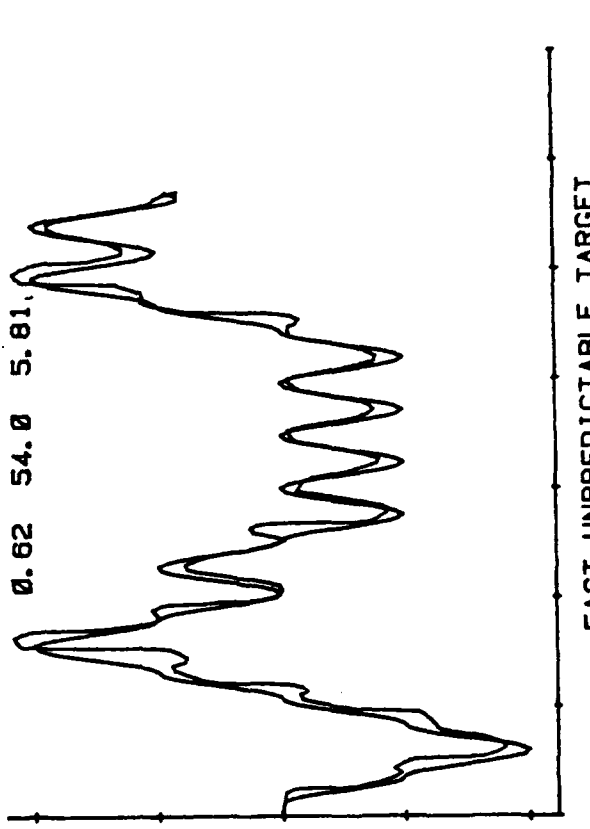
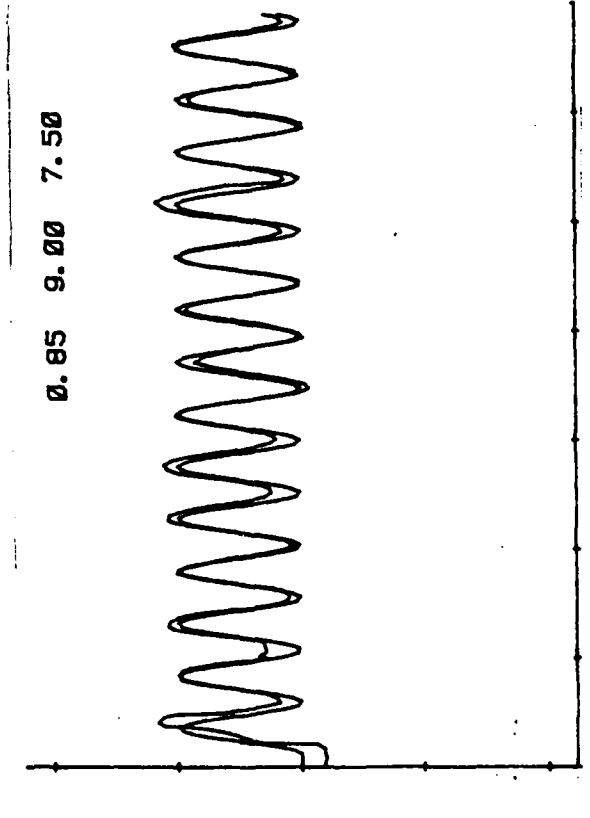
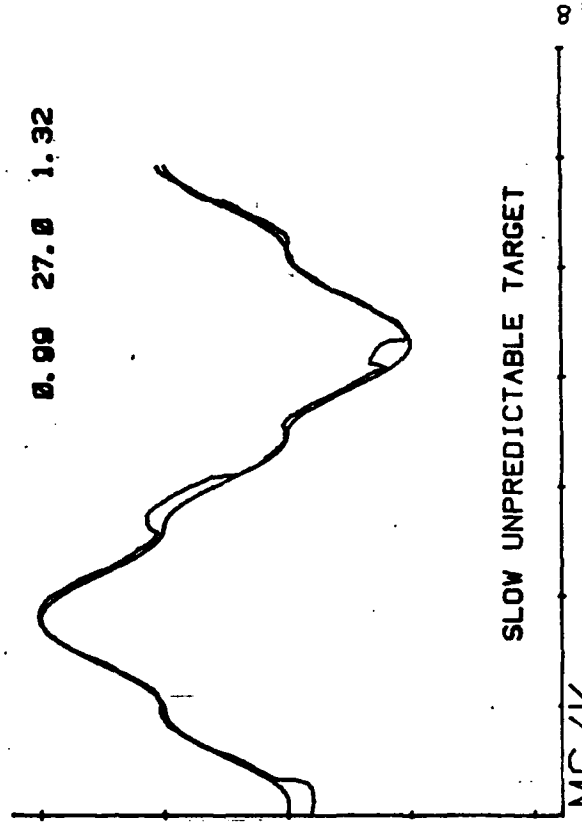
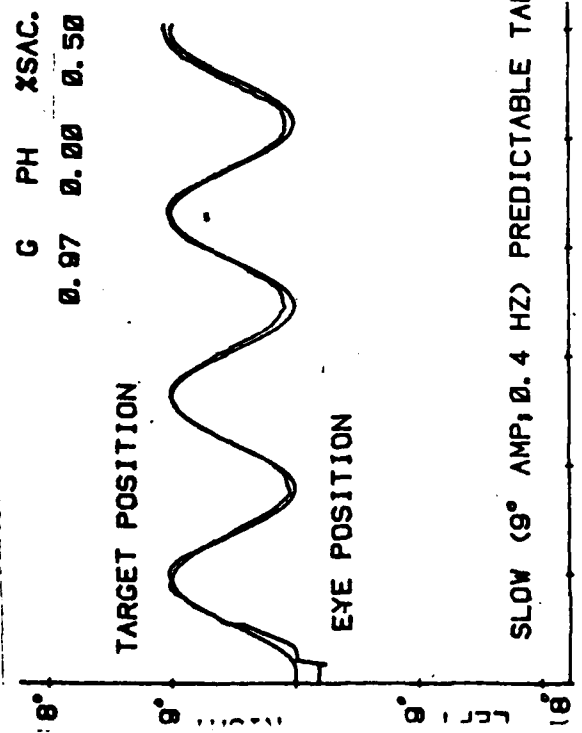


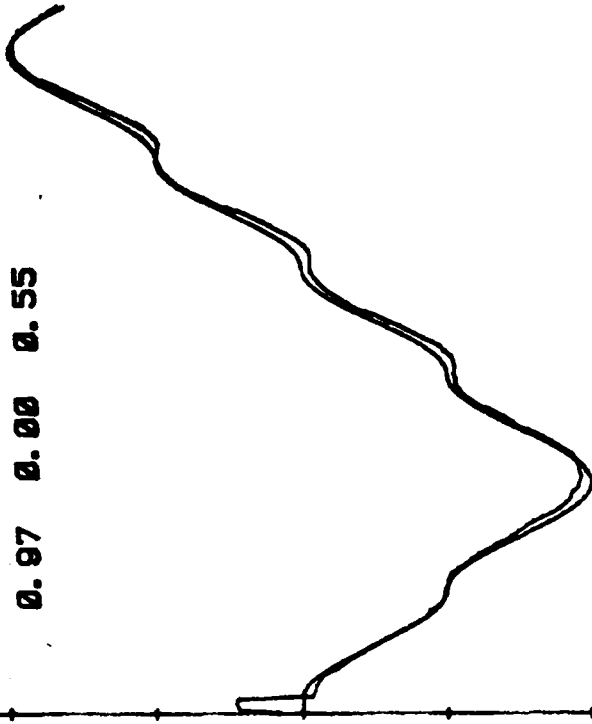
Figure 8

0.14 MG/K

0.95 9.00 0.10



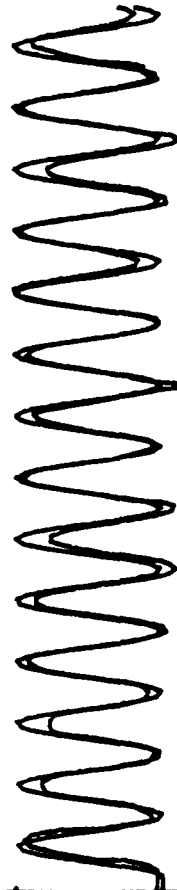
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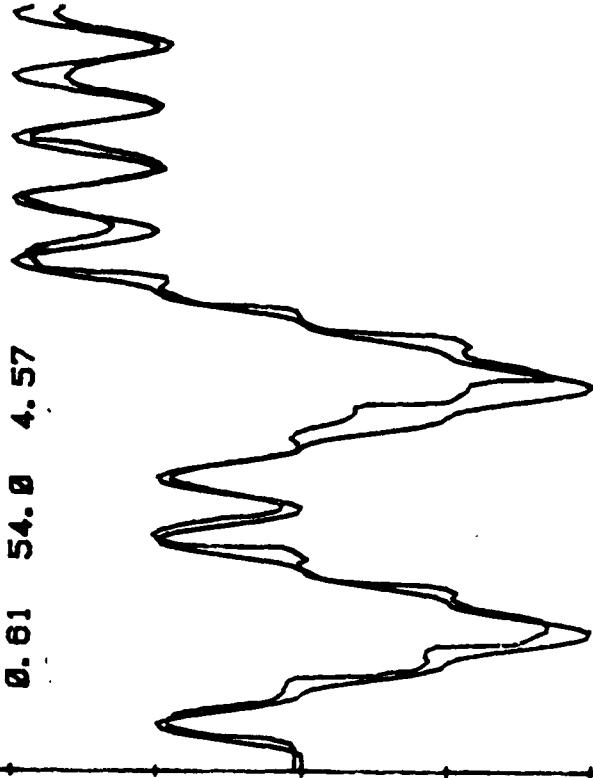
.045 MG/K

Figure 6

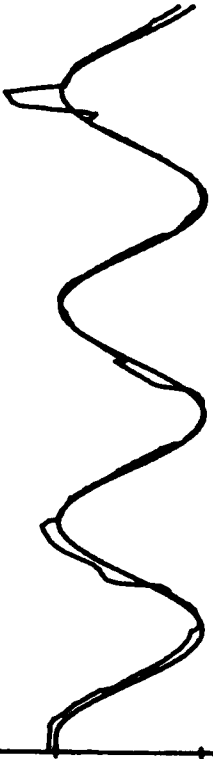
0.86 9.00 2.62



0.61 54.0 4.57

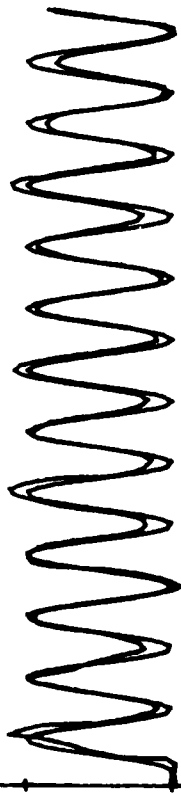


0.96 9.00 2.59

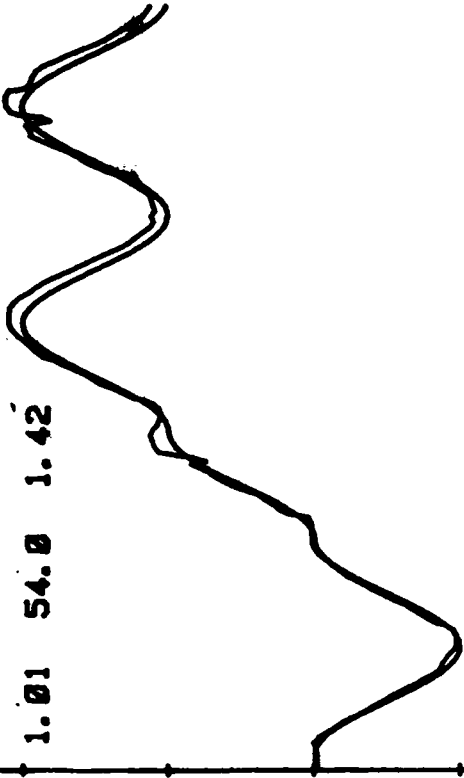


14

0.84 0.00 3.98



1.01 54.0 1.42



MG/K

0.62 45.0 7.61

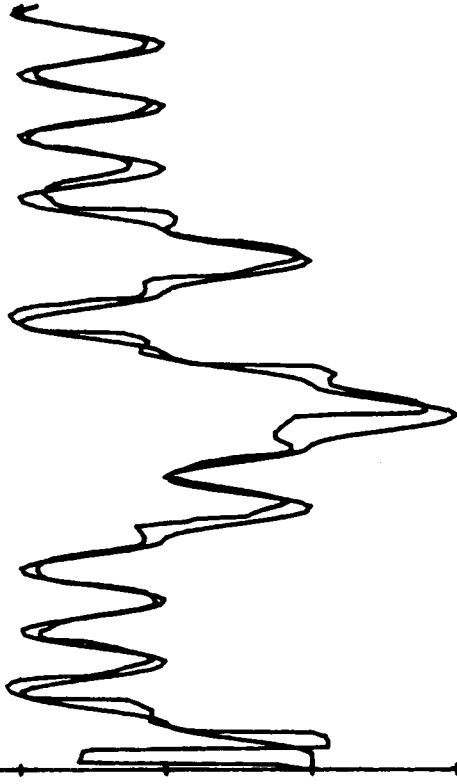
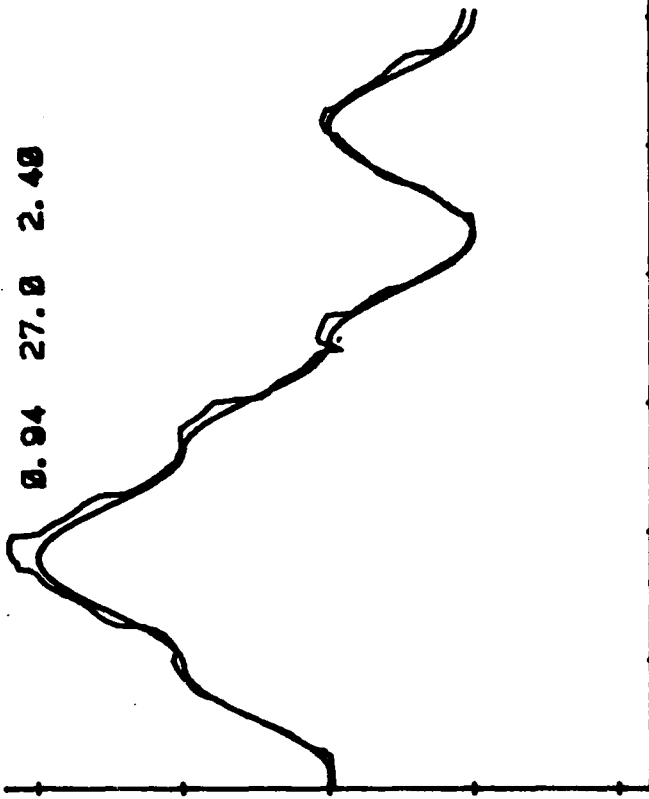
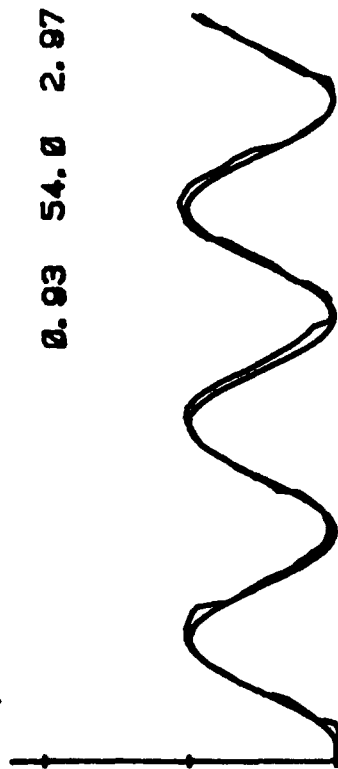
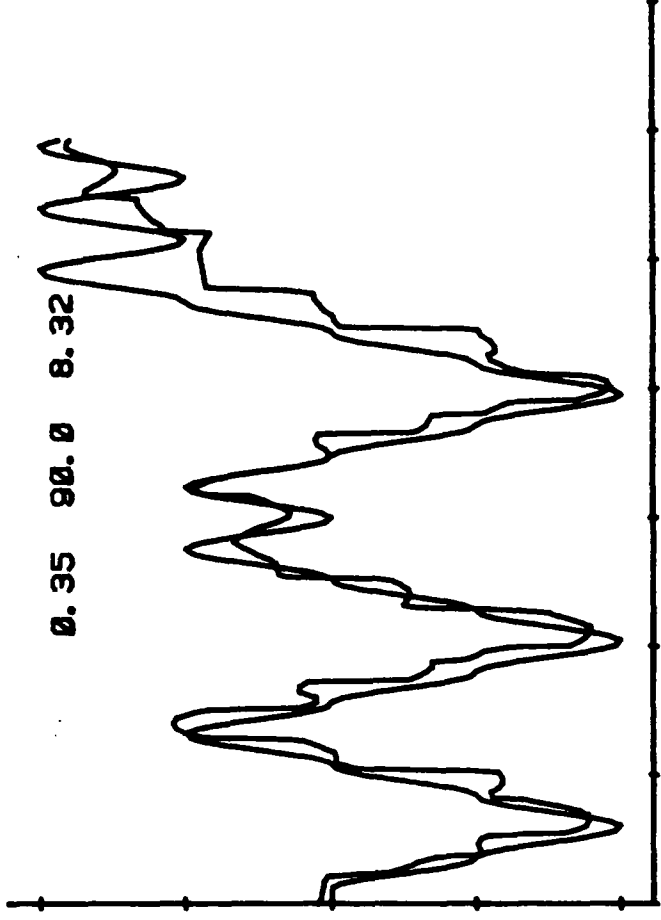
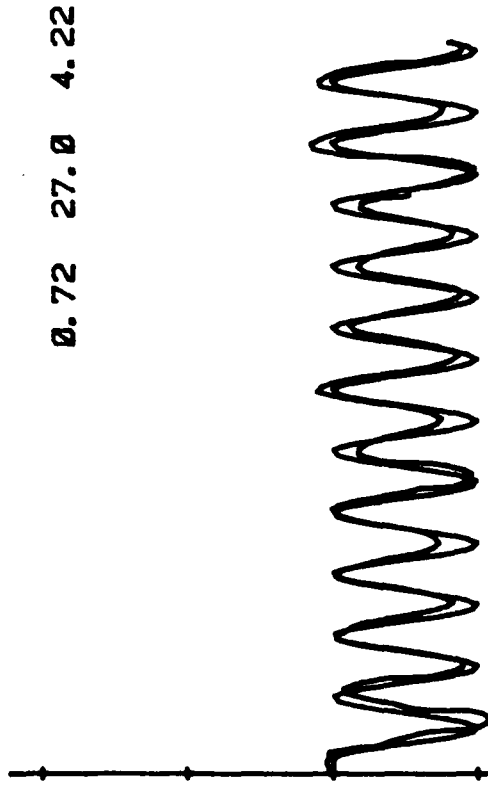


Figure 10



. 25 MG/K

Figure 11

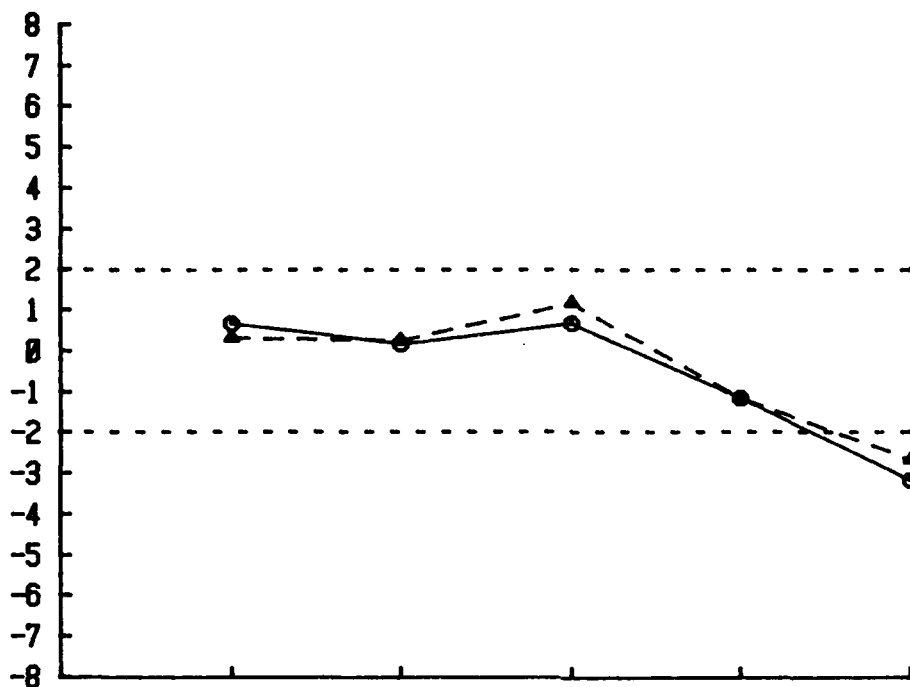


ATROPINE: TRACKING - FAST PRED. GAIN

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

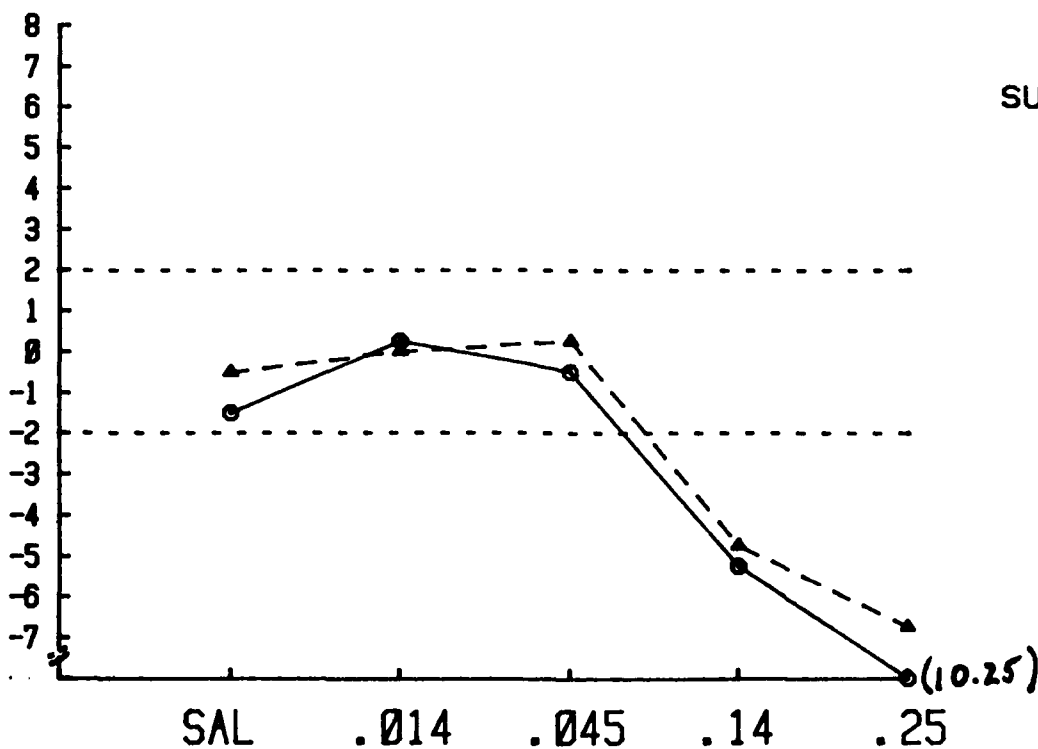
SUBJECT 1

Z SCORE



SUBJECT 2

Z SCORE



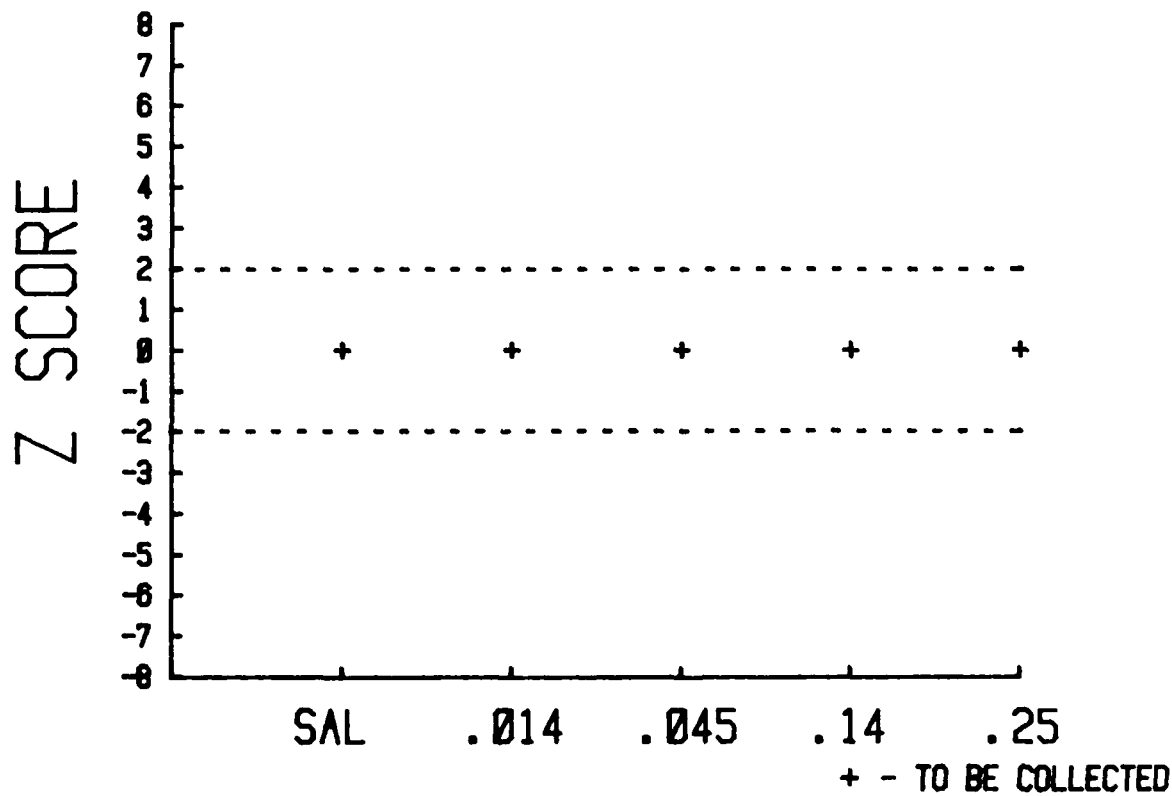
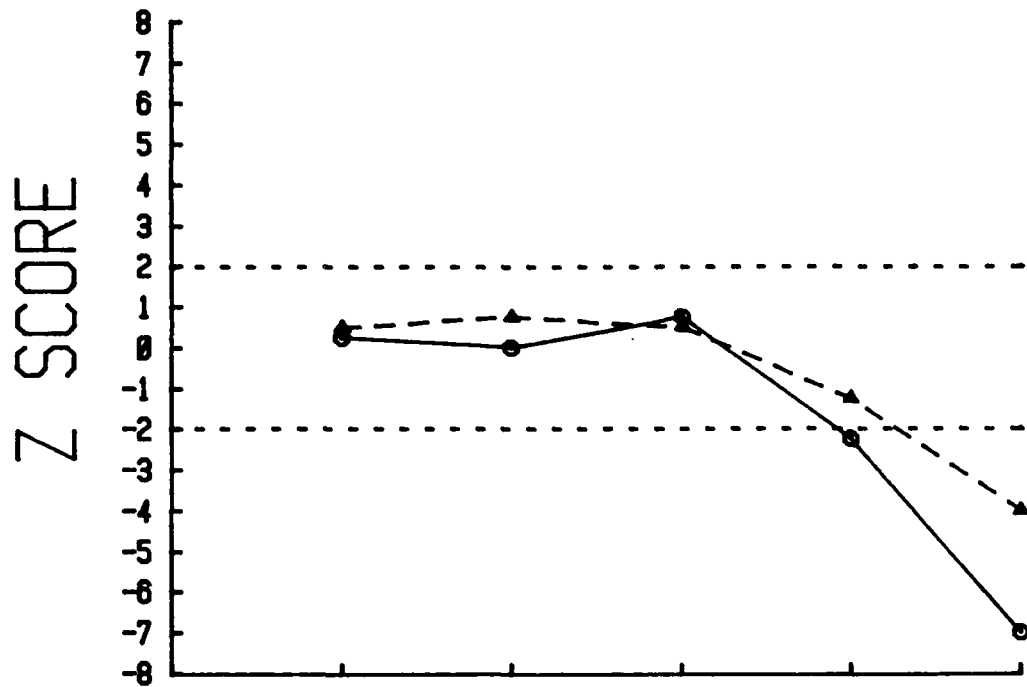
MG/K

figure 12

ATROPINE: TRACKING - FAST PRED. GAIN

▲ - - - ▲ EARLY
● - - - ● LATE

SUBJECT 6



MG/K

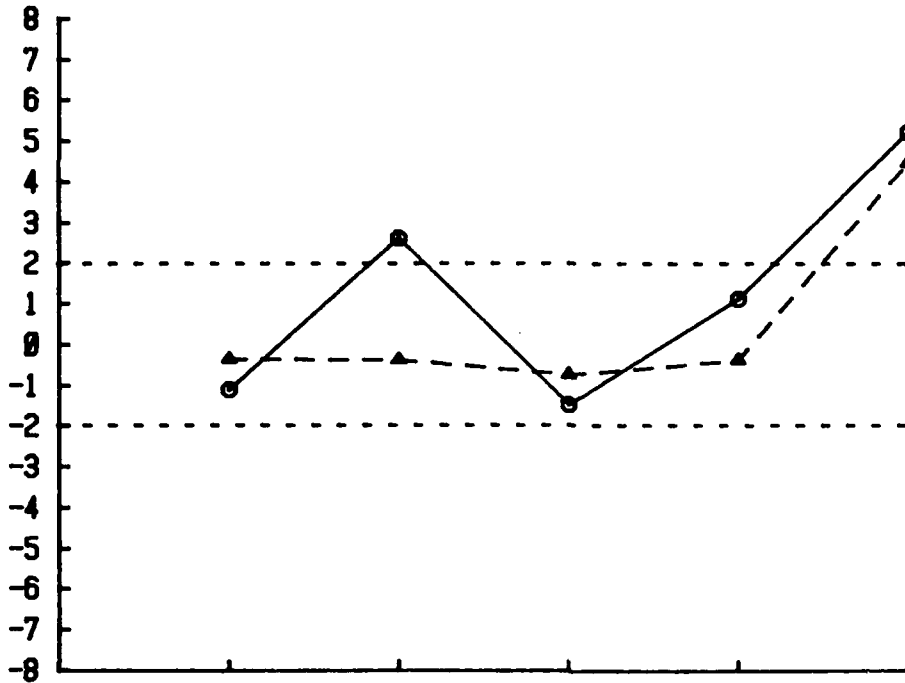
Figure 13

ATROPINE: TRACKING - FAST PRED. PHASE

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

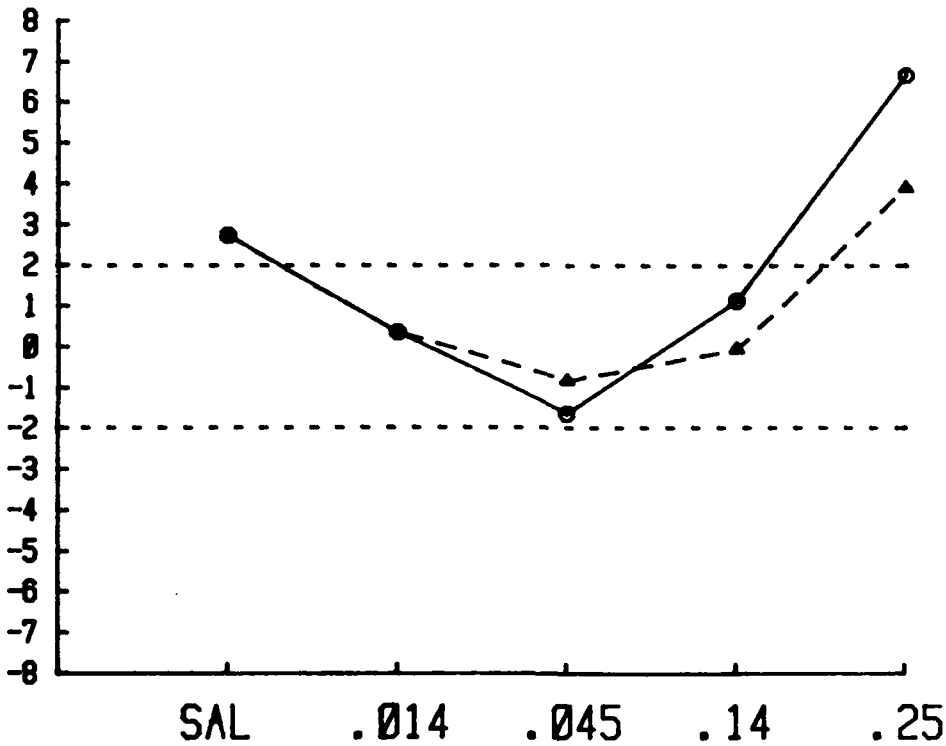
SUBJECT 1

Z SCORE



SUBJECT 2

Z SCORE



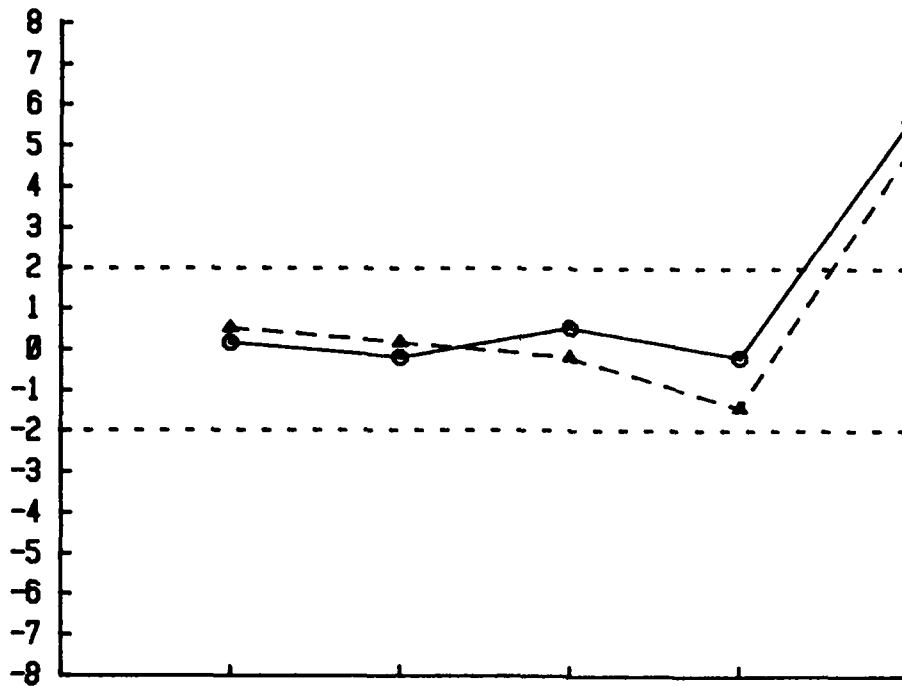
MG/K
figure 14

ATROPINE: TRACKING - FAST PRED. PHASE

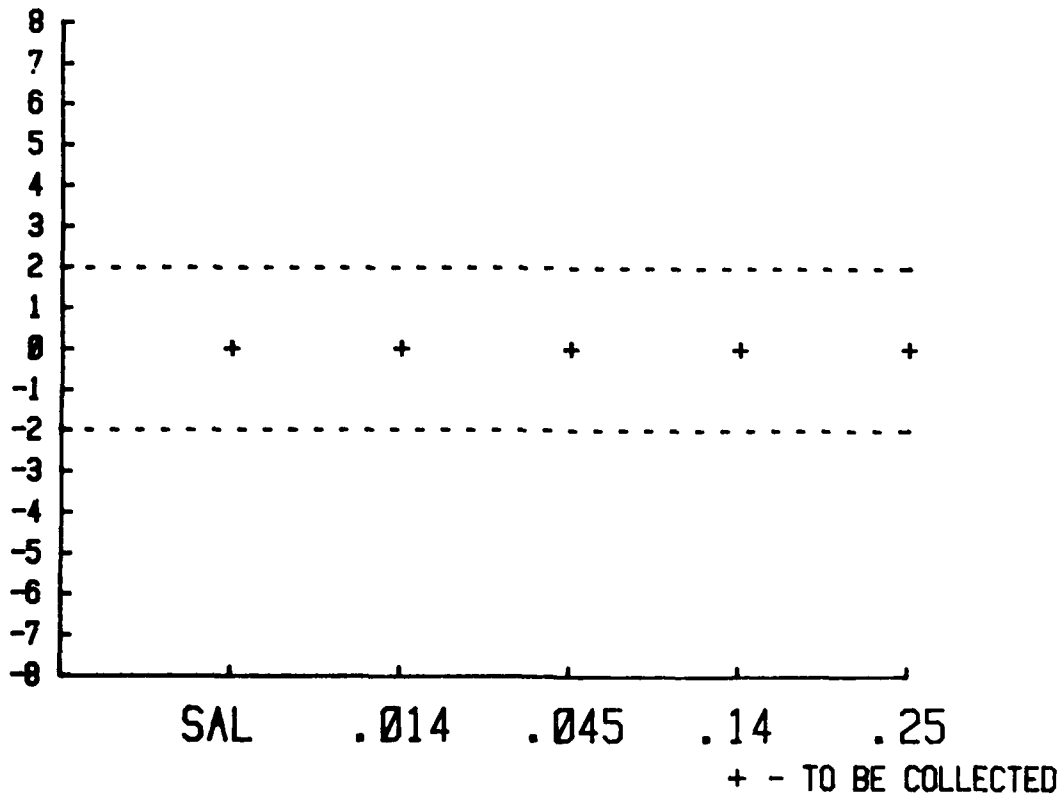
▲ - - - - ▲ EARLY
○ - - - - ○ LATE

SUBJECT 6

Z SCORE



Z SCORE



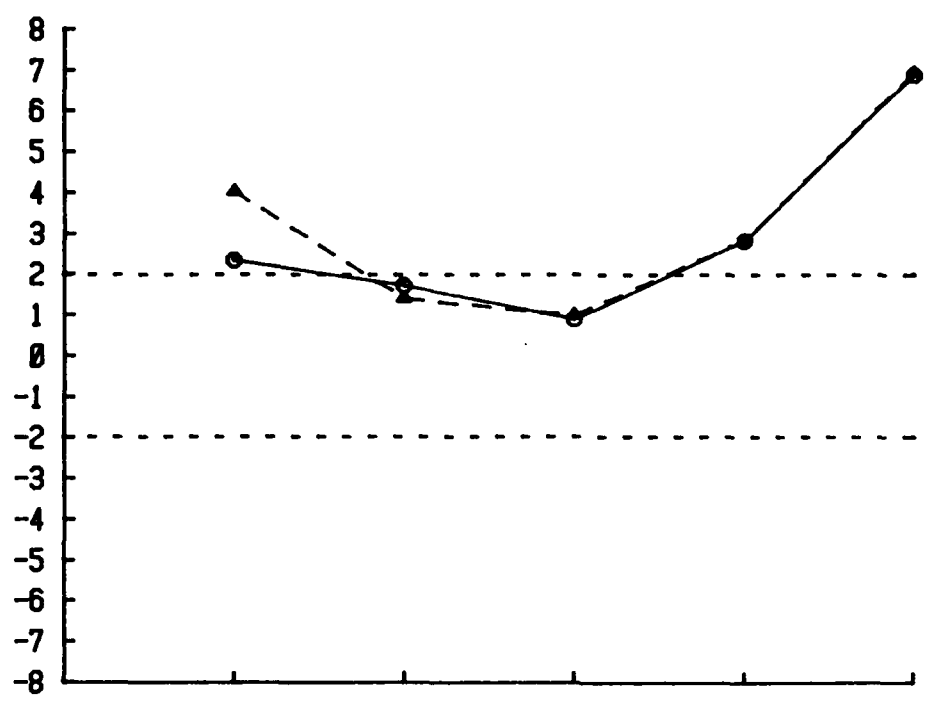
MG/K
figure 15

ATROPINE: TRACKING - FAST PRED.
PERCENT OF TIME IN SACCADES

▲ - - - - ▲ EARLY
● - - - - ● LATE

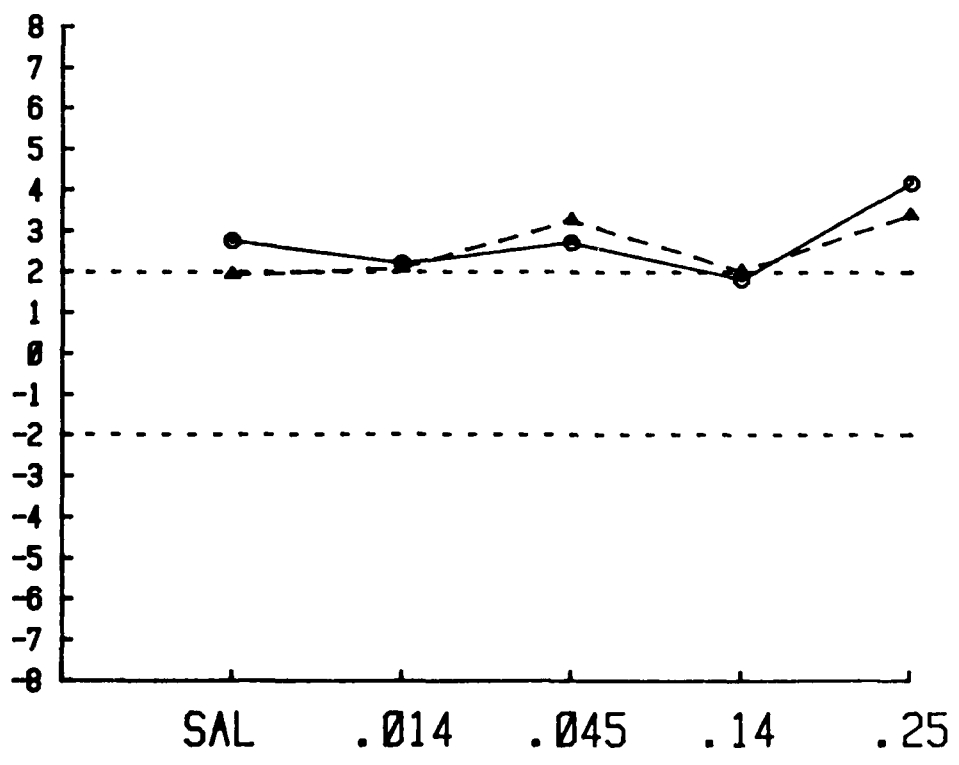
SUBJECT 1

Z SCORE



SUBJECT 2

Z SCORE



MG/K

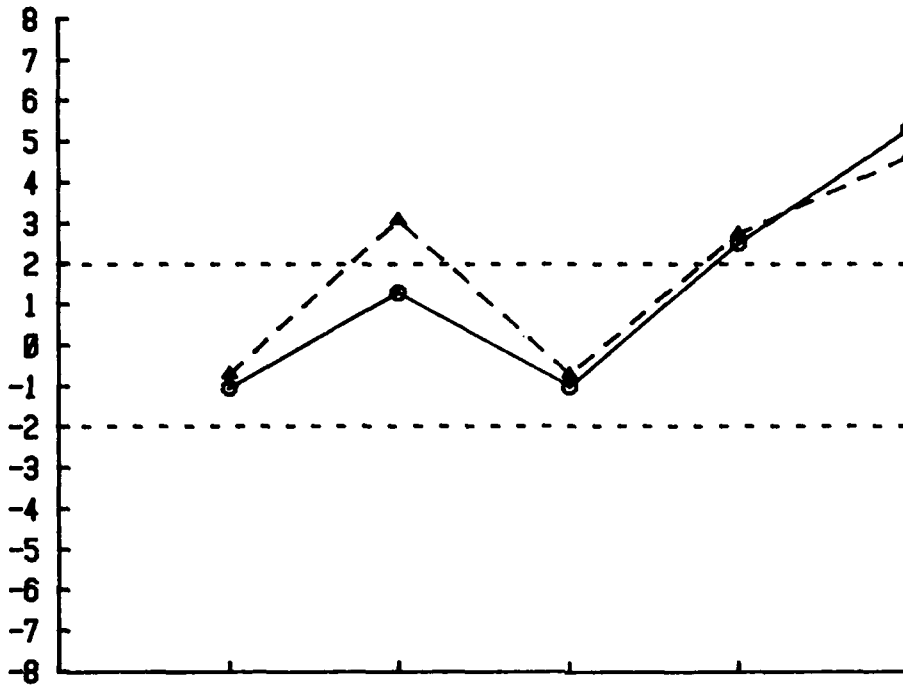
Figure 16

ATROPINE: TRACKING - FAST PRED.
 PERCENT OF TIME IN SACCADES

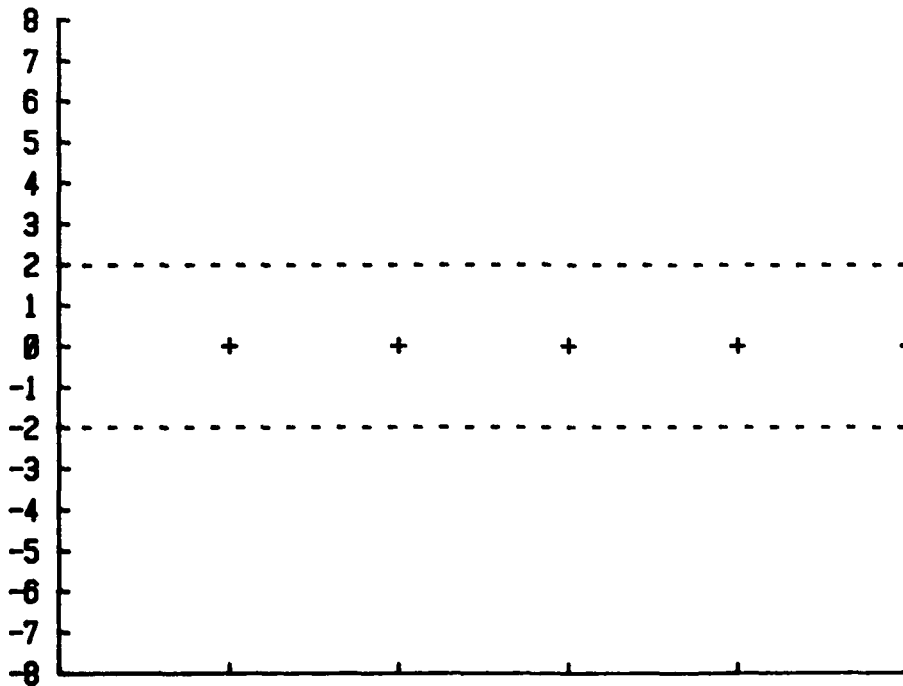
▲ - - - - ▲ EARLY
 ○ - - - - ○ LATE

SUBJECT 6

Z SCORE



Z SCORE



SAL .014 .045 .14 .25

+ - TO BE COLLECTED

MG/K

figure 17

Atropine - Pralidoxime Summary

.014 mg/K atropine + 1.0 mg/K pralidoxime

Neurological status was normal but for the hint of mydriasis. The oculomotor record was also normal.

Visual Search: Normal.

Target Tracking has not yet been tested.

.045 + 2.0 mg/K

Slight to moderate mydriasis but not other neurological symptoms appeared. The oculomotor record revealed shorter fixations, and sloping saccades in both early and late sessions. These abnormalities were subtle in appearance but the differences from normal were supported by shorter average durations of fixations and slowed saccadic velocities.

Visual Search: Consistently normal performance.

.14 + 4.0 mg/K

Neurological and oculomotor status were much the same as the previous lower dose. The mydriasis was obvious but not severe. Fixations were often interrupted by small shifts of gaze and eye blinks but the monkeys were able to hold a point without much drift.

Visual Search: Consistently normal.

.25 + 8.0 mg/K

Mydriasis and, in two animals, ptosis were the only neurological symptoms. The oculomotor records were not dramatically worse than at lower doses.

Visual Search: Normal except for performance during one late session with one subject (1). The "worst case" block scores for this session are shown on the following table.

ATROPINE/PAM EYE MOVEMENTS DURING SEARCH

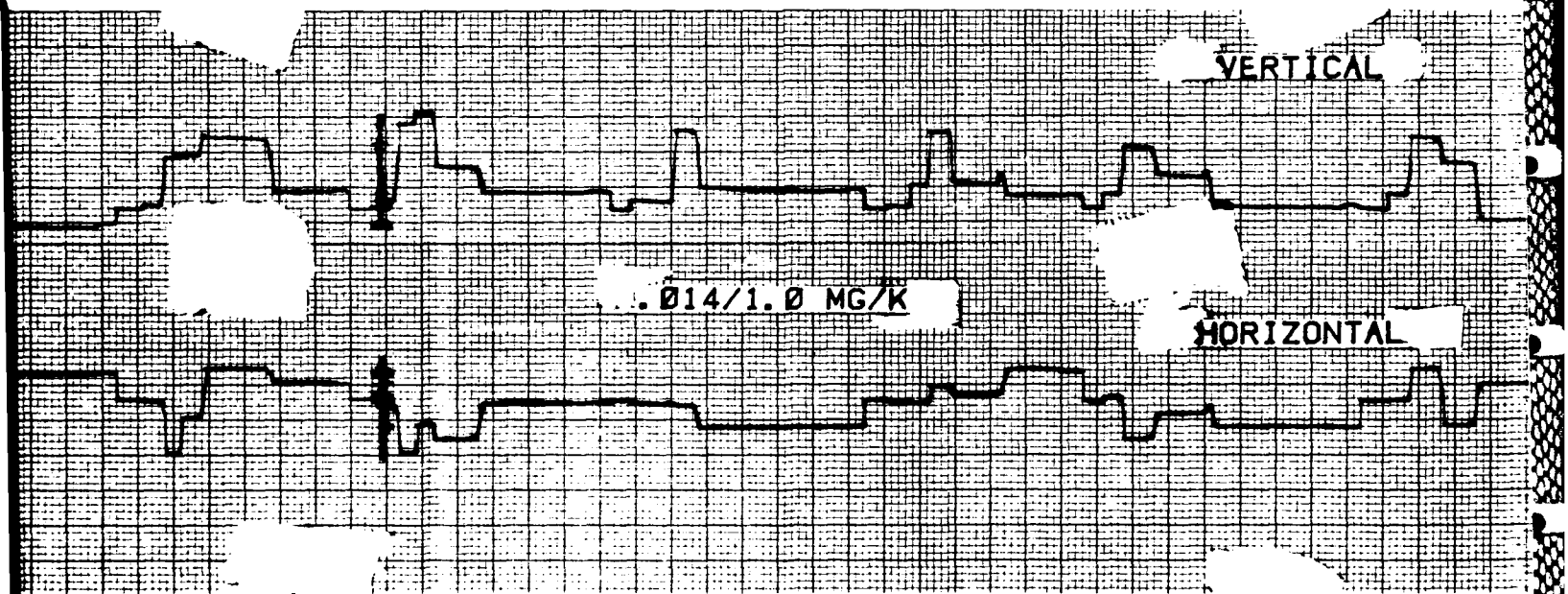
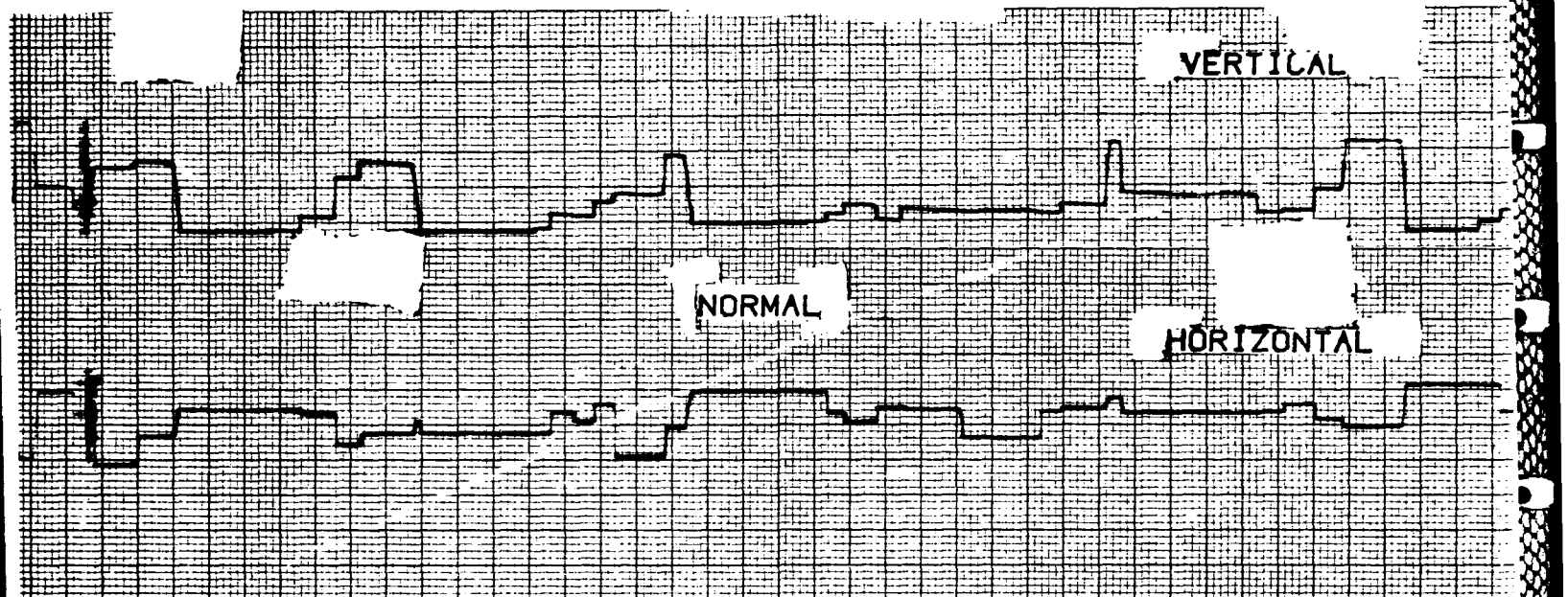


Figure 18

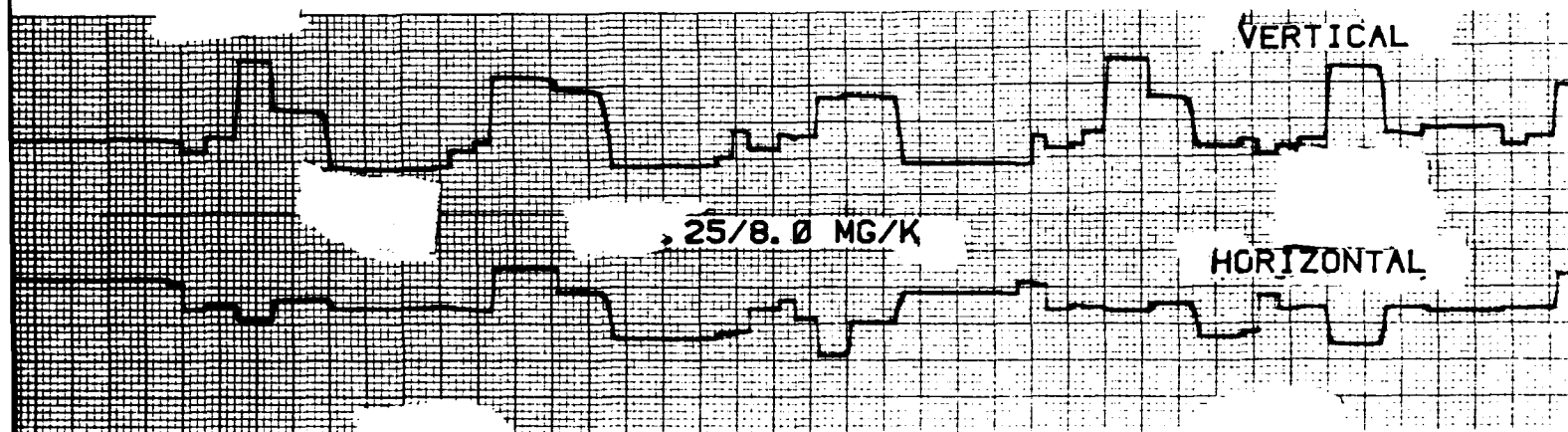
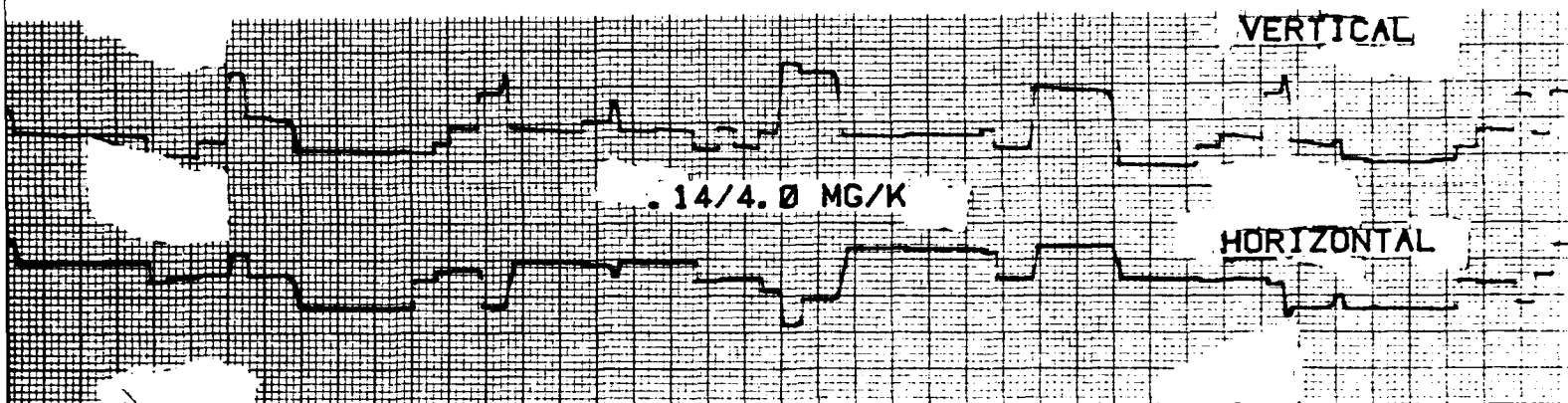
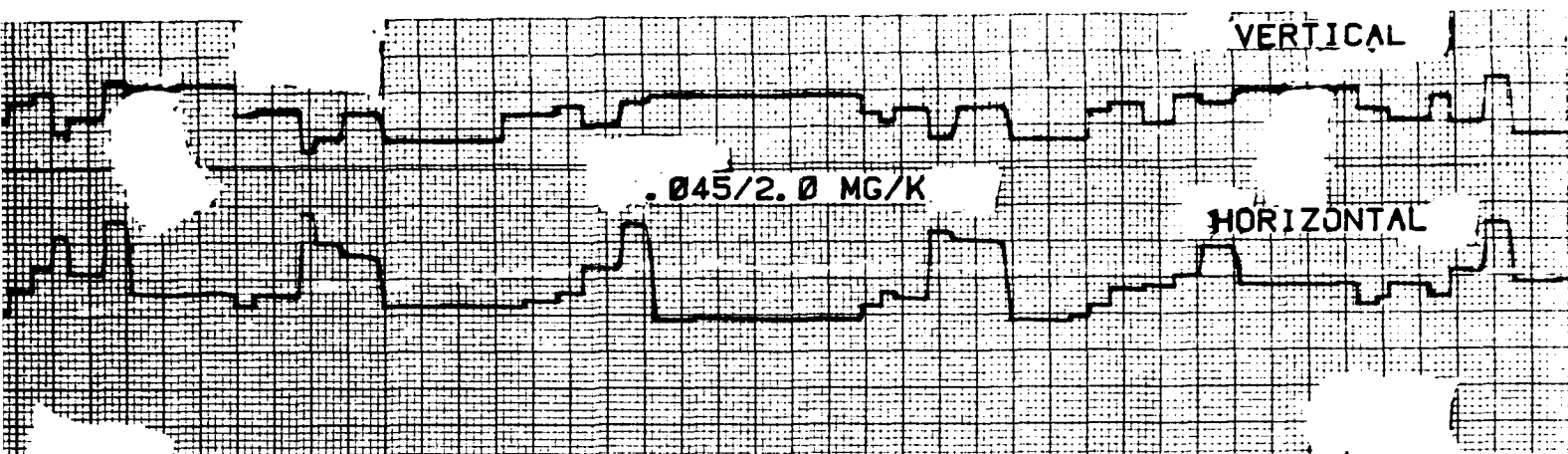


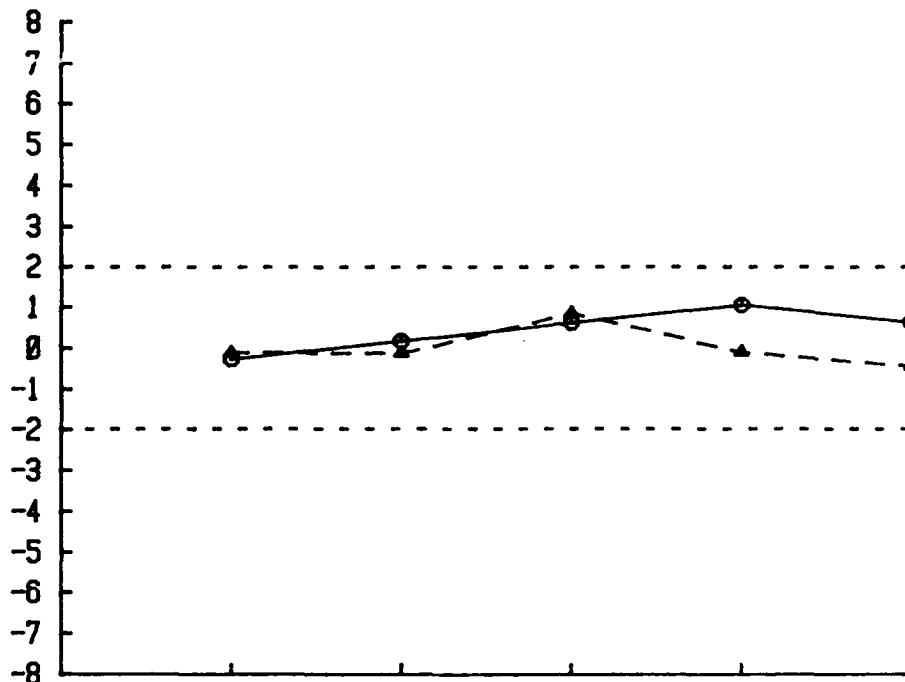
Figure 18

ATR-PAM
PERCENT OF TARGETS FIXATED

▲ - - - ▲ EARLY
○ - - - ○ LATE

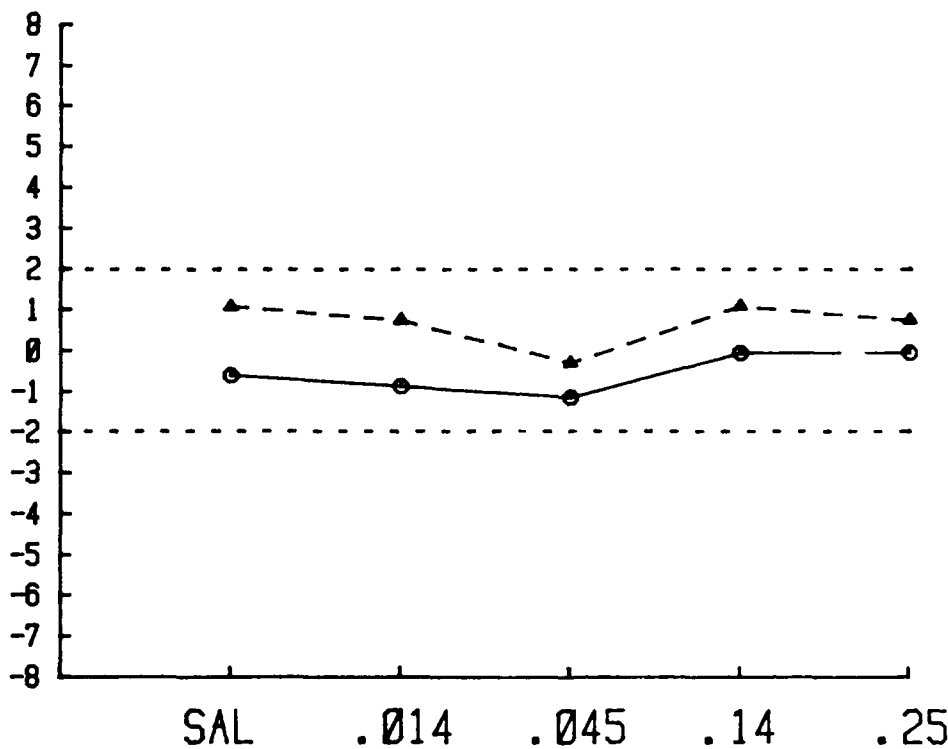
SUBJECT 1

Z SCORE



SUBJECT 2

Z SCORE

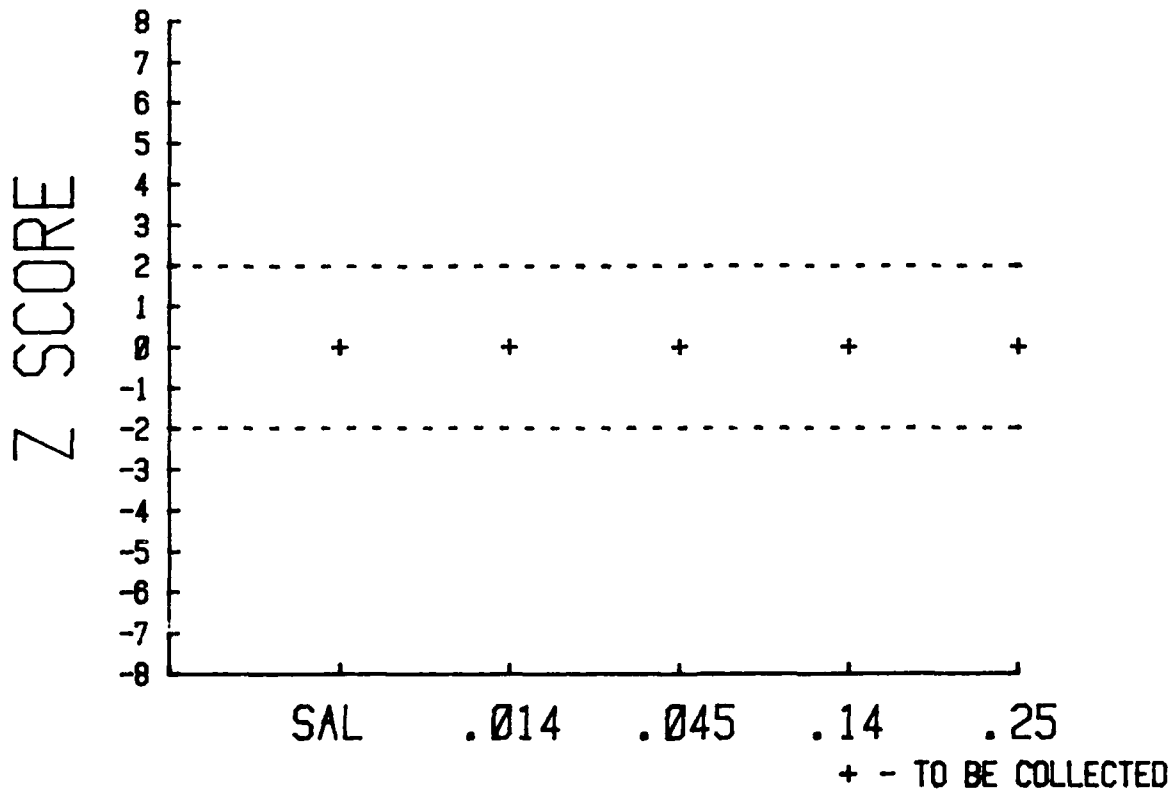
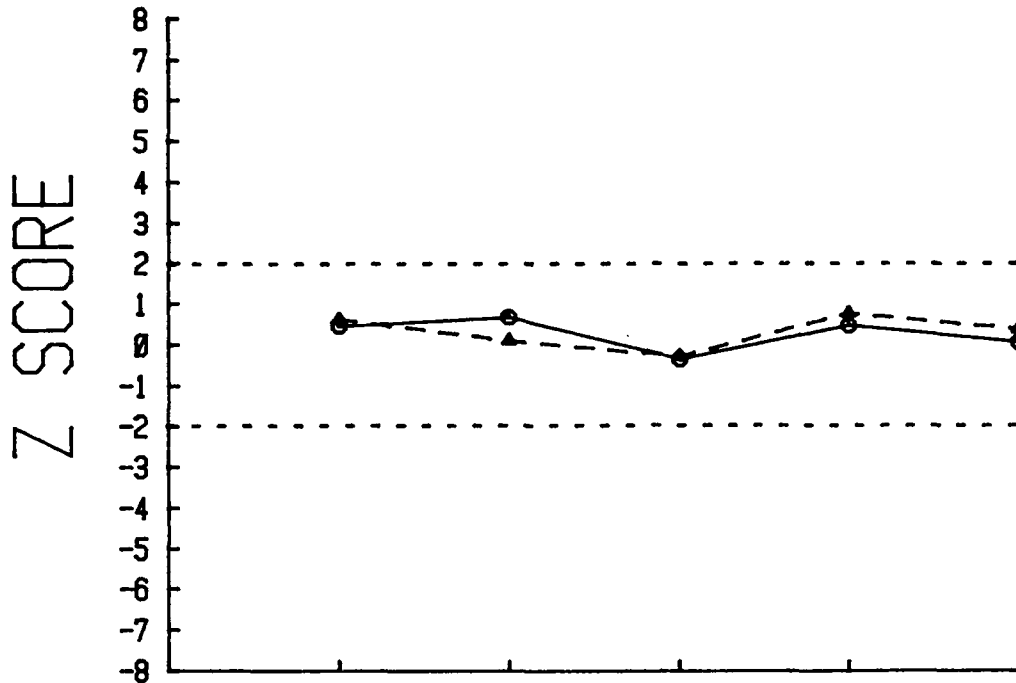


MG/K
Figure 19

ATR-PAM
PERCENT OF TARGETS FIXATED

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

SUBJECT 3



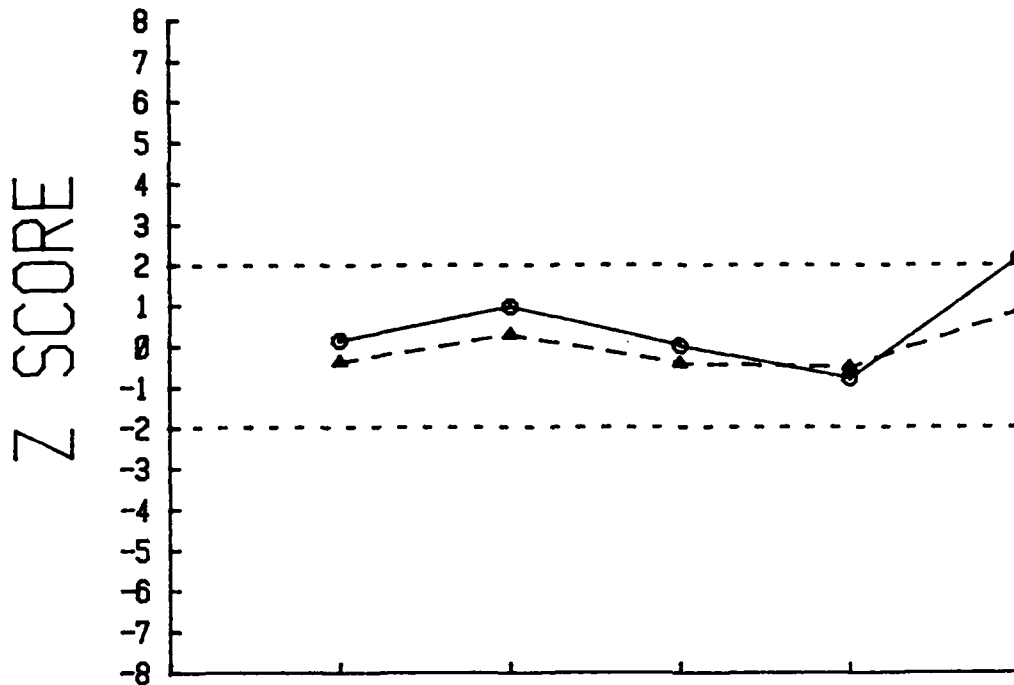
MG/K

Figure 20

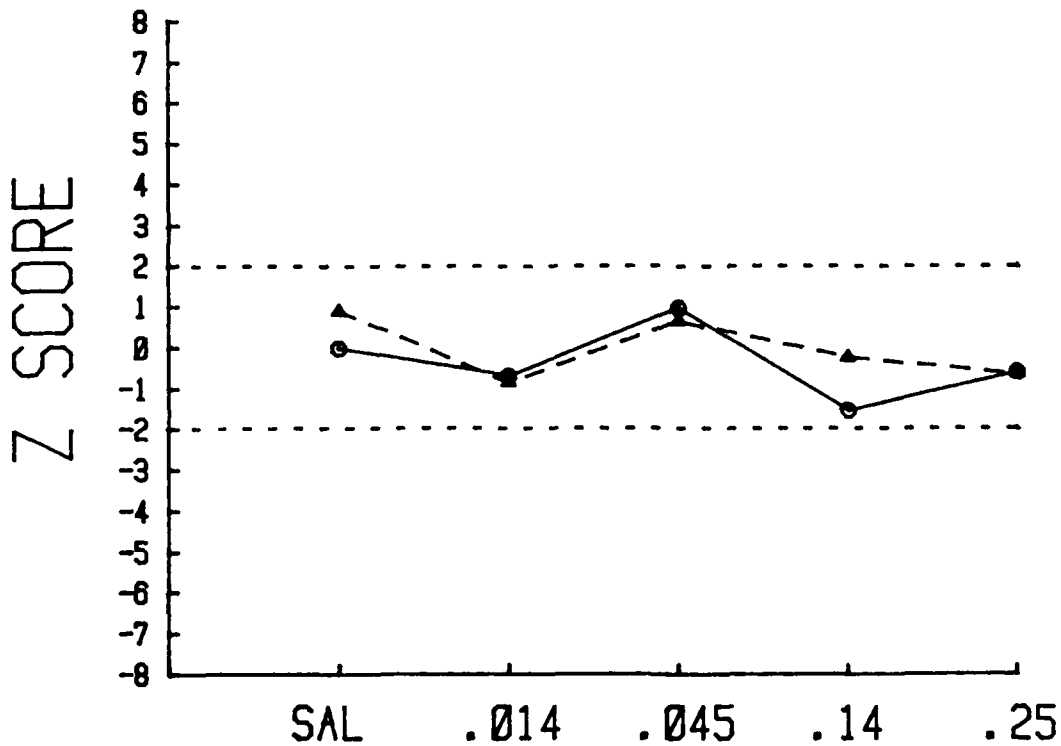
ATR-PAM TIME TO FIND TARGET

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

SUBJECT 1



SUBJECT 2



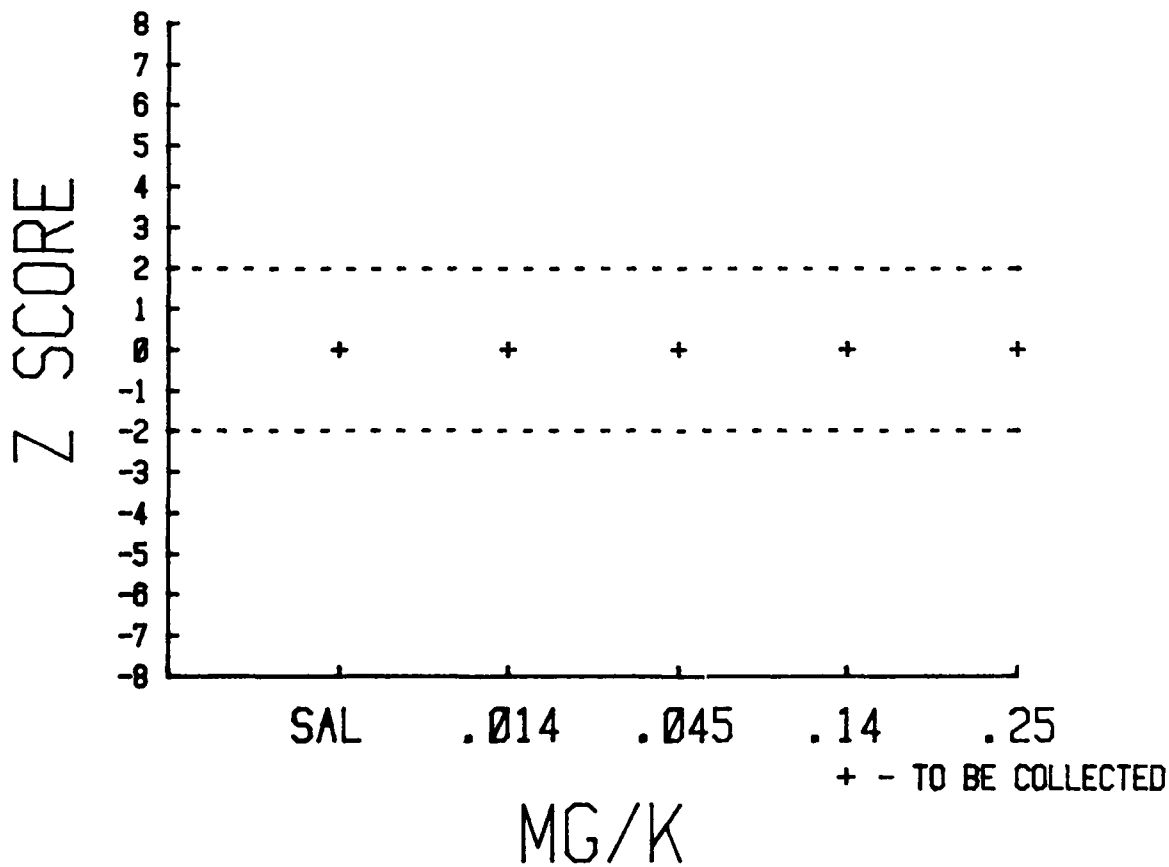
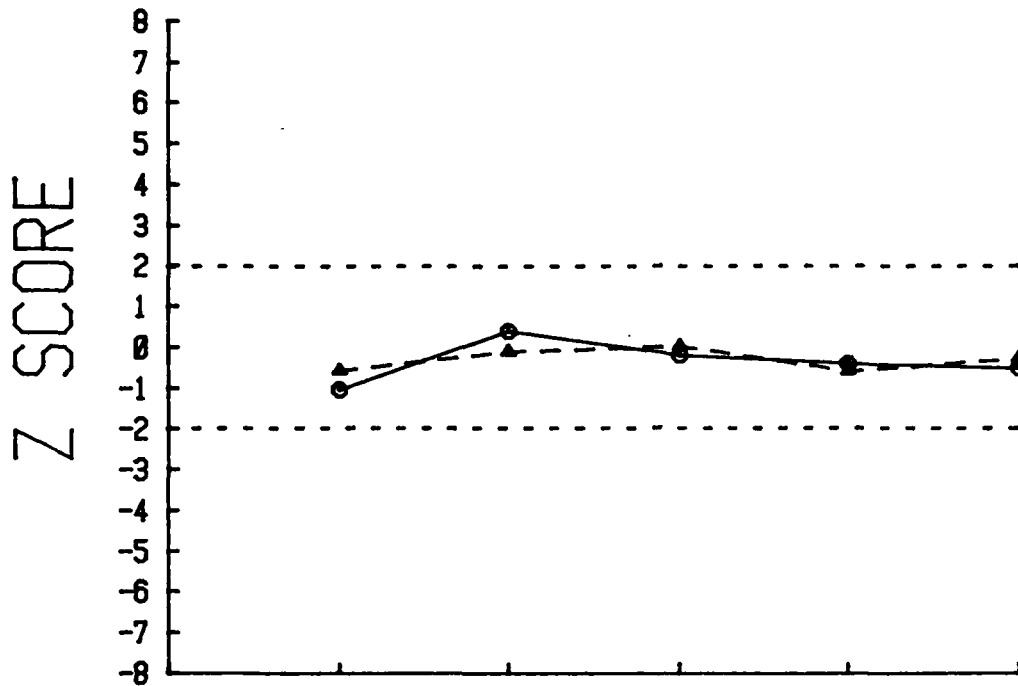
MG/K

Figure 21

ATR-PAM TIME TO FIND TARGET

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

SUBJECT 3



+ - TO BE COLLECTED

MG/K

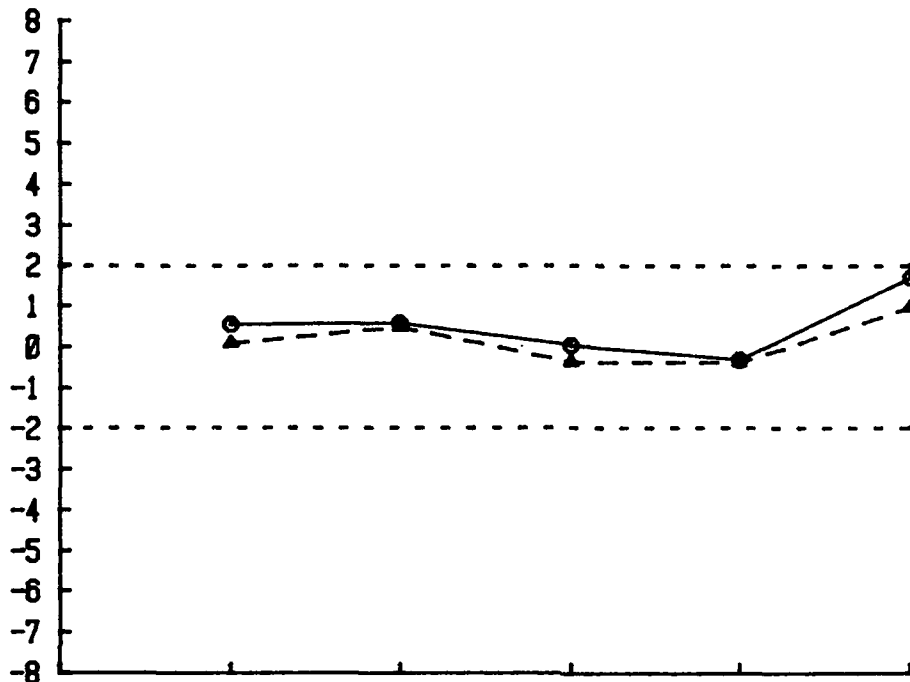
figure 22

ATR-PAM NUMBER OF FIXATIONS TO FIND TARGET

▲ - - - - ▲ EARLY
○ - - - - ○ LATE

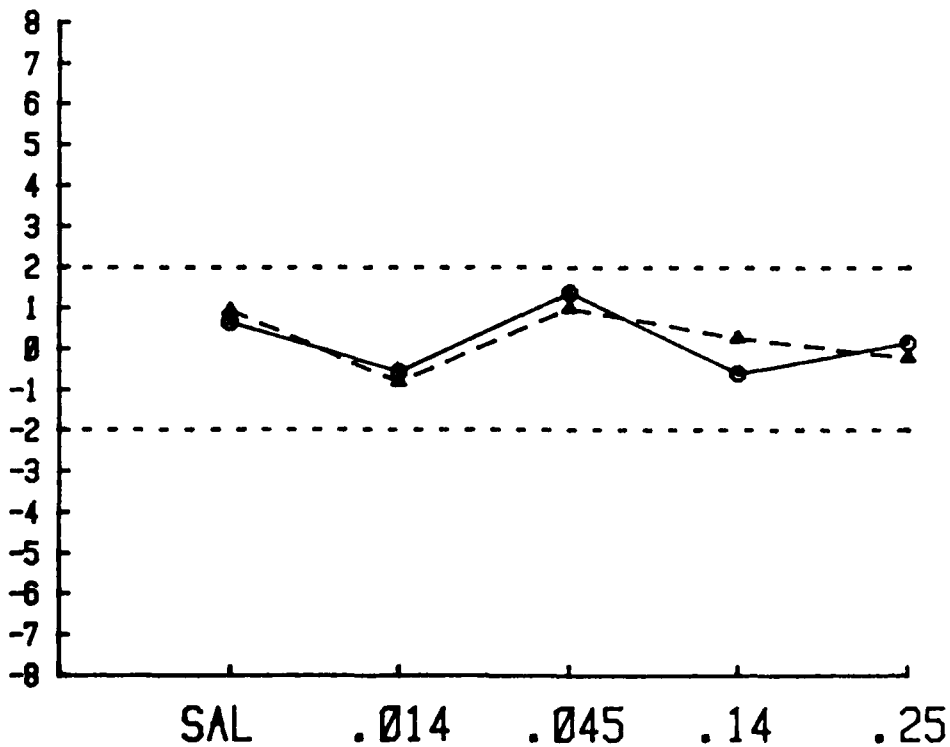
SUBJECT 1

Z SCORE



SUBJECT 2

Z SCORE



MG/K

Figure 23

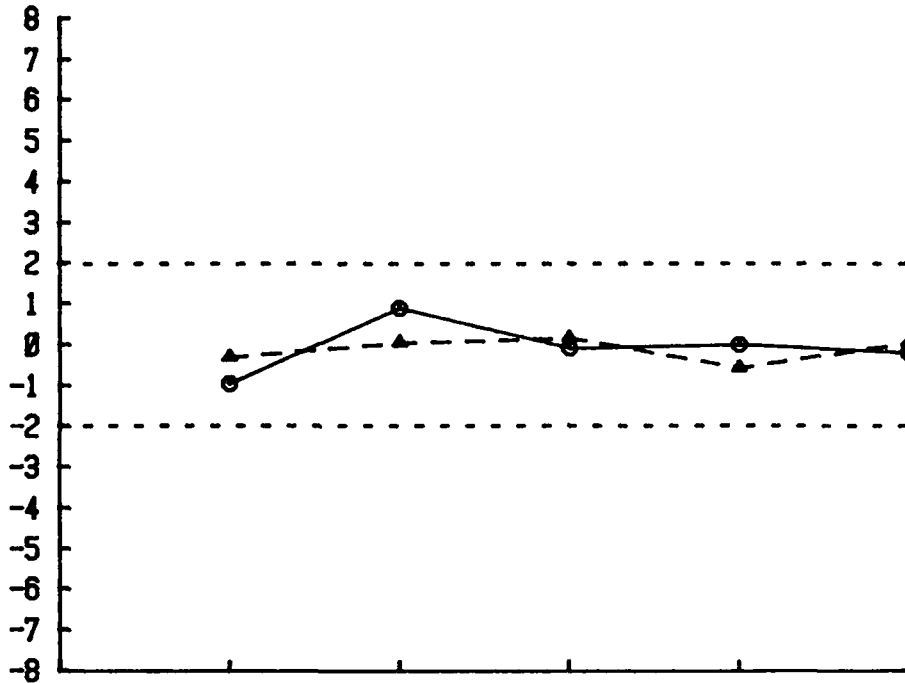
ATR-PAM

NUMBER OF FIXATIONS TO FIND TARGET

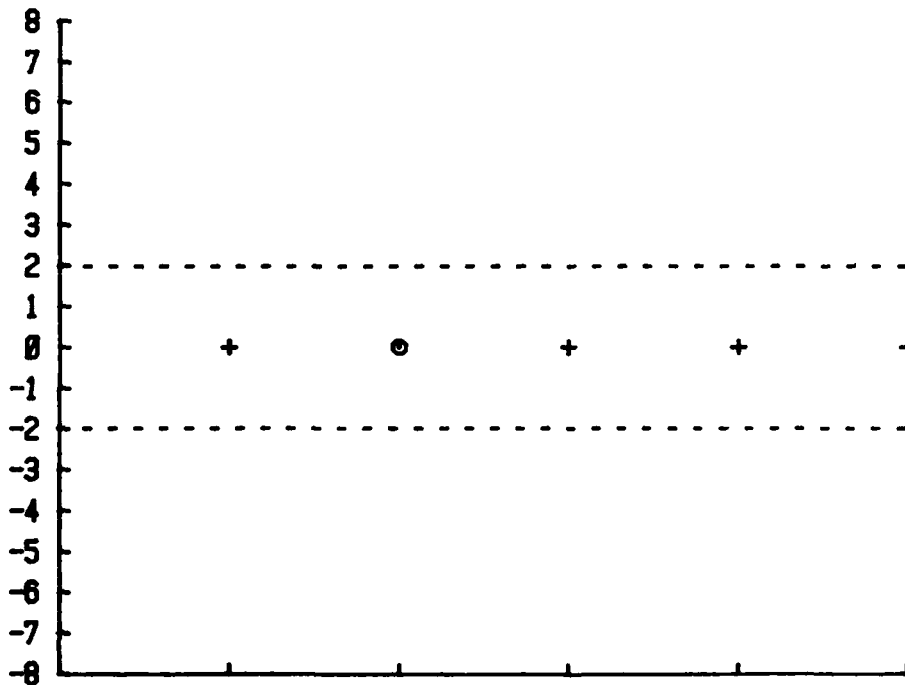
▲ - - - - ▲ EARLY
 ○ - - - - ○ LATE

SUBJECT 3

Z SCORE



Z SCORE



SAL .014 .045 .14 .25

+ - TO BE COLLECTED

MG/K

Figure 24

Atropine - Pralidoxime "Worst Case" Block Scores on Visual Search


Subject 1; .25 + 8.0 mg/K; Late Session

	<u>Baseline Avg.</u>	<u>Baseline Std.</u>	<u>Drug Avg.</u>
Percent of targets fixated	98.3	1.6	98.6
On successful trials:			
Time to find target (msec.)	308	13	365
Number of fixations to find target	1.22	.07	1.50
Oculomotor:			
Saccadic velocity (deg./sec.)	282	5.1	275
Fixation drift (degrees)	.34	.03	.38
Fixation duration (msec.)	605	68	353
Error in fixating target (deg.)	.43	.08	.62

Pyridostigmine - Summary

The protocol for this agent called for the chronic administration of 7 mg/K of pyridostigmine to be given orally twice daily over a period of 14 days. Performance on Visual Search was collected periodically during the two weeks and compared to baseline sessions collected before and after the drug period. We did not detect any convincing abnormalities in neurological status, oculomotor competence or performance on the Visual Search test.

Respectfully submitted,



E. Gregory Keating, Ph.D.
Professor of Anatomy
Project Director

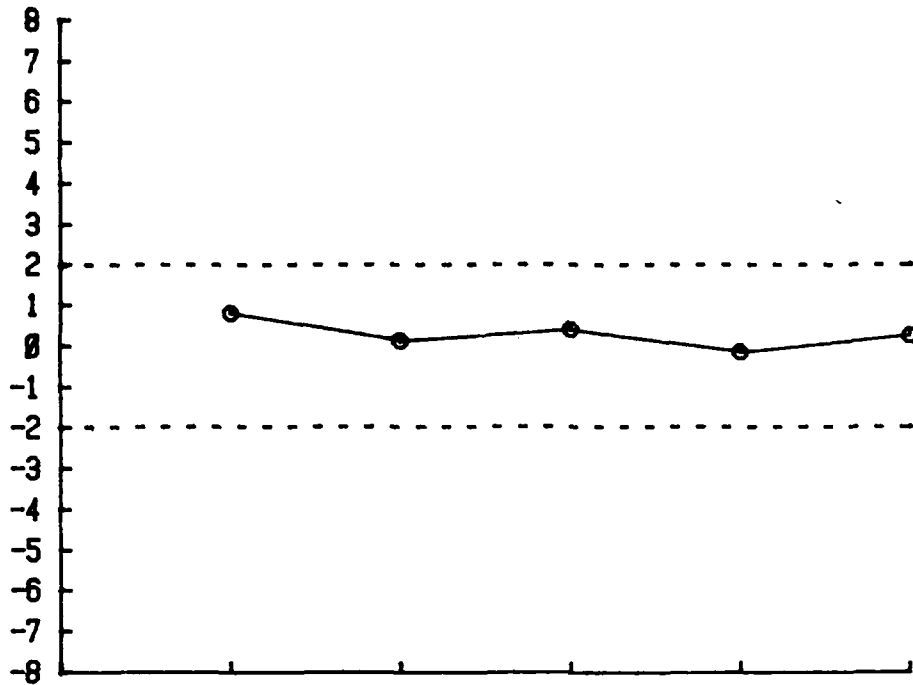
EGK:pic

cc: Capt. Thomas Harting
U.S.A.A.R.L.
P. O. Box 577
Fort Rucker, AL 36362

PYRIDOSTIGMINE - VISUAL SEARCH
PERCENT OF TARGETS FIXATED

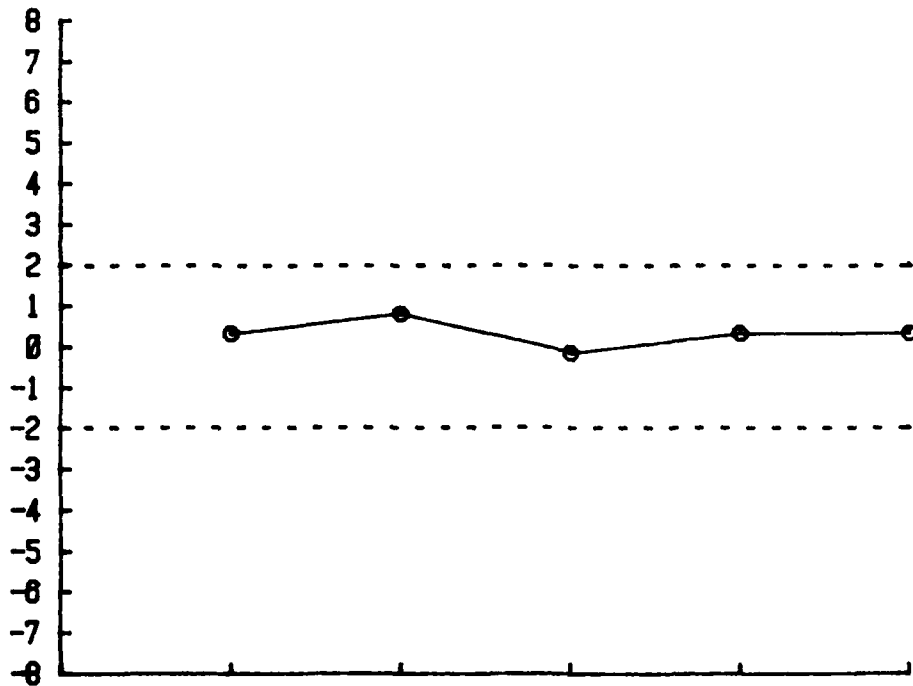
▲ - - - - ▲ EARLY

Z SCORE



SUBJECT 1

Z SCORE



SUBJECT 2

DAY2 DAY4 DAY10 DAY11 POST

MG/K

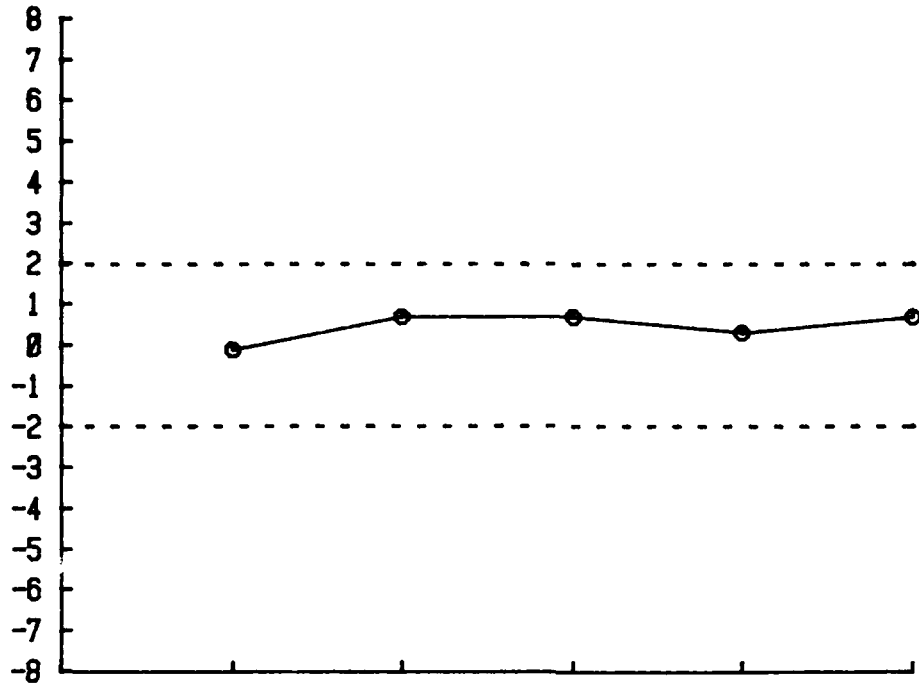
Figure 25

PYRIDOSTIGMINE - VISUAL SEARCH PERCENT OF TARGETS FIXATED

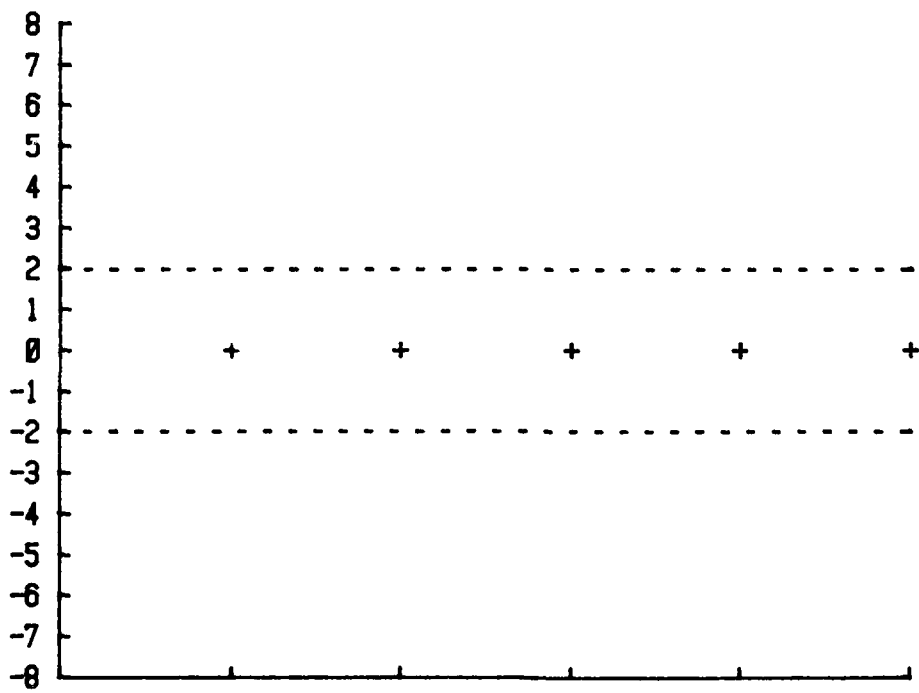
▲ - - - - ▲ EARLY

SUBJECT 3

Z SCORE



Z SCORE



DAY2 DAY8 DAY10 DAY12 POST

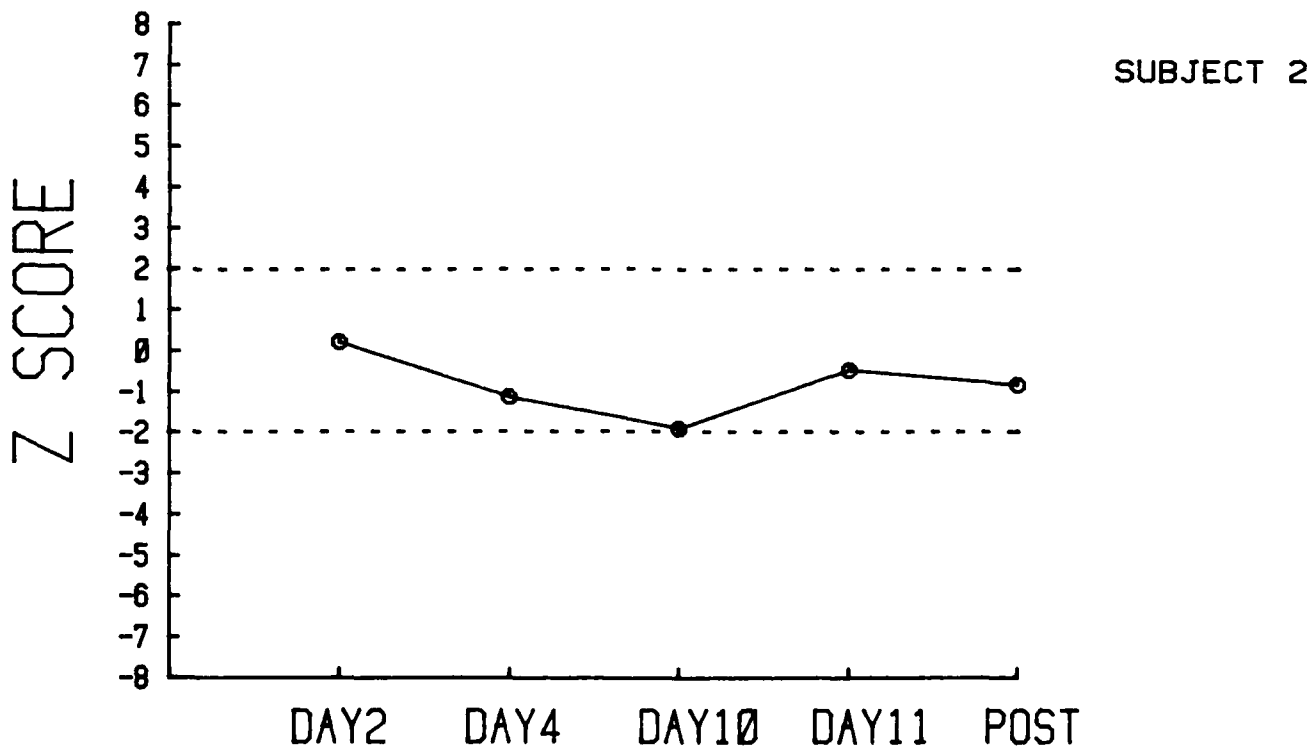
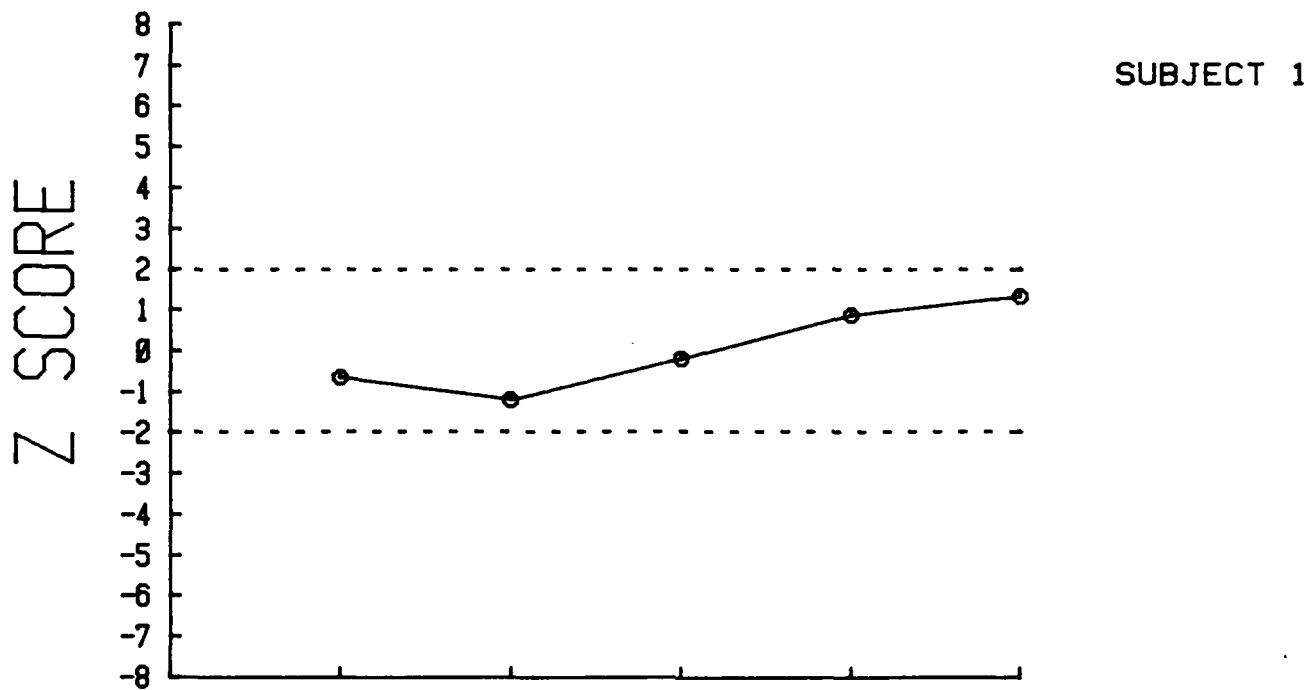
+ - TO BE COLLECTED

MG/K

Figure 26

PYRIDOSTIGMINE - VISUAL SEARCH
TIME TO FIND TARGET

▲ - - - - ▲ EARLY



MG/K

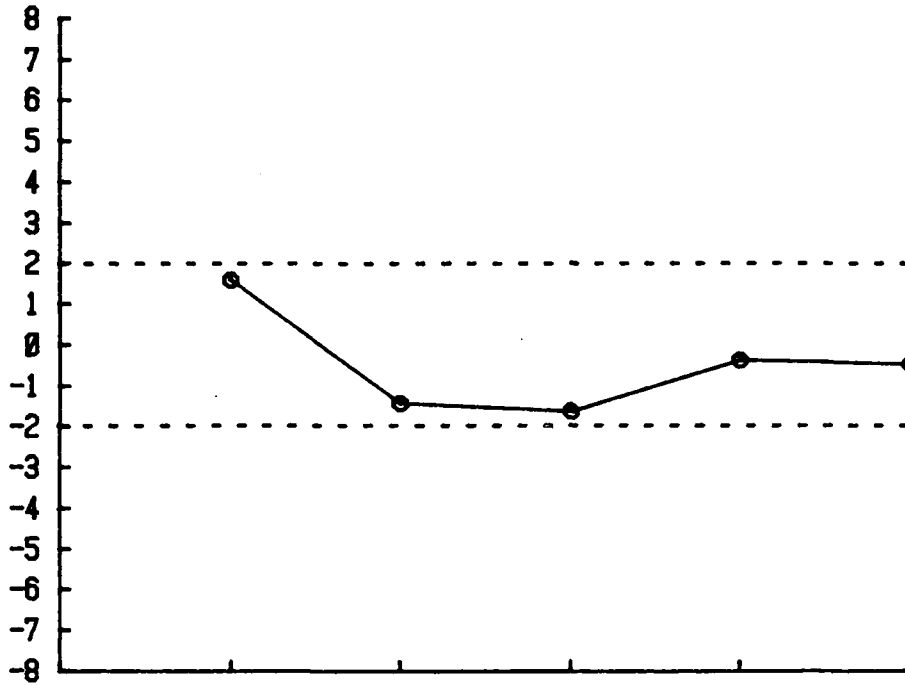
figure 27

PYRIDOSTIGMINE - VISUAL SEARCH
TIME TO FIND TARGET

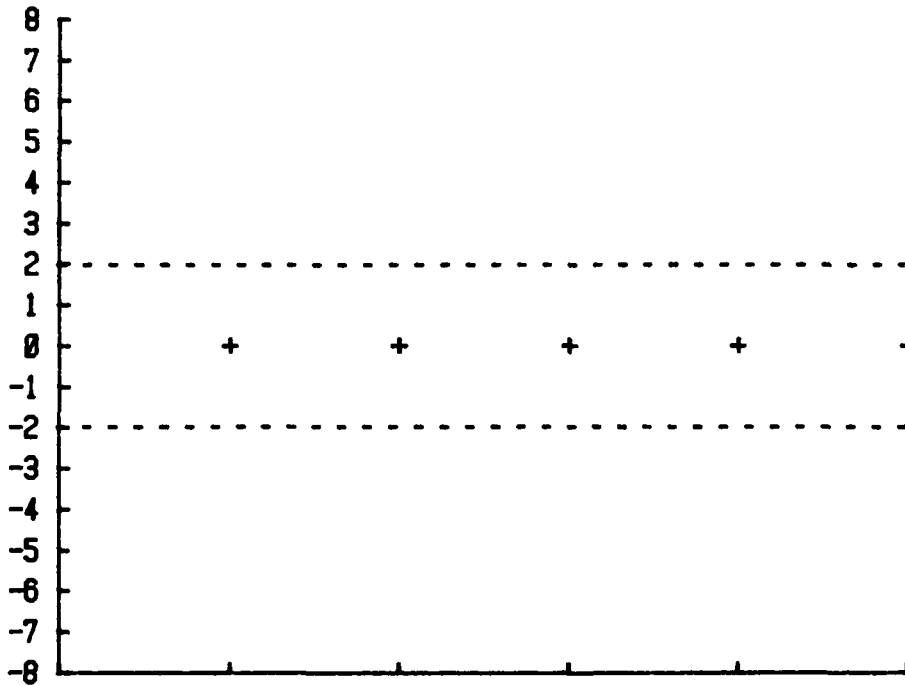
▲ - - - - ▲ EARLY

SUBJECT 3

Z SCORE



Z SCORE



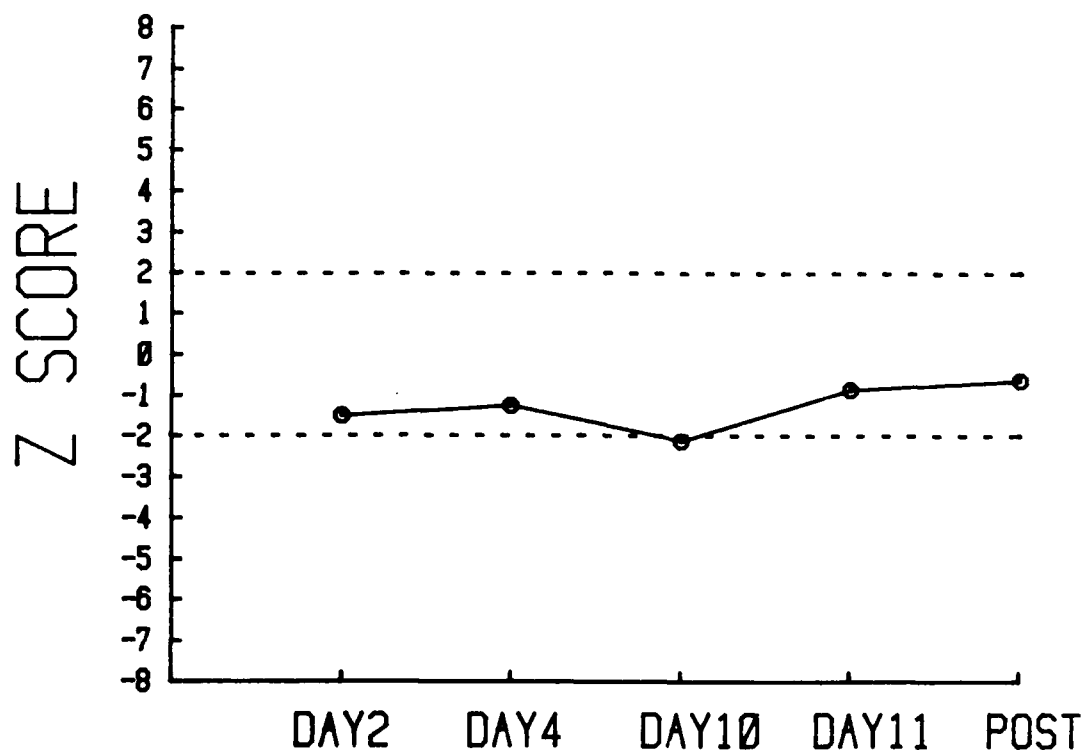
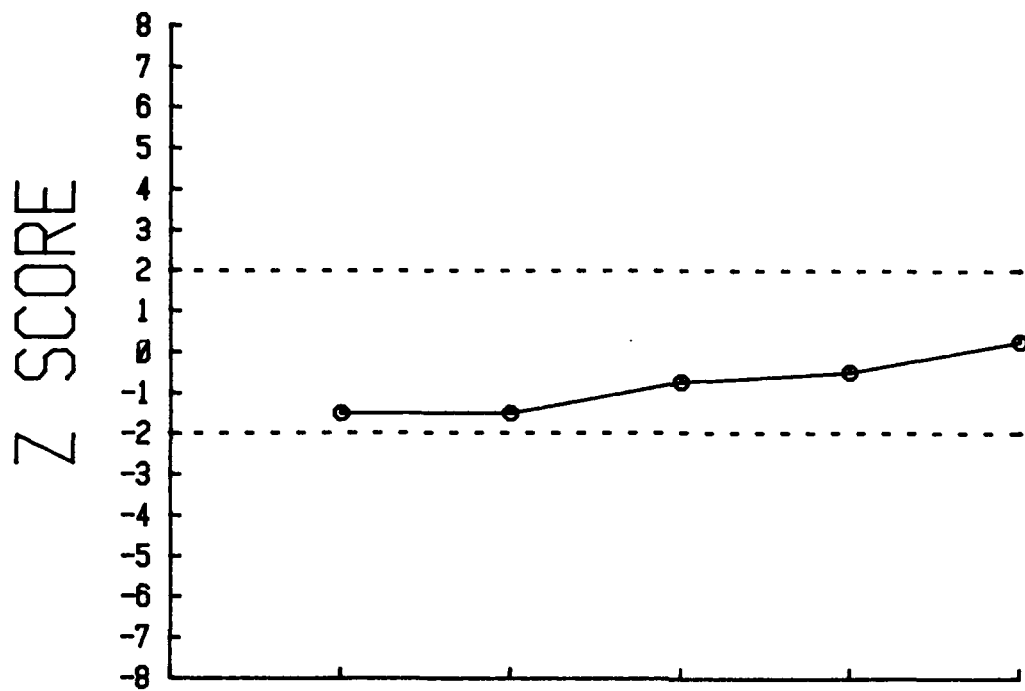
DAY 2 DAY 8 DAY 10 DAY 12 POST

+ - TO BE COLLECTED

MG/K
Figure 28

PYRIDOSTIGMINE - VISUAL SEARCH NUMBER OF FIXATIONS TO FIND TARGET

▲ - - - - ▲ EARLY



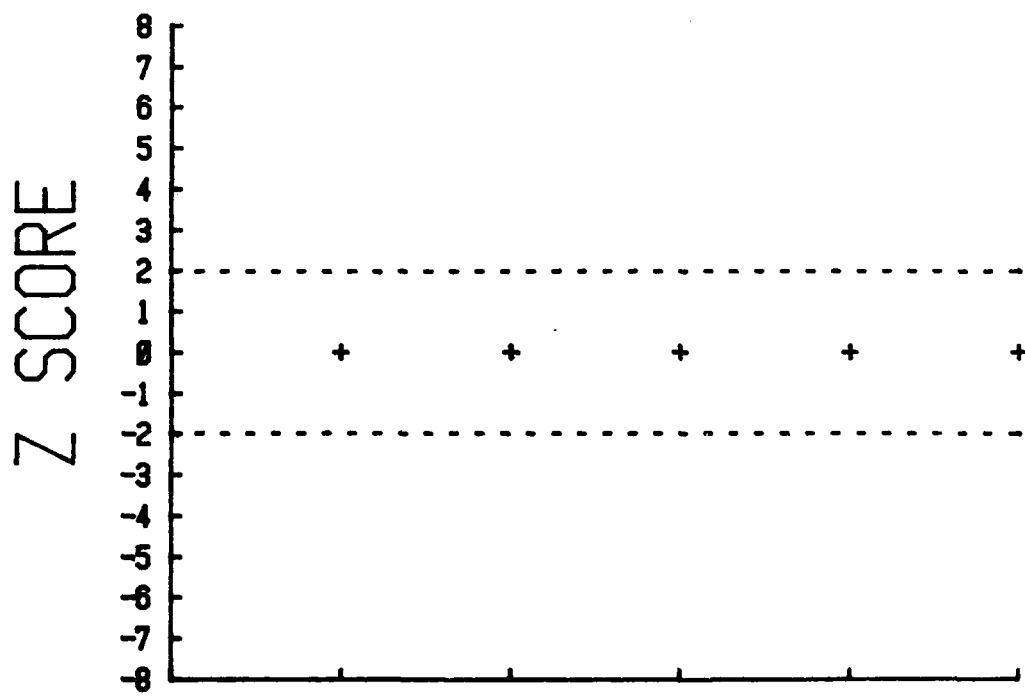
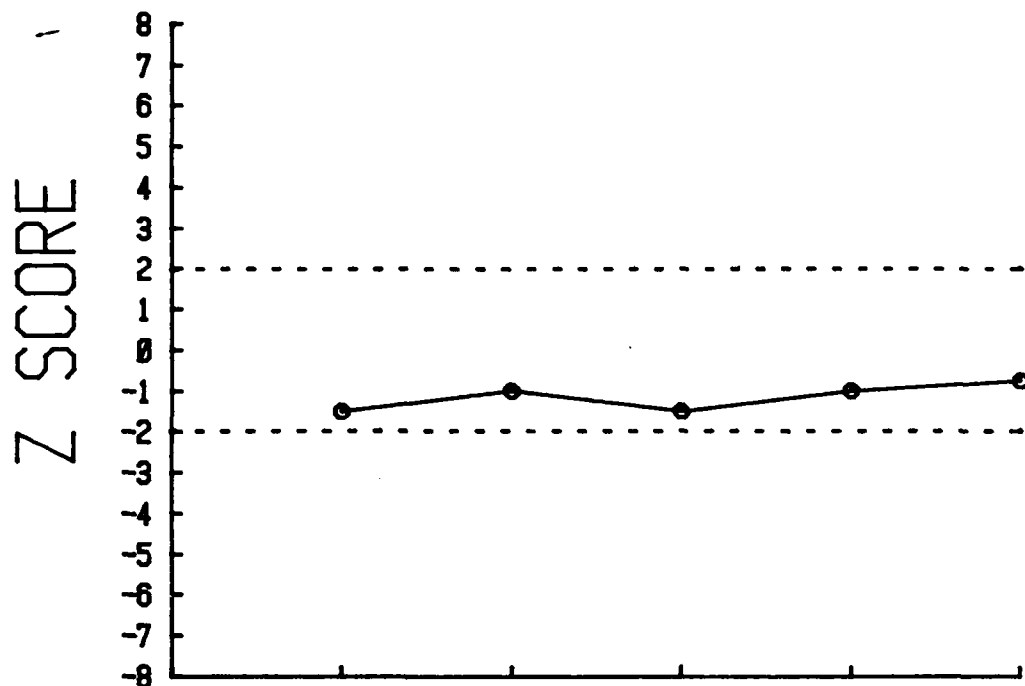
MG/K

Figure 29

PYRIDOSTIGMINE - VISUAL SEARCH NUMBER OF FIXATIONS TO FIND TARGET

▲ - - - - ▲ EARLY

SUBJECT 3



DAY2 DAY8 DAY10 DAY12 POST

+ - TO BE COLLECTED

MG/K
figure 30

END

DATE

FILMED

9-88

DTIC