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Cognitive Effects of ACTH 4-10 in the Elderly[1,2]

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FERRIS, S. H., G. SATHANANTHAN, S. GERSHON, C. CLARK AND J. MOSHINSKY. *Cognitive effects of ACTH 4-10 in the elderly.* PHARMAC. BIOCHEM. BEHAV. 5: SUPPL. 1, 73–78, 1976. The polypeptide ACTH 4-10 has been shown to facilitate learning in animals, and possibly to improve attention and memory in normal human subjects. The purpose of this study was to assess the effects of ACTH 4-10 in cognitively impaired elderly subjects. In a double blind, cross over design, 24 cognitively impaired geriatric outpatients (mean age = 71.4, 12 with mild and 12 with severe impairment) received injections of 30 mg or 15 mg ACTH 4-10 or matched placebo on 3 successive days. A cognitive test battery of memory and nonmemory tests was administered each day both before and after treatment. The 30 mg dosage produced a slowing of simple visual RT, a nonsignificant improvement trend in verbal associative memory, and significant, severity dependent facilitation or impairment in day later visual memory. The results suggest that the ACTH 4-10 effects on cognitively impaired elderly are dependent on the dosage and on the baseline cognitive level of the subjects.

ACTH 4-10 Elderly Cognitive impairment Memory Attention

ACTH 4-10 (Organon OI 63) is a synthetic polypeptide consisting of the sequence of amino acids 4 to 10 of the ACTH molecule. Although ACTH 4-10 has virtually no hormonal or other peripheral effects [1], extensive animal research has demonstrated significant central nervous system activity [1,2]. Specifically, this compound produces dramatic improvement in animal learning, although the question has not been fully resolved as to whether the drug affects learning directly, or whether it improves performance by increasing attention or arousal.

Several human studies with normal volunteers have suggested that ACTH-MSH fragments are behaviorally active. Kastin *et al.* [8] and Miller *et al.* [9] have reported small changes in visual memory, and Gaillard and Sanders [6] have shown that ACTH 4-10 may prevent loss of concentration during a continuous reaction time task. More recently, effects on attention and/or memory have been reported by Sandman *et al.* [13] and Miller *et al.* [10]. However, Dornbush and Nikolovski [3] found no effects of ACTH 4-10 on unisensory short-term memory tasks, but the drug impaired performance on a complex, bisensory memory task. These results were interpreted to suggest that ACTH 4-10 affects general arousal level. Overall, the results with human subjects obtained thus far do not provide a clear cut picture of the nature of the drug's activity, and furthermore, the magnitudes of the effects reported are quite small in comparison to the effects reported in lower animals.

One possible reason for the limited effects of ACTH 4-10 in normal human subjects, as compared to the rather marked effects in animals, is that normal volunteers may be functioning at optimal levels and thus further improvement may be difficult to produce. However, if human subjects whose performance is below normal were tested, the effects of ACTH 4-10 might then be more dramatic. Senile elderly patients represent a major category of individuals whose cognitive abilities are below normal. As such, they are potentially an ideal group for evaluating the mental effects of ACTH 4-10. These patients show marked deficits in short-term memory, and they also are below average in tests of attention. The purpose of this study was to determine the effects of ACTH 4-10 in elderly patients on a wide assortment of cognitive tests, with particular emphasis on memory and attention. This initial double blind study in elderly subjects has been preceded by two open safety studies which established that ACTH 4-10 produces no adverse effects in this subject population.

METHOD

Subjects

Twenty-four geriatric outpatients who were living in the community took part in the study. Their age range was 62-81, with a mean age of 71.4. Each patient had significant, age related cognitive impairment, as documented by clinical evaluation and performance on psycho-

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[2] The EEG data from this study were analyzed by the EEG computer laboratory at the Health Sciences Center, SUNY at Stony Brook. We thank Dr. Max Fink and Mr. Peter Irwin for their considerable advice and assistance.
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metric tests. The patients were assigned to either a Mild Group (N = 12) or an age matched Severe Group (N = 12). The mild patients had scores below the mean for their age and WAIS vocabulary level on at least three subtests of the Guild Memory Scale [7]. These Mild patients were not functionally impaired. The Severe patients had scores which were 1 SD or more below the mean on at least 3 subtests of the Guild. These severe patients also suffered from mild to moderate functional impairment. Half of the patients in each group were males, and half were females.

The subjects had no clinical evidence of illness, as determined by history, physical examination, EKG and laboratory tests (SMA-12, blood count and urinalysis). They had no past history of brain injury, psychosis, mental retardation, alcoholism, epilepsy, or other neurological disorder.

Procedure

A double blind, placebo controlled, cross over design was used. On 3 consecutive days, the patients received by subcutaneous injection one of the following: 15 mg ACTH 4-10, 30 mg ACTH 4-10, or matched placebo. The order of administration to each subject of the 3 treatment conditions was completely counterbalanced across the 24 subjects. Two patients from each subject group (1 male and 1 female) were randomly assigned to each of the 6 possible treatment orders.

A repetitive test battery, consisting of 13 short tests of memory and nonmemory cognitive function, was administered twice each day, once before and once 1 hour following the injection. There were 6 nonmemory or performance tests.

1. Simple reaction time (RT). This is a measure of sensory-motor speed, attention, and maintenance of a state of readiness. The task involved release of a key to the onset of a red light. Each trial was preceded by a verbal ready signal and a 2 sec fixed foreperiod. The measure obtained was the mean of the last 10 trials, following 10 practice trials.

2. Disjunctive RT. In addition to the components of simple RT, disjunctive RT involves the additional cognitive components of sensory and motor discrimination and decision processes. This test is a sensitive index of senile impairment [4]. The task involved presentation of a red, green or yellow light, with release of a key only to red (verbal ready signal and 2 sec fixed foreperiod). Each color was presented 10 times in random sequence. The measure obtained was the mean RT for the red trials.

3. Finger tapping speed. A measure of simple motor speed, determined by the number of times the subject can depress a hand-tally counter in 15 sec, with the index finger of the dominant and nondominant hands. The measure obtained for each hand is the mean of 2 trials.

4. Number cross out. This test measures the speed with which a well-known symbol can be found within a mass of material, and relates to the functions of simple perceptual speed and attention [11]. The 150 sec task is to cross out every digit in rows of random digits which are identical to the digit indicated for each row.

5. Hidden word test. This 150 sec task involves finding as many four-letter words as possible embedded in 22 rows of otherwise meaningless continuous sequences of capital letters [11]. This test is a measure of speed of perceptual closure.

6. Digit symbol substitution test. This standard test from the WAIS relates to perceptual-motor speed, attention, and learning the relationship between symbols. The subject must quickly write the appropriate symbols which correspond to each of a long sequence of numbers. There is a 90 sec time limit.

Also included in the test battery were 7 tests of immediate memory, short-term memory, and short-term associative memory:

1. Digit span forward. A standard measure of immediate memory span. The score is the longest sequence of digits correctly recalled following verbal presentation of the digit sequence.

2. Digit span backward. A more difficult memory span test in which the numbers presented must be recalled in reverse order.

3. Recognition of faces. A test of nonverbal short-term memory [12]. Following a 1 min presentation of a composite of 16 facial photographs, the subject must identify these 16 faces within a composite of 32 faces. The measure obtained is the mean number correct for presentation of 2 different forms of the test.

4. Paragraph recall. A subtest of the Guild Memory Scale, this test measures short-term memory for meaningful verbal material. Following verbal presentation of a short paragraph, the subject must recall as many phrases as possible. After this measurement of immediate recall, the paragraph is read a second time, and recall is then tested 5 min later as a measure of delayed recall.

5. First and last names. A test of short-term associative memory for verbal material [5]. After a 3 min inspection of a list of 10 paired first and last names, a list of only the last names is presented. The measure obtained is the number of first names correctly recalled.

6. Paired associate learning. A subtest of the Wechsler Memory Scale [14], this test provides a measure of improvement with practice in short-term, associative memory. A list of 10 word pairs is verbally presented, followed by presentation of only the first member of each pair. The subject must respond with the appropriate word associate. There are three presentations and test trials of the same list. The measure obtained is the number correct for each trial.

7. Design recall. A subtest of the Guild Memory Scale, this test provides a measure of nonverbal associative memory. A series of 10 simple drawings is presented, each containing a number from 1–10. The same designs without the numbers are then presented, and the subject must recall the number corresponding to each design. The measure obtained is the number of correct paired associates.

Most of the tests in the battery are available in a sufficient number of equivalent forms so as to minimize the item specific practice effects of repeated administration. In no case were the same materials presented predrug and postdrug. The duration of the test battery was about 45 min. In addition to the standard battery, on the second and third treatment days, day-later recall tests for memory materials from the previous day were also administered, prior to the predrug testing. The purpose of this recall testing was to determine any effects on long-term retention for materials learned following drug administration on the previous day.

In addition to the cognitive testing, vital signs (pulse and blood pressure) and 15 min of EEG on tape were recorded both before and after cognitive testing, before and after drug administration. Finally, in order to assess any behav-

TABLE 1

COGNITIVE TEST RESULTS: SIGNIFICANT F-RATIOS

Test	Source of Variance	Severity(S)	Treatment(T)	T x S	Pre-Post(P)	P x S	P x T	P x T x S
	df	1/22	2/44	2/44	1/22	1/22	2/44	2/44
Performance Tests								
1. Simple RT							2.51*	
2. Disjunctive RT								
3. Tapping Speed								
Dominant								
Nondominant				2.56*				
4.Number Cross-Out								
5. Hidden Word					34.8‡			
6. Digit Symbol		3.18*			3.8‡			
Memory Tests								
1. Digit Span								
Forward		6.49†						
Backward								
2. Faces		8.66†	2.44*	2.54*				
3. Paragraphs								
Immediate		13.9‡						
Delayed		20.6‡						
4. First-Last Names		13.6‡			5.80‡			3.26†
5. Paired Associates		23.6‡			32.9‡	5.90†		
6. Designs		30.8‡			6.91†			

For this measure, Trial (t) was an additional repreated factor: t ($F = 101.5$, ‡$df = 2/44$) and txS ($F = 3.35$, †$df = 2/44$).
*$p<0.10$.
†$p<0.05$.
‡$p<0.01$.

ioral changes produced by ACTH 4-10, the Modified Patient Mood Scale (Raskin and Crook, 1973, unpublished) was administered. This reliable geriatric self-rating scale consists of 48 adjectives which are rated on a 4 point scale. In scoring this scale, the items are clustered into 8 mood factors.

RESULTS

The results for each measure were analyzed statistically by means of three-way analyses of variance (Severity × Treatment × Pre-Post), with repeated measures for two of the factors (Treatment and Pre-Post). All significant F-ratios and nonsignificant trends ($p<0.10$) for the cognitive tests are listed in Table 1. The two Severity groups did not differ on the performance tests, but with the exception of Digit Span Backward, the Severe group was consistently worse than the Mild group on the memory tests. Averaging across the other factors, there were no significant treatment differences, and there were no Treatment × Severity interactions. For two performance tests (Hidden Word and Digit Symbol) and for two memory tests (Names and Designs), performance was better following treatment. However, except for Names, the absence of any Pre Post × Treatment interactions indicates that the improvement was not drug related. Since the test materials presented postdrug differed from the materials used predrug, the overall postdrug improvements were probably due to general practice effects. For Paired Associates, performance was worse following treatment, but this change was also not drug related. There was also a Pre–Post × Severity interaction, reflecting less postdrug decrement for Mild than for Severe. Finally, for Paired Associates there was also significant improvement over the three learning trials, with a Trial × Severity interaction reflecting more rapid improvement for the mild subjects.

For one of the memory tests, First and Last Names, the results do suggest drug related effects. The data analysis revealed a significant Pre–Post × Treatment × Severity interaction. The nature of this interaction effect is shown graphically in Fig. 1. In addition, multiple paired-comparisons were made among the means for the twelve conditions, using the Tukey (a) method [15]. All of the means for the Severe group were significantly lower than for the Mild group (critical difference = 1.70, $p<0.01$). For the Mild group, performance improved postdrug for 30 mg, but not for 15 mg or placebo. For the Severe group, improvement occurred for 15 mg, but not for 30 mg or placebo. However, these drug related postdrug improvements merely represent suggestive trends, since the mean differences were not quite statistically significant (critical difference = 1.37, $p>0.05$).

Marginal drug related effects were also found for one of the performance tests, Simple RT. Although the Pre Post × Treatment interaction was significant only at $p<0.10$, our particular interest in the RT measure in the light of previous findings [6] led us to carry the data analysis further. The nature of the Pre Post × Treatment interaction is shown in Fig. 2. Although it appears that RT was slower postdrug on 30 mg and faster postdrug for both 15 mg and placebo, a Tukey (a) test revealed that only for placebo was the Pre Post difference statistically significant (critical difference = 25.1, $p<0.05$). However, the mean RT postdrug for 30 mg was significantly greater than the

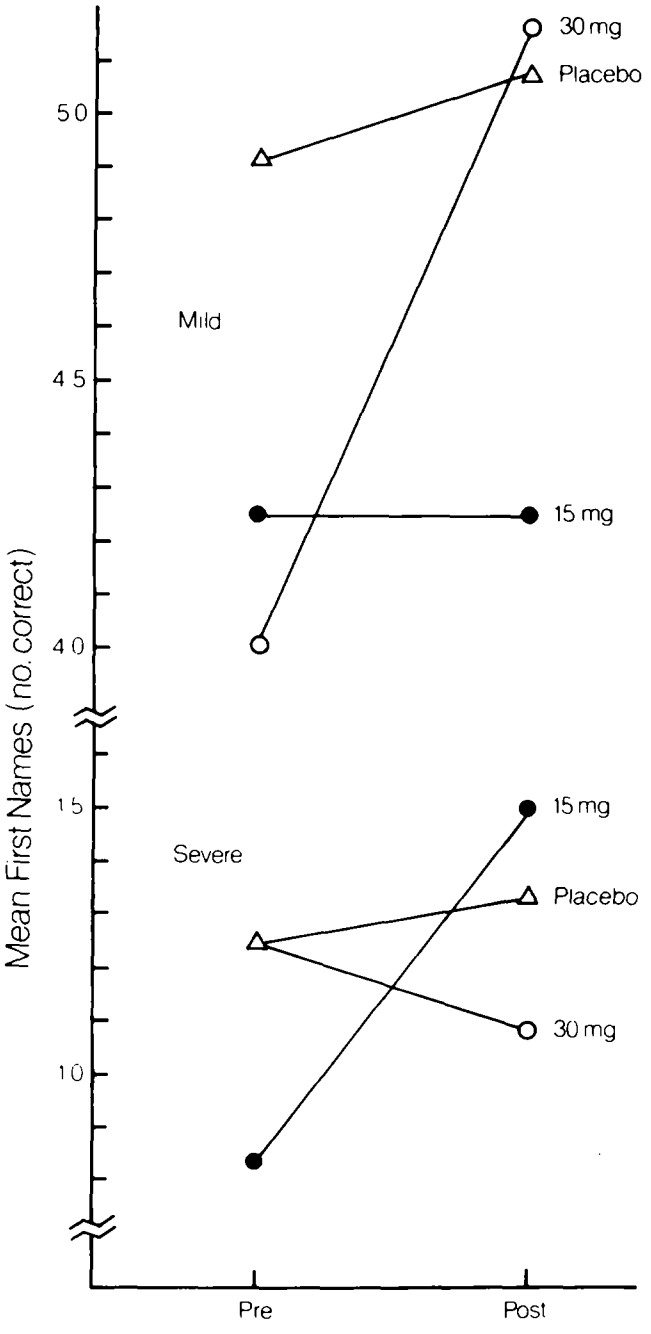

FIG. 1. Mean number correct on the First and Last Names Test, before and after treatment with 15 mg ACTH 4-10, 30 mg ACTH 4-10 or placebo, for both the Mild and the Severe subjects.

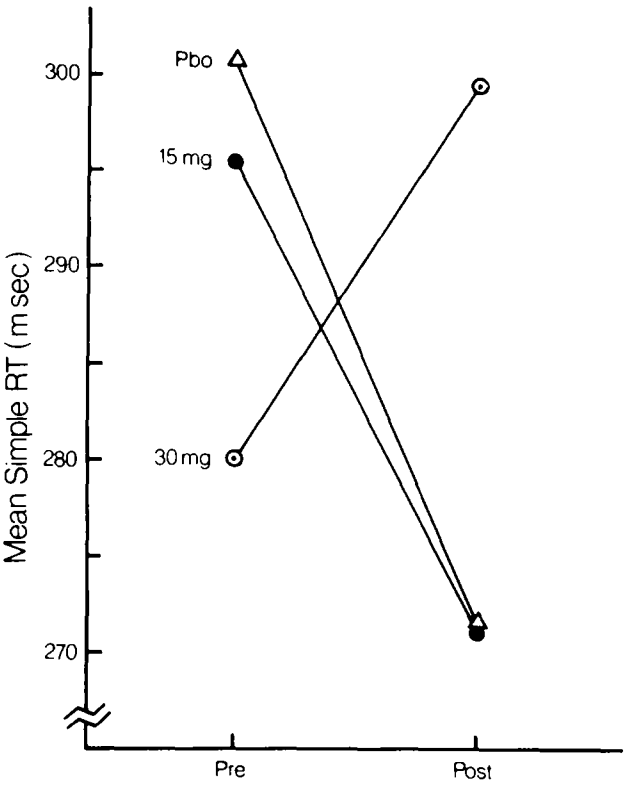

FIG. 2. Mean Simple RT before and after treatment with 30 mg ACTH 4-10, 15 mg ACTH 4-10, or placebo.

postdrug means for both 15 mg and placebo. Since the predrug baseline for 30 mg was actually lower than the baseline for 15 mg or placebo, these results may be interpreted to mean that the 30 mg injection produced slower simple RTs than did 15 mg or placebo.

For day-later recall, there were also some drug related effects. Since each subject received recall testing for only 2 of the 3 treatment conditions, separate statistical analyses were done for 30 mg vs placebo, 15 mg vs placebo, and 30 mg vs 15 mg. Thus, 3 two-way analyses of variance (Severity × Treatment) were done for each recall measure, with N = 4 for each Severity group. The analyses indicated that for 4 of the 5 tests (Paragraphs, Names, Paired Associates, and Designs) the Mild subjects recalled more items the next day than the Severe patients ($p<0.05$). Furthermore, for the 2 tests of nonverbal (visual) memory, there were statistically significant treatment effects for the analyses comparing 30 mg with placebo. For Recognition of Faces, there was a significant Drug × Severity interaction, $F(1,6) = 18.1$, $p<0.01$, reflecting the fact that the Mild patients scored higher after placebo than after 30 mg, whereas the Severe patients scored higher after 30 mg (see Fig. 3). The Tukey (a) test revealed that the Severe Placebo condition differed significantly from the other three conditions (critical difference = 2.37, $p<0.05$). For Design Recall, there was a significant treatment difference (placebo better than 30 mg, $F(1,6) = 10.4$, $p<0.05$), and also a significant Drug × Severity interaction, $F(1,6) = 10.4$, $p<0.05$, indicating that the better recall for placebo only occurred for the Mild group (see Fig. 4). The Tukey (a) test indicated that the Mild Placebo condition differed significantly from the other 3 conditions (critical difference = 2.39, $p<0.01$). Thus for both Designs and Faces, memory was better after placebo for the Mild subjects. For Faces, however, the Severe subjects performed better after 30 mg.

The mean subject self ratings for each of the 8 Mood Scale factors were also analysed using 3-way analyses of variance. Although there were some mood differences related to Severity Group and pretreatment vs posttreatment, there were no statistically significant drug related changes for seven of the mood factors (depression, competency, fatigue, carefree, friendliness, anxiety and

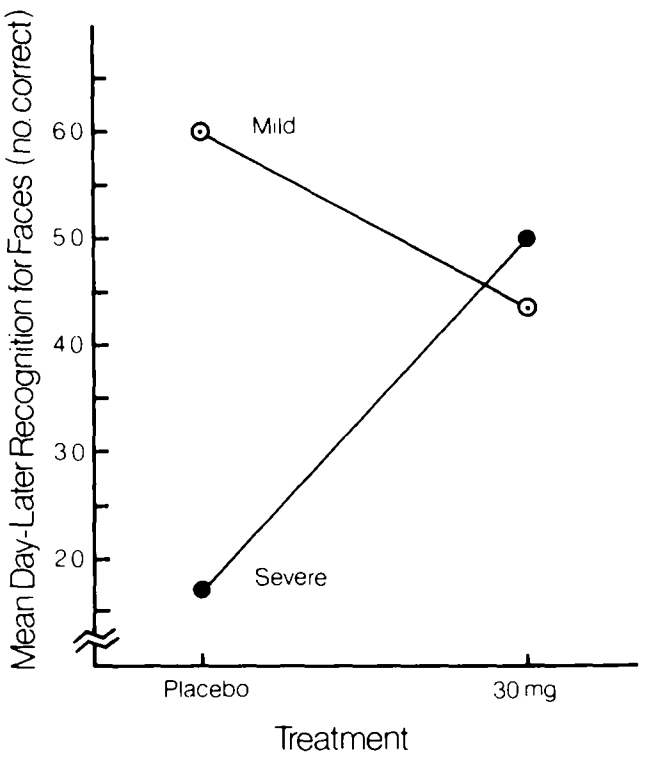

FIG. 3. Mean number of faces correctly recognized on the Memory for Faces Test, on the day following injection of either 30 mg ACTH 4-10 or placebo, for both the Mild and the Severe subjects.

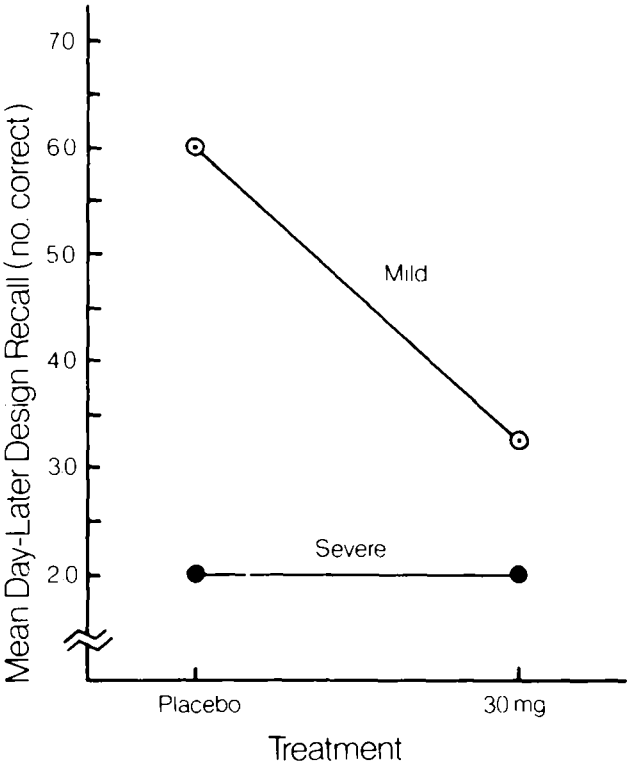

FIG. 4. Mean number correct on the Memory for Designs Test, on the day following injection of either 30 mg ACTH 4-10 or placebo, for both the Mild and the Severe subjects.

hostility). For 1 factor, confusion-forgetfulness, there were significant Treatment × Pre Post, $F(2,44) = 4.26$, $p<0.05$ and Treatment × Pre Post × Severity, $F(2,44) = 5.40$, $p<0.01$. The self-rating of confusion-forgetfulness tended to increase following 30 mg, remain the same for 15 mg, and decrease slightly for placebo, and these changes tended to be greater for the Severe group than for the Mild group.

Finally, there were no statistically significant changes in vital signs, nor were there any drug related changes in the EEG. A computer analysis of the various EEG parameters revealed some differences between the EEG sessions before and after cognitive testing, but there were no differences related to the 3 drug conditions.

DISCUSSION

It is apparent that in cognitively impaired elderly subjects, 15 30 mg of ACTH 4-10 does not produce general effects on immediate or short-term memory, or on nonmemory cognitive function. However, small changes were produced in certain measures, thereby indicating that the compound does in some way alter certain aspects of cognitive functioning in impaired elderly subjects.

Specifically, simple visual RT was slower following the 30 mg injection as compared to 15 mg or placebo. Since a test of motor speed (Finger Tapping) and other visual tasks (Number Cross Out and Hidden Word) were unaffected by ACTH 4-10, it is unlikely that the decrement in Simple RT was due to motor or sensory slowing. Thus the RT slowing is most easily explained as due to impairment of attention or ability to maintain a state of readiness. Since disjunctive RT was not affected by ACTH 4-10, the higher cognitive processes of discrimination and decision were apparently not impaired.

Although the RT results in this study may appear to contradict the findings of Gaillard and Sanders [6], the RT conditions of the two studies were quite different. The impairment in the present study was produced during a relatively short series of trials, whereas the improvement found by Gaillard and Sanders was apparently dependent on the prevention of inattention or fatigue during a complex and extremely long (30 min) continuous RT task.

Only 1 of the 6 tests of short-term memory provided data consistent with the view that ACTH 4-10 facilitates memory shortly after drug administration. The results for the First and Last Names Test suggest only the possiblity (since the trends were not statistically significant) that verbal associative memory may be enhanced by this compound, and furthermore, that the response as a function of the severity of baseline memory impairment may be dependent on the dosage injected. Only the 30 mg dosage produced an improvement trend in the mild patients, and only 15 mg produced improvement in the severe patients.

Perhaps the most interesting result of the study relates to the effects on day-later recall for memory materials presented after treatment on the previous day. For the Mild patients, performance was impaired on the day following the 30 mg injection on the 2 tests of nonverbal, visual memory (Faces and Designs). On the other hand, the recognition for faces of the Severe patients was improved following 30 mg of ACTH 4-10. However, the reliability of these results may be questioned due to the small sample sizes for the day-later recall analyses. Therefore, any

attempts at interpreting these interesting findings in terms of effects on long term consolidation or retrieval of visual memory should await further study of the possible effects of ACTH 4-10 on day-later recall.

A final issue concerns the question of the effective dose range for this compound. Since in this study the 15 mg dose produced only one trend which was not statistically significant, it does not appear that 15 mg is an adequate dose in elderly patients. Although 30 mg did produce some behavioral effects, insufficient data is available to rule out the possibility that a higher dose might have either more dramatic or even quite different effects.

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