

Cholinergic system and constructional praxis: a further study of physostigmine in Alzheimer's disease

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SUMMARY Subcutaneous or intravenous administration of physostigmine improved the copying of geometric figures in three out of six patients with presumed Alzheimer's disease who showed a remarkable constructional disturbance. This improvement reached its maximum 30 to 60 minutes after the physostigmine administration. These results not only provide further evidence supporting the hypothesis that central cholinergic potentiation ameliorates some of the impairments of Alzheimer's disease, but implicate a possible important role of the cholinergic system in the integration of constructional praxis.

Since the first reports of beneficial effects of physostigmine on the cognitive functions of patients with Alzheimer's disease appeared in 1979,¹⁻³ several trials have confirmed that memory disturbance in some patients could be ameliorated by the use of centrally active anticholinesterases. Some of these trials produced substantial improvement,^{4,5} which was considered to be consistent with the hypothesis of selective loss of central cholinergic neurons in Alzheimer's disease.^{6,7}

The effect of physostigmine on constructional disability in Alzheimer's disease, which we first noted in a single case in 1979,³ has not yet been confirmed. Since our first report, we have examined five additional patients with Alzheimer's disease of mild to moderate severity who could undergo repeated psychometric tests for drug evaluation under relatively constant conditions. Of the total sample of six patients, three showed an improvement in constructional ability when given physostigmine, as assessed by copying of geometric figures. In this report we describe further observations on the effect of physostigmine on constructional disability in Alzheimer's disease.

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Patients and methods

A description of six patients who participated in this study and the overall results appear in table 1. The patients were selected from sixteen patients clinically diagnosed as having presenile dementia of the Alzheimer type whom we have followed for the past four years. The criteria for selection were as follows: (1) remarkable constructional disturbance, (2) mild to moderate dementia and (3) willingness to undergo repeated psychometric tests under relatively constant conditions. Clinical diagnosis of Alzheimer's disease was based on published research criteria.⁸ Other treatable and non-treatable causes of dementia were ruled out by extensive physical, neurological, neuroradiological and laboratory examinations. All patients scored four or less on the ischaemic score of Hachinski *et al.*⁹ Clinical features of these six patients was quite similar. They had mild to moderate degree of amnesia and disorientation. Most of them had difficulty in writing but their ability to read was relatively well preserved. Patients 1, 3 and 4 also showed dressing apraxia. Patient 3 had a moderate degree of amnesic aphasia. Although no patient showed obvious pyramidal or extrapyramidal signs, patients 1, 3 and 4 showed occasional jerky movements of the limbs and trunk, probably myoclonus. All patients showed diffuse brain atrophy of mild to moderate severity on the CT scan. The EEG was abnormal with theta-dominant slowing, but without paroxysmal discharges in all patients. It was difficult to estimate objectively the rapidity of the progress of dementia in these patients because most of them were in the early stage of the disease. However, at least at the time of this study, it was our impression that the disease progressed relatively rapidly. This was especially true in the case of patients 1, 2, 3 and 6, whose constructional disturbance deteriorated so rapidly that within half a year they could no longer do the same tasks as they did in the present

Table 1 Age, sex, duration of illness and method of drug administration of the six patients who participated in this study. Overall effects of physostigmine on memory and constructional ability are also shown

Patient No	Age (yr)	Sex	Duration of illness (yr)	Administration of physostigmine		Effect on memory test	Effect on copying figures
				Route	Dose		
1	57	M	3	subcutaneous	1 mg	partly improved†	improved
2	51	F	3	intravenous	0.3, 0.5, 0.8 mg*	improved	improved
3	63	M	3	intravenous	0.3, 0.5, 0.8 mg	nd	improved
4	62	M	4	oral	1, 2, 3 mg	tendency to improve‡	tendency to improve‡
5	60	F	4	intravenous	0.3, 0.5, 0.8 mg	NS	NS
6	54	F	3	intravenous	0.3, 0.5, 0.8 mg*	NS	NS

NS: not significant, nd: not done. *0.8 mg was avoided after one trial because of side effect. †the number of intrusions of SRT significantly reduced while LTR and TR remained unchanged. ‡statistically non-significant.

study. Informed consent was obtained for the investigation both from patients and their relatives.

Patients 2, 3, 5 and 6 were given 0.3, 0.5 or 0.8 mg of physostigmine or placebo diluted in 5% dextrose in water to 100 ml by a constant intravenous infusion for 30 minutes on non-consecutive days in a randomised order. The placebo consisted of 0.5 mg of neostigmine, a peripherally active anticholinesterase. Each patient received four or five infusions of each dose except patients 2 and 6, who became nauseated at 0.8 mg and were not given this dose again. Patient 1, as described in our previous report,³ was given 1 mg of physostigmine by subcutaneous injection. One mg of methscopolamine, a peripheral anticholinergic drug, was given by the same route five minutes before to prevent peripheral side effects. Saline was used as a placebo. In the case of patient 4, who did not consent to receive repeated injections, 1, 2, or 3 mg of physostigmine was given orally once after breakfast, each dose being maintained for a week. The order of administering these different doses was randomised and each treatment week was followed by a week of placebo administration. The drug was administered using either the double blind crossover (patients 2, 3, 6) or single blind crossover (patients 1, 4, 5) method.

To evaluate cognitive functions, memory tests and tests of copying geometric figures were administered. Although it would be preferable to employ the same, well-established battery of tests throughout the study, the range of impairment varied greatly among these patients, and it was necessary to choose tests capable of detecting the subtle changes expected in each patient. Furthermore, since the effect of physostigmine is of relatively short duration, and most of the patients were unable to concentrate for longer than half an hour, the testing time was limited to 30 minutes. We employed one task of copying figures and one task of memory for each patient. For the copying task, the Bender-Gestalt test scored by the Pascal-Suttel method¹⁰ was used in patients 2, 5 and 6, while simpler figures were used to test the other patients. For the memory test, the Selective Reminding Test (SRT)¹¹ was used which was modified according to each patient's level of impairment.

The psychometric tests were given before the drug administration and 30, 60, 120 and 180 minutes after. Only in the case of patient 1, the second test was started at 20 instead of 30 minutes. In the case of patient 4, the test at 90 minutes was added and the whole procedure was repeated on separate days during each physostigmine week. Repetitive testing of cognitive functions presents

such problems as practice effects and prior-test intrusion. To minimise these effects, completely different but comparable sets of items were used for each memory test. The models for the copying test were not changed throughout the trial for each patient, because no learning or practice effects were noted in preliminary studies.

The test scores were analysed by the two tailed Mann-Whitney U test because the number of samples was too small for Student's *t* test or a paired non-parametric test.

Results

Of the six patients, three showed a statistically significant improvement and one showed a non-significant tendency toward improvement in copying figures, while the other two showed no change. No patient showed a deterioration in copying. No apparent side effects were observed except for patients 2 and 6 who developed nausea with the 0.8 mg of physostigmine. Therefore peripheral anticholinergic drugs were not required except for patient 1.

PATIENT 1

An improvement in copying figures after double blind administration of physostigmine in this patient has already been reported.³ Here we describe the time course of this improvement, which was investigated separately after the reported trial was completed. The method of evaluating the figure copying was the same as described before.³ In short, each reproduction was assigned a "constructional score" using a three-point scale to indicate how accurately and efficiently the model was reproduced, and a "closing-in score" using a two-point scale to indicate the degree of overlap with the model. In this scoring system, a more severe constructional disturbance is indicated by a low constructional score and a high closing-in score.

Mean constructional scores were 1.0 before injection, 5.8 one hour after and 0.0 three hours after injection. Mean closing-in scores were 2.8 before injection, 1.3 one hour after and 7.5 three hours

after injection ($n = 4$). Significant differences were observed at one hour for both the constructional and closing-in scores ($U = 0$, $p < 0.028$) compared to the scores before injection. The closing-in score three hours after injection was significantly greater ($U = 0$, $p < 0.028$) than that before injection indicating that the closing-in phenomenon deteriorated three hours after injection. There were no changes after placebo administration. An example of this patient's copying is shown in fig 1.

Although a time course for memory performance was not investigated in this patient, we reported previously that the long term recall (LTR) and total recall (TR) on the SRT were not improved on the days of physostigmine injection.³ However, according to the reports that the number of intrusions,^{1, 12, 13} was reduced with physostigmine treatment, we calculated the number of intrusions for this patient. We found a reduction in number of intrusions on the days of physostigmine injection (2, 8, 5, 7) compared with the days of placebo injection (12, 12, 17, 9: $U = 0$, $p < 0.028$) or the baseline days (10, 20, 8, 7, 12, 15, 9, 14: $U = 2$, $p < 0.016$), although LTR and TR were unchanged. Therefore physostigmine improved both the constructional disability and some aspects of memory impairment in this patient.

PATIENT 2

The Bender-Gestalt test (BGT) scored by the Pascal-Suttel method and a six-item SRT were administered before and 30, 60, 120 and 180 minutes after intravenous infusion of 0.3 or 0.5 mg of physostigmine or placebo (0.5 mg neostigmine). At 0.3 mg, no statistically significant differences

were found although a few figures appeared to be copied more accurately. As shown in fig 2 the BGT scores were improved (that is, lowered) 30 and 60 minutes after the infusion of 0.5 mg of physostigmine. However this score deteriorated 180 minutes after the infusion. An example of this patient's reproduction of the figure 7 of the BGT is shown in fig 3.

In the memory test, LTR on the SRT was increased only at 30 minutes after infusion (fig 2). No changes were observed after placebo infusion.

PATIENT 3

As with patient 1, eight simple geometric figures were presented for the copying task. The scoring system was different from that of patient 1 because of the poorer performance in this case. The reproduction of any one line of the model earned one point toward the constructional score. Therefore the highest possible score for a pentagon, for example, was five. The closing-in score was determined in the same way as for patient 1.

As shown in table 2, the constructional and closing-in scores improved 30 minutes after physostigmine infusion, although the small number of samples of physostigmine 0.8 mg militates against statistical significance only at this dosage. When the constructional scores at 30 minutes were compared with each other, significant rank correlation ($r = 0.952$, $p < 0.001$) between the dose of physostigmine (0.5 mg of neostigmine was equated to 0 mg of physostigmine) and the constructional score was noted by the method of Jonckheere,¹⁴ suggesting a dose-dependent effect. An example of the copying

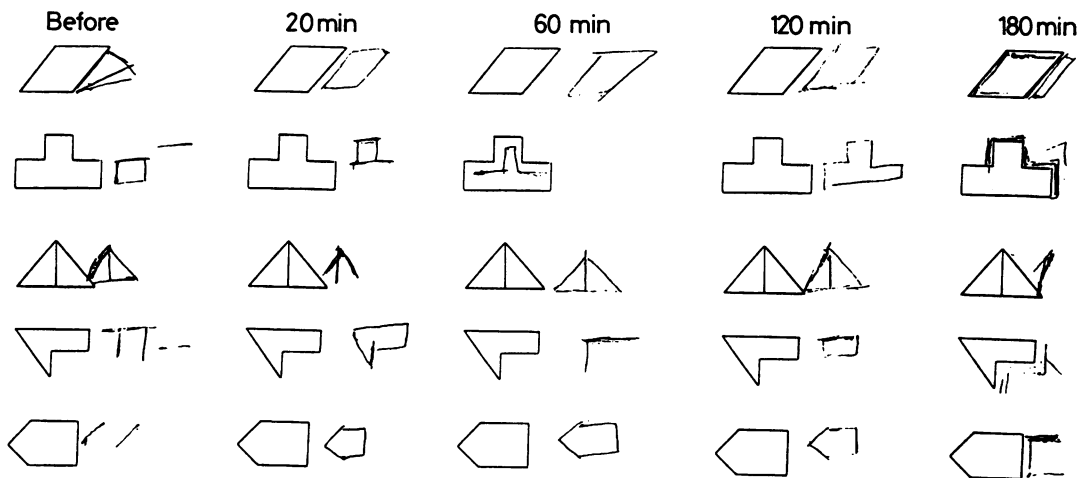


Fig 1 An example of figure copying of patient 1 after subcutaneous injection of 1 mg of physostigmine. Note marked deterioration of performance with aggravated closing-in at 180 minutes.

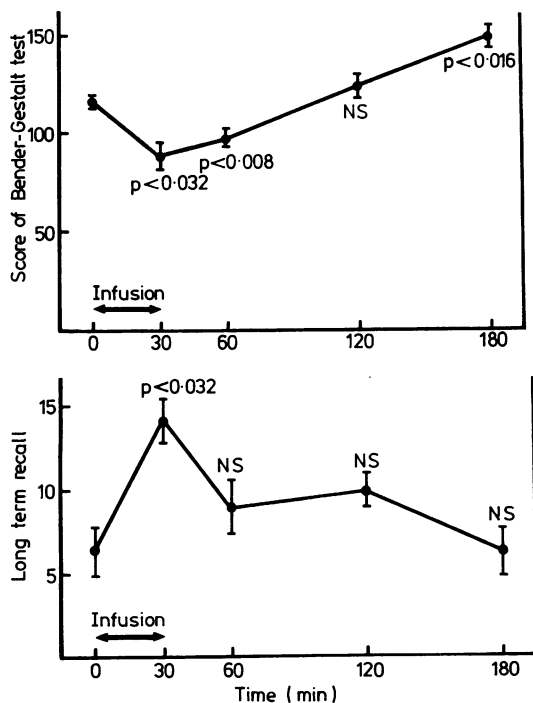


Fig 2 Effects of intravenous infusion of 0.5 mg of physostigmine on the score of the Bender-Gestalt test and the Long Term Recall of the Selective Reminding Test in patient 2. Data are expressed as mean \pm SEM of five testings. Significant probabilities were calculated in comparison with the values at zero time. $U = 0$ and 1 for the score of BGT at 60 and 180 minutes respectively. $U = 2$ for the score of BGT and the LTR at 30 minutes.

of this patient is shown in fig 4. Unfortunately a severe dysphasia in this patient precluded the evaluation of memory.

PATIENT 4

Scores on the copying task obtained before and after oral administration of various doses of physostigmine failed to reach statistical significance. However during the week of 3 mg of physostigmine, notable

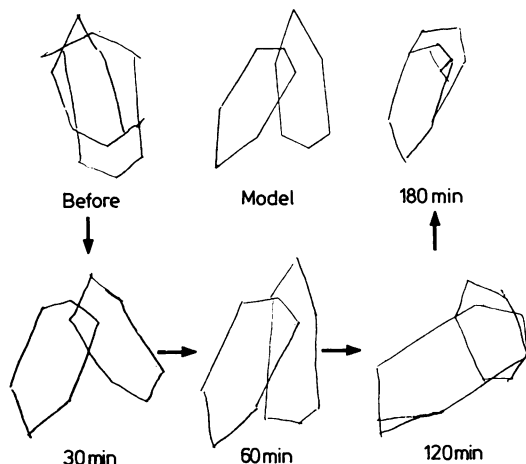


Fig 3 An example of the reproduction of the fig 7 of the Bender-Gestalt test by patient 2 after intravenous infusion of 0.5 mg of physostigmine.

improvement was observed on a few occasions (fig 5). During this week, there was a non-significant tendency toward improved baseline performance, that is performance just before the drug ingestion.

Results from the SRT showed a non-significant tendency toward improved baseline performance during the week of 3 mg of physostigmine. Otherwise no appreciable change was observed in memory performance. These trends were not observed during the period of placebo administration.

PATIENTS 5 AND 6

In these cases, intravenous infusion of 0.3, 0.5 or 0.8 (patient 5 only) mg of physostigmine did not produce any measurable changes in the scores on the BGT and SRT.

Discussion

The observations in these six patients suggest that physostigmine improves constructional disability in

Table 2 Effect of intravenous infusion of various doses of physostigmine in the constructional and closing-in scores of patient 3, 0.5 mg at neostigmine was used as placebo

		Constructional score			Closing-in score		
		Before	30'	180'	Before	30'	180'
Neostigmine	0.5 mg (4)	4.5 \pm 1.15	6.3 \pm 0.74	4.5 \pm 0.56	14.3 \pm 0.73	14.5 \pm 0.82	15.3 \pm 0.41
Physostigmine	0.3 mg (4)	4.8 \pm 1.29	16.3 \pm 1.63*	4.3 \pm 1.19	13.0 \pm 0.87	8.8 \pm 0.41*	15.0 \pm 0.50
Physostigmine	0.5 mg (4)	4.0 \pm 0.79	20.0 \pm 1.58*	4.5 \pm 1.09	12.5 \pm 1.48	8.5 \pm 0.83*	15.0 \pm 0.50
Physostigmine	0.8 mg (3)	6.3 \pm 0.98	31.7 \pm 2.77†	3.0 \pm 0.94	14.0 \pm 0.82	5.3 \pm 0.27†	14.7 \pm 0.27

Mean \pm SEM of three or four testings.

* $U = 0$, $p < 0.028$ compared to the score of before of corresponding dose of physostigmine, or 30' of neostigmine.

† $U = 0$, $p < 0.056$ compared to the score of 30' of neostigmine, or $U = 0$, $p < 0.100$ compared to the score of before of physostigmine 0.8 mg.

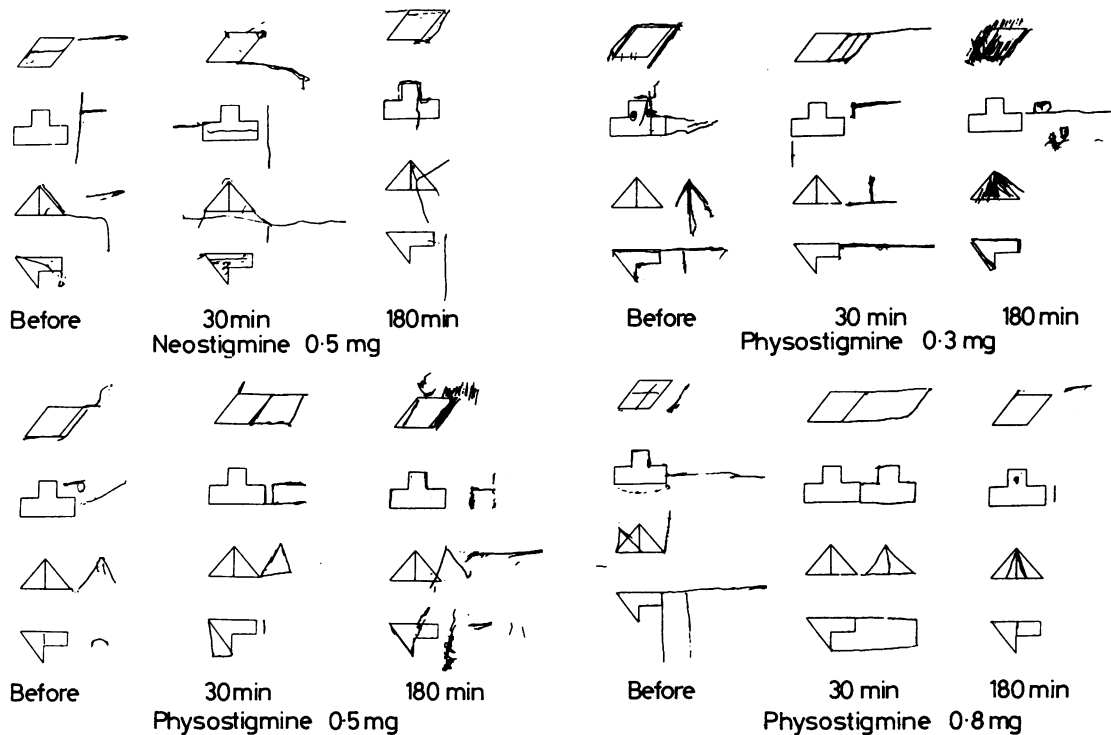


Fig 4 An example of figure copying of patient 3 after intravenous infusion of placebo (0.5 mg of neostigmine) or various doses of physostigmine. Note that the improvement in copying observed at 30 minutes after infusion was apparently dose-dependent.

at least some cases of Alzheimer's disease, which could be considered another piece of evidence to support the hypothesis that central cholinergic potentiation ameliorates some impairments of Alzheimer's disease. Practice effect in general can be ruled out by the fact that the placebo administration with the otherwise identical test procedure failed to show any significant change. In this small sample, all beneficial effects of physostigmine were shown to be time-limited, lasting no longer than three hours. This does not necessarily preclude the possibility that chronic administration of physostigmine also would be effective. Indeed, chronic oral administration of physostigmine has been reported to improve memory.^{12,15} In patient 4, we observed statistically non-significant but appreciable improvement in baseline performances for both memory and copying tasks, which may have masked the improvement after drug administration. In general, however, the data support the inference that there exists a very rapid and short-lasting phase of action rather than a long-lasting one, which is compatible with a rapid destruction of injected physostigmine in man.¹⁶

In this connection it is interesting to note that figure copying significantly deteriorated three hours after drug administration in patients 1 and 2. In patient 4, although statistical analysis failed to show any significant change, performance with the top of the three model figures of fig 5, which the patient had consistently copied correctly, abruptly disintegrated at three hours. This type of deterioration was sometimes observed with 3 mg of physostigmine in this patient. Fatigue in general cannot explain this finding since no deterioration was observed with placebo. Moreover, in patient 2 this deterioration was observed only for the copying task, LTR of the SRT remained relatively unchanged. If we had evaluated performance only at three hours after drug administration, we would have concluded that physostigmine impaired constructional performance in these cases. Although the high-dose deterioration in memory performance with physostigmine was reported by Davis *et al*¹⁷ and Peters and Levin,¹⁸ it is unlikely that a build-up of drug level is responsible for this rebound deterioration at three hours since physostigmine injected in man is largely destroyed in two hours.¹⁶ Therefore, the mechanism and

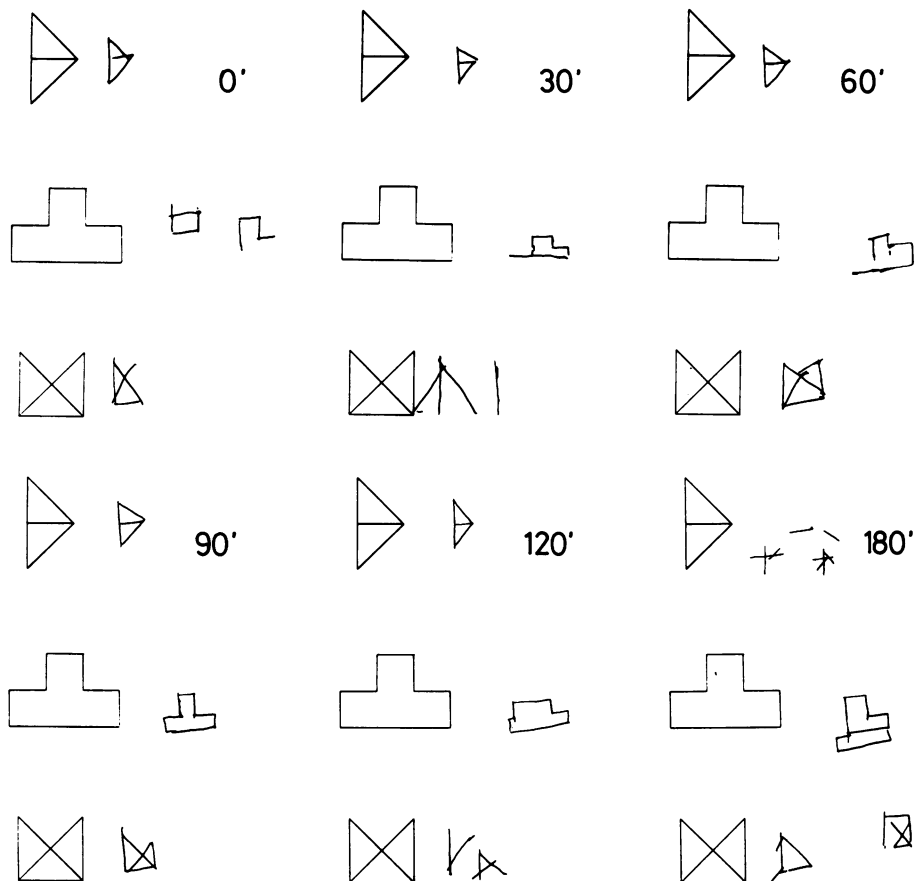


Fig 5 An example of figure copying of patient 4 after oral administration of 3 mg of physostigmine. Copying of the middle and bottom figures appeared to improve 60 to 120 minutes after the drug administration. Copying of the top figure, on the other hand, apparently deteriorated at 180 minutes.

significance of this apparent rebound deterioration is not yet clear.

We cannot be conclusive about the dose-responsiveness of physostigmine because it was studied only in patient 3. In this case the improvement in figure copying seemed to be dose-responsive in 0.3 mg to 0.8 mg range. This finding is apparently inconsistent with a previous report by Christie *et al*⁴ that there was a narrower therapeutic window for memory improvement than the range described above. Whether this discrepancy may be attributable to the difference between memory and constructional ability remains uncertain.

There are several explanations for the failure of two patients to respond to physostigmine. First, as is often pointed out, the diagnosis of Alzheimer's disease on purely clinical grounds may be suspect. It is possible that these non-responders had a non-

Alzheimer type presenile dementia, although the clinical features were compatible with Alzheimer's disease. Another possibility is that there are subgroups of responders and non-responders to cholinergic therapy, similar to those reported by Etienne *et al*¹⁹ for lecithin treatment. Further studies of clinical features, neuropathology, and neurochemistry are needed to elucidate the characteristics of those patients who respond to physostigmine.

In view of the relatively small number of patients who showed improvement in our series, overall usefulness of this agent must await further study with a larger sample. However, the cholinergic system may play a potentially important role not only in memory but in some aspects of constructional ability. The contribution of peripheral cholinergic enhancement by physostigmine does not seem to be important

because neostigmine, a purely peripheral type of anticholinesterase used as placebo in patients 2 and 4, produced no appreciable change in the patients' performances. To the best of our knowledge, no previous report has explicitly stated the relationship between the central cholinergic system and constructional ability. However, it is well known that constructional disability can be caused by a relatively localised lesion in the parietal lobe of either hemisphere, and there is evidence that cholinergic fibres that project from the neurons of the basal forebrain to the neocortex are abundant in this area.^{20 21} In view of these facts, it seems quite possible that the cholinergic system may play an important role in the integration of constructional ability in the parietal lobe. However it is not yet clear which aspect of the process of copying is improved by the cholinergic treatment, that is visual perception, visual-motor integration, or motor output.

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