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Intrusion Errors in Patients with Degenerative or Vascular Dementia: The Cholinergic Connection?

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Abstract. Behavioral data from demented patients and scopolamine-impaired normal subjects, and morphological data from patients with Alzheimer's disease (AD) suggest that intrusion errors may mirror the dysfunction of the cholinergic system. The Picture Recall and Recognition Task used in this study was designed to systematically measure intrusion errors (i.e. false recognition of items semantically related to target items), and false alarms (i.e. false recognition of items semantically unrelated to target items). The results taken from the baseline data of a clinical trial with geriatric patients with major depressive episode and varying degrees of cognitive impairment indicate that intrusion errors occur more often than false alarms in those patients with more severe cognitive decline. Because this pattern was only observed in patients with dementia of nonvascular origin, the results support the hypothesis that intrusion errors are a relatively specific indicator of the cholinergic deficit accompanying AD.

Since the first publication of behavioral data implicating the role of the cholinergic system in human memory functioning [1], this cholinergic hypothesis has received wide support from both behavioral and neuropathological data. In particular, Alzheimer's disease (AD), known for its prominent clinical symptom of widespread memory loss, has been linked to a deficit of the cholinergic system in a multitude of publications [reviewed in ref. 2]. In one such publication examining the cognitive impairment observed in normal volunteers treated with the antimuscarinic agent scopolamine, the authors reported that on a category retrieval task, more than half the subjects intruded words that did not belong to the given category [3]. This was the first study that documented the occurrence of intrusion errors in subjects cognitively impaired as a result of a cholinergic deficit.

Behavioral data from three types of research support the relationship between the incidence of intrusion errors in demented patients and the dysfunction of the cholinergic system. First, intrusion errors are one of the most reliable symptoms of AD patients [4]. Fuld [5] and Fuld et al. [6] reported that word intrusions were observed in 88% of patients with a neurological diagnosis of AD, even in those patients without severe memory impairment or language problems. Second, intrusion errors and similar errors (i.e. false-positive responses) are usually observed in animals following the administration of anticholinergic drugs [4]. This memory deficit appears to be specifically related to the anticholinergic properties of the drug, and not to decreases in arousal or attention, because the effects can not be reversed by subsequent amphetamine administration [7]. Third, the reduction of intrusion errors is a characteristic outcome [4], and frequently the only significant effect [8], of cholinergic drug administration in AD patients. In a review of methods assessing memory in clinical trials, Brinkman and Gershon [2] identified learning tasks that provide an index of intrusions as one of the most useful methods for detecting treatment effects.

There are also morphological data supporting the relationship of intrusion errors to the cholinergic system. Intrusion errors were significantly associated with low levels of choline acetyltransferase and high counts of senile plaque [5], and the reduction in intrusion errors

was highly correlated with a decrease in cholinesterase activity in cerebrospinal fluid [9]. Fuld [5] proposed that word intrusions may mirror the dysfunction of the cholinergic neurotransmitter system of the brain, because there is almost a one-to-one correlation between the amount of cholinesterase in the brain and the number of intrusions.

These pharmacological and morphological data provide a solid justification for examining intrusion errors in drug treatment studies. In the past, the measurement of intrusion errors was unsystematic because there is not a task that is designed specifically to elicit them. Additionally, the previous method of assessing intrusion errors could require several hours of testing with a multitude of tasks, still detecting only one or two intrusions per patient [5]. For this reason, Fuld et al. [6] caution against concluding that a patient who does not exhibit intrusions does not have AD, unless considerable data are obtained from each subject 'so that a patient prone to manifesting intrusions will be likely to do so' (p. 158). Rather than waiting for the spontaneous occurrence of intrusions, as in the past, the Picture Recall and Recognition Task (PRRT) attempts to provoke them in a time-economical manner more suited to the demented patient.

Another difference between the PRRT and previous measures of intrusion errors concerns the definition of an intrusion. Intrusion errors have previously been defined as the inappropriate recurrence of a response from a preceding test item, test, or procedure [5]. However, observations that many naming errors in demented patients are semantic in nature [10, 11], and evidence for the existence of a semantic memory disturbance at the comprehension level in AD patients [12] suggest that the semantic relationship of intrusion errors be considered. The features of the dysphasia of dementia have been reviewed extensively [13]. There appears to be a loss of semantic distinctions in demented patients causing semantically related items to become interchanged [10]. Therefore, a broader definition of intrusion errors would include not only errors with items that were previously presented to the patient, but also with items that are semantically related to the target items. To the demented mind, these items would also intrude on the target items, as if they had been presented before.

We predicted that intrusion errors, operationally defined for this study as false recognitions of those items that are semantically related to the target items, would occur more often than false alarms (i.e. false recognitions of items semantically unrelated to target items) in demented patients. In keeping with the cholinergic hypothesis, this pattern should only be observed in those patients with a cholinergic deficit (i.e. AD), and not in those patients with other types of dementia (i.e. multi-infarct dementia). Although the cholinergic hypothesis is only one of several competing hypotheses concerning the etiology of AD, considering the strong evidence for a relationship between the cholinergic system and intrusion errors, a division of patients according to a possible cholinergic deficit seemed an appropriate place to begin research in this field.

Patients and Methods

461 patients were included in these analyses. All patients participated in an ongoing placebo-controlled, double-blind, multicenter trial of drug treatment effects on depression and cognitive symptoms with the MAO-A inhibitor moclobemide (Aurorix®); only the baseline data from this study were considered here. Before entry into the study, all patients were required to meet general and psychiatric inclusion and exclusion criteria; males and females of all races between the ages of 60 and 90 years were eligible to participate either as in- or outpatients. All patients met the DSM-III criteria for either major depressive episode, with additional cognitive deficits, or dementia, with depression [14]. Additionally, patients had to score at least 6 on the Geriatric Depression Scale [15], at least 15 on the first 17 items of the 24-item Hamilton Depression Scale [16], between 12 and 27 on the Mini-Mental State Examination (MMSE) [17], and > 8 for the first four items, and > 40 for all 18 items of the Sandoz Clinical Assessment Geriatric Scale [18]. Patients with specific physical impairments that could influence any of the assessments or with other psychiatric disorders were excluded from the study. Clinical details and outcomes of this study will be presented elsewhere.

The average age of the subjects was 74 years, and the majority (79%) were female. According to the DSM-III criteria, 92 patients were diagnosed by the treating physician as having primary degenerative dementia with depression, 69 were diagnosed as having vascular dementia with depression, and 299 as having major depressive episode with cognitive deficits (these data were missing for one patient).

Three parallel forms of the PRRT matched on name agreement, image agreement, familiarity, and visual complexity were constructed from a set of standardized pictures [19] in a modified color version [20] (drawings used by permission of the authors). The recognition set contained the eight pictures presented during the learning period (target items; e.g. cigar), eight pictures which were identified as semantically related distractors (e.g. cigarette), and eight semantically unrelated pictures (e.g. tree). The semantic relationship was defined as items that belong to the same superordinate category (e.g. tobacco products). The recall and recognition procedures are described in detail in an earlier report [21].

Additionally, patient complaints of problems in the following areas of cognitive impairment were recorded: memory, learning, orientation, attention, performance, speech, and abstract ideation.

Results

Patients were classified as either primarily depressed (DEP) or primarily demented based on their MMSE score, divided around the median MMSE score of 20 (primarily demented ≤ 20; DEP > 20). Primarily demented patients were further divided based on the score from the modified Hachinski Ischaemia Scoring Scale (MHISS) [22] around the recommended cut-off score of 4 [degenerative dementia (PDD) < 4; vascular dementia (PVD) ≥ 4]. This method of patient classification highly agreed with the physicians' diagnoses of the type of dementia. The κ reliability statistics comparing the two methods of classification were highly significant ($\kappa = 0.63$, $p \leq 0.0001$). Hereafter, all patient classifications will refer to those made according to the MMSE and MHISS scores and not according to the physician's diagnosis in order to prevent a possible confound between those symptoms influencing a global patient diagnosis (e.g. dysphasia) and the specific symptom examined in this study (i.e. intrusion errors); the classification based on test scores was considered to be more objective in this regard.

Table 1 presents the means and standard deviations for all five measures of the PRRT according to the diagnosis of the patient. A repeated-measures 3 (diagnosis) $\times 2$ (distractor type) ANOVA revealed that there were significant differences in the number of errors between the patient groups, $F(2, 458) = 23.703$, $p \leq 0.01$, and distractor types (related or unrelated), $F(1, 458) = 6.205$, $p \leq 0.05$. There was also a significant interaction between diagnosis and distractor type, $F(1, 458)$, $p \leq 0.01$, illustrated in figure 1. Follow-up tests (Tukey HSD test and t tests with significance levels determined by Bonferroni's procedure using an experiment-wise α of $p \leq 0.05$) to determine the source of the interaction revealed the following significant differences: the only patient group that showed a significant difference between distractor types was the PDD group ($n = 142$), $t = 3.34$, $p \leq 0.01$; PDD patients made significantly more intrusion errors ($p \leq 0.01$) than did both the PVD and DEP patients, although the latter two groups did not differ; both groups of primarily demented patients made significantly more false alarms ($p \leq 0.01$) than did the DEP group, but on this measure the demented groups did not differ from each other. If the occurrence of each type of error is treated as a dichotomous variable (present or absent) and the percentage of patients from each diagnostic group making each type of error is calculated, the data can be described in terms of the probability of making an error. As illustrated in figure 2, this representation highlights the same differences that were illustrated in figure 1.

Table 1. Means (± SD) for PRRT scores

Task	Primarily demented		Primarily depressed
	degenerative	vascular	
Immediate recall	4.2 ± 2.8	3.5 ± 2.9	5.1 ± 1.9
Delayed recall	2.1 ± 1.5	1.7 ± 1.6	4.0 ± 1.4
Recognition	4.7 ± 2.7	4.0 ± 3.1	7.1 ± 1.4
Intrusion errors	1.6 ± 1.9	0.8 ± 1.5	0.4 ± 1.0
False alarms	1.1 ± 1.9	0.9 ± 1.8	0.3 ± 1.0

With regard to the memory measures obtained by the PRRT, there were significant group differences for immediate recall [$F(2, 458) = 12.95$, $p \leq 0.001$], delayed recall [$F(2, 458) = 108.30$, $p \leq 0.001$], and recognition [$F(2, 458) = 85.30$, $p \leq 0.001$]. Follow-up Tukey HSD tests indicated that for both immediate recall and recognition, DEP patients performed significantly better than both demented-patient groups, and PDD patients performed better than PVD patients. On the delayed-recall task, again DEP patients scored higher than both demented-patient groups; however, there was no difference between PDD and PVD patient groups on this measure.

χ^2 tests to detect any relationships between the diagnosis of the patient and complaints of specific cognitive problems (listed under Patients and Methods) found only one; more PVD patients (47%) complained of speech problems than did PDD patients (27%), $\chi^2 = 5.93$, $p \leq 0.05$. This suggested that speech complaints might be related to the differences in intrusion errors that were found, but a χ^2 test revealed that there was not a significant relationship between speech complaints and intrusion errors. There was, however, a significant relationship between speech complaints and false alarms ($\chi^2 = 11.61$, $p \leq 0.001$).

Discussion

The results are consistent with other research findings that patients with more severe cognitive impairment (primarily demented) are more likely to make an intrusion error than less impaired patients [5, 6, 21]. Additionally, the results suggest that this pattern emerges only with patients without vascular dementia. While PVD

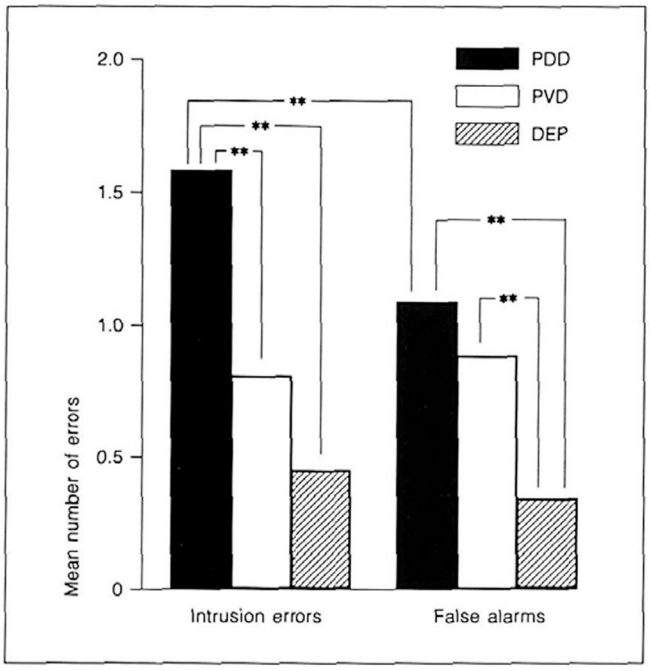

Fig. 1. Average number of intrusion errors and false alarms in PDD (n = 142), PVD (n = 49), and DEP (n = 270) cases (** $p \leq 0.001$).

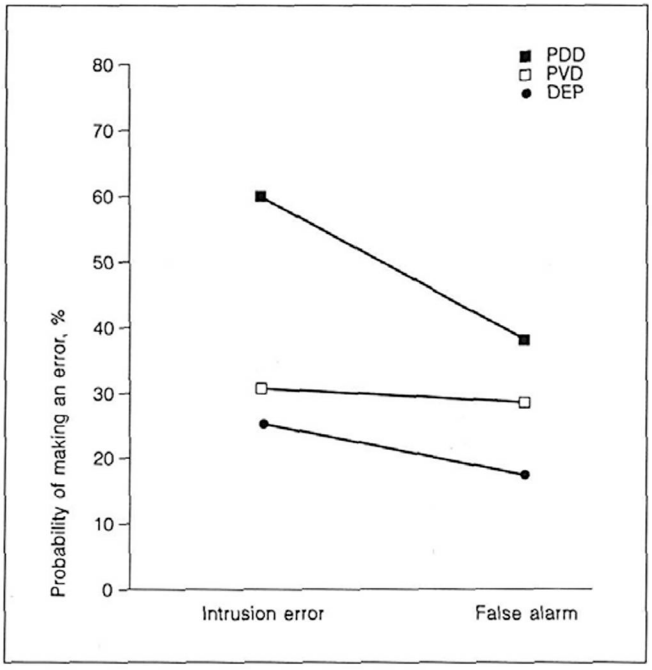

Fig. 2. The likelihood that a patient in each of the diagnostic groups would make either an intrusion error or a false alarm.

patients are equally likely to make either an intrusion error or a false alarm, PDD patients are much more likely to make the former. It seems that the type of distractor is irrelevant to PVD patients, but for PDD patients, when the distractor is related to the target item (intrusion errors), the probability of an error occurring nearly doubles. As a result, PDD patients made significantly more intrusion errors on average than did both the PVD and DEP patients.

Are intrusion errors a direct result of the dementia in PDD patients, or are they merely a consequence of other deficits that accompany the disorder? In order to address this question, we examined the patient reports of problems in cognitive areas that are typically impaired in demented patients. With the exception of speech problems, there were no differences between the percentages of PDD and PVD patients complaining of the various cognitive symptoms; therefore, differences in patient symptomatology between the demented groups cannot be used to account for the different error patterns. With regard to the difference in speech problems, there was no significant relationship between complaints of speech difficulties and the occurrence of an intrusion error (on the contrary, there was a significant relationship between speech complaints and the occurrence of false alarms). Furthermore, when only those patients without complaints of speech problems were considered, intrusions were far more characteristic of PDD (63%) than of PVD patients (39%), although there was no difference between the percentages of PDD and PVD patients that made false alarms (45 and 46%, respectively). This mimics the pattern seen in the total patient sample.

Because complaints of memory problems were used as a study inclusion criterion for all patients, we had to consider the possibility that if PDD patients showed more severe memory deficits than PVD patients, it could be argued that intrusion errors were merely a consequence of severe memory impairment in either type of dementia. The results indicate the reverse: PDD patients performed equal to or better than PVD patients on all three memory measures. Furthermore, when only demented patients demonstrating mild memory impairment were considered (< 1 SD below the mean of depressed patients on all three memory tasks), twice as many PDD patients made intrusion errors than made false alarms (38 compared to 17%), while there was no difference with PVD patients (13 and 14%). Therefore, intrusions are characteristic of PDD patients even in those patients with only mild memory impairment, or without complaints of speech problems, suggesting that

intrusion errors are indeed a consequence of the specific deficit in PDD patients, and not of other functional impairments.

One hypothesis for the differences between PDD and PVD patients is that the pattern of intrusion errors mirrors the dysfunction of the cholinergic system related to each diagnosis. Although the group of patients designated as PDD is not completely homogeneous and a score <4 on the MHISS does not necessarily indicate degenerative dementia, the high majority of patients with nonvascular dementia are victims of AD [2]. Therefore, if we assume the cholinergic hypothesis to be correct, there is a cholinergic deficit in the PDD group that is absent in the PVD group of patients. If we interpret the results in the light of this statement, we can make the following two claims. First, errors to semantically unrelated distractors are not related to the deficit of the cholinergic system, but to other factors accompanying dementia (e.g. speech disorders), because both groups of demented patients performed worse than the depressed patients but not different from each other. And secondly, errors to semantically related items, the intrusion errors, are related to the dysfunction of the cholinergic system because only the group of demented patients with a cholinergic deficit performed worse than depressed patients.

This study alone, however, does not allow such unequivocal statements to be made. In order to test this hypothesis, more distinct patient groups would have to be evaluated. All of the patients in this study, as part of the trial inclusion criteria, were required to show some signs of cognitive decline; therefore, all of the patients classified as DEP were, to some degree, cognitively impaired, and this might be attributable to a cholinergic deficit. For this reason, the DEP patients in this study cannot be considered the ideal control group for the demented patients. This may also have contributed to the high amount of overlap between the scores from different patient groups, and to the small, albeit significant, difference between the number of errors made.

Additionally, future studies should consider other types of dementia, and their relationship to the cholinergic system. A study of Butters [23] reported the number of prior-story intrusions in a short story recall task for normal subjects, and patients with Huntington's chorea (HC), alcoholic Korsakoff's syndrome (AK), and AD. Normal controls and patients with HC performed at an equal level, with <0.5 errors on average, patients with AK made an average of nearly 1.5 intrusion errors, and patients with AD made an average of >2 intrusion errors. The link between each of these diseases and the cholinergic system can be used to explain these results. First, in HC there is a deficit of the dopaminergic, not the cholinergic system [reviewed in ref. 24], so no difference from normal controls would be expected if our hypothesis is correct. Second, in AK, one result of the thiamine deficiency is the destruction of the nucleus basalis of Meynert (nbM) [25]. This is a subcortical structure wich is a major source of cholinergic input to the cortex, and the number of cell bodies in the nbM is reduced in AD as well [26]. So while the dysfunction of the cholinergic system may not be as great in AK as it is in AD, there is evidence for some impairment of cholinergic pathways. This fits perfectly with the results reported by Butters [23] that patients with AK make significantly more errors than normal patients, although fewer than AD patients. Studies like this one, which consider intrusion errors in a variety of patient populations, will help to confirm the hypothesis that the occurrence of intrusion errors is related to the dysfunction of the cholinergic system.

The definition of intrusion error used in this study also warrants discussion. As previously described, the definition we used relies on the semantic relationship of the intruding item to the target item. This relationship appears to be critical in obtaining the significant difference between PDD patients and the other patient groups, as the pattern is entirely different for the unrelated false alarms. What do items that are semantically related to target items have in common with items that were presented previously, as former research defined intrusions? And how similar must two words be to reliably provoke an intrusion? These are two questions that future studies must address in order to fully understand what appears to be a critical sign of a cholinergic deficit.

Although the results from this study are not capable of definitively establishing a relationship between the occurrence of semantically related intrusion errors and the deficit of the cholinergic system, we have presented a systematic method of measuring intrusion errors that is fast and easy to administer, is simple enough for patients with mildly or moderately severe dementia, and is not susceptible to either floor or ceiling effects. The results of this study are consistent with other research findings that demented patients are more likely to make intrusion errors, and additionally we have shown intrusion errors to be capable of discriminating between dementias of different types, possibly based on their link to the cholinergic system. Caution must be taken not to assume that

memory deficits are the sole cause of intrusion errors, or that the presence of a cholinergic deficit was the only difference between patient groups. Future studies will be crucial in the further definition and establishment of the relationship between the deficit of the cholinergic system and the occurrence of intrusion errors in patients with AD.

References

1 Crow TJ, Grove-White IG: An analysis of the learning deficit following hyoscine administration to man. Br J Pharmacol 1973; 49:322–327.

2 Brinkman SD, Gershon S: Measurement of cholinergic drug effect on memory in Alzheimer's disease. Neurobiol Aging 1983; 4:139–145.

3 Drachman DA, Leavitt J: Human memory and the cholinergic system: A relationship to aging. Arch Neurol 1974;30:113–121.

4 Gainotti G, Nocentini U, Sena E: Can the pattern of neuropsychological improvement obtained with cholinergic drugs be used to infer a cholinergic mechanism in other nootropic drugs? Prog Neuropsychopharmacol Biol Psychiatry 1989;13:847–859.

5 Fuld PA: Word intrusions as a diagnostic sign in Alzheimer's disease. Geriatr Med Today 1983;2:33–41.

6 Fuld PA, Katzman R, Davies P, Terry RD: Intrusions as a sign of Alzheimer dementia: Chemical and pathological verification. Ann Neurol 1982;11:155–159.

7 Drachman DA: Memory and cognitive function in man: Does the cholinergic system have a specific role? Neurology 1977;27: 383–390.

8 Smith CM, Swash M: Physostigmine in Alzheimer's disease. Lancet 1979;i:42.

9 Thal LJ, Fuld PA, Masur DM, Sharpless NS: Oral physostigmine and lecithin improve memory in Alzheimer's disease. Ann Neurol 1983;13:491–496.

10 Schwartz MF, Marin OSM, Saffran EM: Dissociations of language function in dementia: A case study. Brain Lang 1979;7: 277–306.

11 Warrington EK: The selective impairment of semantic memory. Q J Exp Psychol 1975;27:635–657.

12 Chertkow H, Bub D: Semantic memory loss in dementia of Alzheimer's type: What do various measures measure? Brain 1990; 113:397–417.

13 Ross GW, Cummings JL, Benson DF: Speech and language alteration in dementia syndromes: Characteristics and treatment. Aphasiology, in press.

14 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 3. Washington, American Psychiatric Association, 1980.

15 Yesavage J, Brink T, Rose T, Lum O, Huang O, Adey V, Leirer V: Development and validation of a geriatric screening scale: A preliminary report. J Psychiatr Res 1983;17:37–49.

16 Hamilton M: Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296.

17 Folstein MF, Folstein SE, McHugh PR: 'Mini-Mental State': A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

18 Shader RI, Harmatz JS, Salzman C: A new scale for assessment in geriatric populations: Sandoz Clinical Assessment Geriatric (SCAG). J Am Geriatr Soc 1974;22:107–113.

19 Snodgrass JG, Vanderwart M: A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. J Exp Psychol 1980;6:174–215.

20 Kessler J, Denzler P, Markowitsch HJ: Der Demenztest. Weinheim, Beltz, 1987.

21 Lorscheid T, Thompson S: Intrusion errors: A new look at an old measure; in Hindmarch I, Hippius H, Wilcock G (eds): Dementia: Molecules, Methods and Measures. London, Wiley, in press.

22 Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A: Pathological verification of ischemic score in differentiation of dementias. Ann Neurol 1980;7:486–488.

23 Butters N: Alcoholic Korsakoff's syndrome: Some unresolved issues concerning etiology, neuropathology and cognitive deficits. J Clin Neuropsychol 1985;6:17–36.

24 Kapur N: Memory Disorders in Clinical Practice. London, Butterworths, 1988.

25 Arendt T, Bigl V, Arendt A, Tennstedt A: Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans and Korsakoff's disease. Acta Neuropathol (Berl) 1983;61: 101–108.

26 Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, DeLong MR: Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. Science 1982;215:1237–1239.

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