nections between cortex, limbic system, hypothalamus and brain stem, as experimental stimulation of such structures demonstrates[1 6 7]

Autonomic symptoms are more frequently reported in temporal lobe epilepsy, but this may only be because consciousness is generally preserved.[8] In common with other types of seizure, bradyarrhythmias are less prevalent than tachyarrhythmias.[6 9-11] Simultaneous EEG and ECG monitoring of the present patient's attacks did not prove possible, but was achieved in two of the three previously reported instances of sino-atrial arrest during temporal lobe seizures.[3] In these, asystole occurred shortly after seizure onset and lasted for 8 to 10 seconds prior to the development of a generalised convulsion. The earliest reported patient also showed abrupt asystole, lasting for up to 8 seconds, following an epigastric aura or *angor animi*.[2] In the present case, termination of the asystolic episodes by atropine confirms that they were neurally mediated. There was no past history of simple syncope, and the onset of bradycardia was always preceded by *déja vu*. He had had other *déja vu* attacks without cardiac sequelae, and was found to have temporal lobe EEG abnormalities and a tumour presumed responsible for these. We therefore feel confident that temporal lobe epilepsy was the primary cause of his asystolic episodes, and that only the subsequent loss of consciousness and jerking could have been attributable to cardiac-induced cerebral ischaemia. Whether or not the hypothalamic distortion produced by the tumour predisposed to autonomic dysfunction is not clear.

The importance of detecting a primary cardiac arrhythmia in cases of both non-epileptiform and epileptiform attacks is well established.[12 13] The reverse situation, that of significant cardiac arrhythmia caused by primary epileptic disturbance, may be more common than generally supposed.[1] Awareness of this possibility, supported where needed by combined ECG and EEG monitoring, will help avoid one of the potentially fatal consequences of an otherwise relatively benign condition. Moreover where, as in this case, a structural lesion is responsible, it can be removed.

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Mental status changes induced by eye drops in dementia of the Alzheimer type

Sir: Topical administration of eye drops can produce serious systemic complications in the pulmonary, cardiovascular, musculoskeletal and central nervous system.[1-6] Dementia of the Alzheimer type patients are particularly vulnerable to these side effects because of the known neurochemical abnormalities that occur in this disorder.[7] Recent work has demonstrated reduced activity of choline acetyltransferase and acetylcholinesterase in biopsy and post mortem brain tissues of affected patients.[8 9] Other neuropeptides and neurotransmitters may also be significantly altered in dementia of the Alzheimer type.[9 10] Toxic reactions from ophthalmic agents may unmask or increase the cognitive deficits, behavioural and personality changes which clinically characterise dementia of the Alzheimer type.[7]

Clinical reports have documented central nervous system (CNS) reactions such as confusion, hallucinations, ataxia, agitation, dysarthria and psychosis after the use of anticholinergic eye drops.[11-13] Cholinomimetic agents such as pilocarpine and aceclidine are generally administered to reduce intraocular pressure in patients with certain types of glaucoma.[14-15] Their clinical use has not been associated with mental changes although pilocarpine has been shown to produce complex behavioural and electrophysiological alterations in experimental animals.[16-18] We report three patients who developed CNS manifestations following pilocarpine administration and were subsequently found to have dementia of the Alzheimer type.

Three elderly patients were referred to the Dementia Clinic of Thomas Jefferson University Hospital for progressive cognitive dysfunction following administration of ophthalmic drops. They had a normal medical evaluation, which included: complete blood count, sedimentation rate, thyroid, renal and liver function tests, serum Vitamin B12 and folate levels, electrolytes, urinalysis, electrocardiogram and chest radiograph. Neurological studies consisted of computed tomography (CT) of the brain, electroencephalogram (EEG) and cerebrospinal fluid (CSF) studies in all patients. Cerebral digital subtraction angiography and neuropsychological testing were done in cases 2 and 3 and magnetic resonance imaging (MRI) in case 1. All patients underwent several complete neurological examinations.

Case 1 was a 72-year-old, right-handed, white male, who presented with a 5 year history of progressive decline in short term memory and episodes of confusion and irritability, especially at night. His symptoms started after he was treated with 4% pilocarpine and 2% epinephrine eye drops for glaucoma. At that time, he also had visual hallucinations and lability of affect. He was treated with haloperidol, but this was discontinued because of tremors. His wife and daughter reported intermittent visual hallucinations and mood swings within an hour after each application of the ophthalmic medications. Neurological examination revealed an alert, elderly man, who was oriented only to person. He had no insight into his medical illness and his recent and remote memory were markedly impaired. The patient was unable to do serial 7s, name fingers, draw objects and follow a four-part command. He had a labile affect and right-

left confusion. He could write his name and read. His pupils were constricted and the fundi could not be visualised. His hearing, speech and swallowing were normal. His face was symmetrical and sensation on both sides of the face was intact. He walked with short steps and a slightly broad-based gait. He could not do tandem walk. Cog-wheel rigidity, bradykinesia and tremors were absent. He had normal muscle strength and sensation. He had mild diminution of vibration sensibility in both feet. His deep tendon reflexes were 2+ bilaterally and his plantar responses were flexor. Snout, palmomental and glabellar reflexes were positive. He had no difficulty with bowel or bladder control and there was no family history of dementia.

Case 2 was a 76-year-old, right-handed, white female, who was brought by her family for "decreasing memory". Her family traced the onset of her symptoms to cataract surgery performed 4 years prior to consultation. During that hospitalisation, she became confused and agitated following administration of 2% pilocarpine and isoptic eye drops. Her family claimed that after discharge, she developed progressive memory loss and irritability. On neurological examination, the patient was markedly demented and disoriented to person, place and time. She did not remember her age, address, or the names of her children. She was not aware of any medical problem. She had severe recent and remote memory impairment. She was unable to do simple calculations, write her name, name common objects and body parts, copy simple figures and distinguish left and right body parts. She demonstrated mood swings during her examination. The pupils were 2 mm. and equally reactive to light and to accommodation. Horizontal and vertical eye movements were full. Fundi were benign. She did not have dysarthria, dysphagia or hearing loss. Her face was symmetrical and she felt pin prick on both sides of the face. Her tongue was in the midline. She had moderately increased muscle tone in all extremities, more pronounced on the right. She had no weakness of any muscle group. Cog wheel rigidity and tremors were not appreciated. Cerebellar examination demonstrated bilateral impairment of finger to nose movements, rapid alternating movements, fine finger movement and heel to shin coordination. Deep tendon reflexes were symmetrical and her plantar responses were flexor. She had snout, glabellar and grasp reflexes. She denied any urinary or bowel incontinence. There was no family history of dementia.

Case 3 was a 77-year-old, right-handed, retired male physician, who referred himself for intermittent "disorientation, short term memory loss, apprehension and inability to keep still." According to his wife, his symptoms began 3 months earlier following trabeculectomy for primary open angle glaucoma. At that time, he was given isoptocarpine 2%, epifrin 2% and maxitrol suspension. He continued to take the first two medications until the neurological evaluation. Neurological examination revealed an agitated, but well oriented male with marked recent memory loss. His remote memory was intact. He had difficulty with serial 7s and he followed four-part commands with hesitancy. His proverb interpretation was concrete. He could read, write, name objects, body parts and colours. His speech was normal. He had difficulty copying simple figures. The pupils were 2·5 mm in diameter, equal and reactive to light and accommodation. The extraocular movements were full. He had normal visual fields by confrontation and fundi. Speech, swallowing, hearing and gag reflexes were unremarkable. His face was symmetrical with intact sensation to pin prick, light touch and temperature. Gait, muscle tone and strength were normal. He had no cog wheel rigidity, bradykinesia or tremor. Sensory examination to pin prick, light touch, vibration and position were intact. Deep tendon reflexes were normoactive and the plantar responses were flexor. Snout, glabellar and grasp reflexes were negative. He had mild bilateral dysmetria on finger to nose testing. He had slight difficulty with tandem walking. Romberg's test was negative. He had no bowel or urinary incontinence. There was no family history of dementia.

The presenting manifestations of our cases included memory loss, hallucinations, lability of affect, confusion and agitation. These symptoms were initially observed by relatives and attending ophthalmologists within hours after the patient received eye drops for primary open angle glaucoma. No pulmonary and cardiovascular complaints were reported. Pilocarpine eye drops were given to every patient and epinephrine to case 1 and 3. Maxitrol, an antibiotic suspension was also prescribed to case 3. Pilocarpine was discontinued in all patients after neurological evaluation.

The neurological diagnosis in all cases was dementia of the Alzheimer type. Visual hallucinations and lability of affect disappeared in case 1 and agitation was markedly diminished in case 3 after pilocarpine was withdrawn. Case 3 did not show any change in clinical status. Except for a slight increase of right sided muscle tone and dysmetria in case 2, there were no other focal neurological findings. Neuropsychological testing using a Luria-Nebraska battery documented global cognitive deficits and progressive dementia in cases 1 and 3. The same test could not be performed on case 2 owing to advanced dementia. In this patient, sustained delta activity over the left frontal-temporal region was not associated with electrical and clinical seizures, progressive neurologic deficits, structural lesions by CT scan or CSF abnormalities. EEG showed generalised slowing in all cases. The CT scan and MRI of case 1 both revealed mild generalised cortical atrophy. The CT scans demonstrated mild to moderate cortical atrophy. The CSF studies were normal and distal subtraction angiography on cases 1 and 3 failed to reveal significant vascular lesions.

This is the first clinical description of mental status changes associated with pilocarpine eye drops in elderly patients. The concomitant use of epinephrine in cases 1 and 3 may have produced synergistic or additive cardiovascular effects although none were documented either acutely or during neurological examinations. Moreover, case 2 did not receive epinephrine but her symptoms were similar to those of cases 1 and 3. Although all patients developed dementia of the Alzheimer type, it is our opinion that pilocarpine merely exacerbated their cognitive deficits.

The mechanism(s) that mediates our patients' manifestations are difficult to ascertain at present because of the lack of previous clinical studies and animal experiments designed to evaluate the long term behavioural, structural, and neurochemical changes induced by cholinergic agents. In rabbits, intravenous injection of acetylcholine and anticholinesterase have been found to evoke a characteristic cortical arousal or activation which can be reduced or blocked by atropine and related compounds.[18] Using microelectrophoretic techniques, Curtis and Crawford demonstrated some of the central actions of acetylcholine in various neuronal groups.[19] Recent investigators showed that intrahippocampal injection of bethanecol, a specific muscarinic receptor agonist, produced significant brain damage accompanied by electrophysiological changes and seizures.[20] The same group of workers also documented limbic epilepsy and behavioural, electroencephalographic and neuropathological abnormalities in rats following intraperitoneal administration of pilocarpine.[17] These experimental data are extremely important clinically, since pilocarpine, a natural cholinomimetic alkaloid with dominant mus-

carinic action, is a commonly prescribed eyedrop for middle aged and elderly patients.

In dementia of the Alzheimer type, deterioration of intellectual function and behavioural changes have been linked to the neurochemical deficiency and morphological lesions involving the cholinergic system. Diminished activity of choline acetyltransferase is believed to result in acetylcholine deficiency while the loss of cholinergic neurons in the nucleus basalis of Meynert is thought to decrease cholinergic input into different cortical and subcortical regions.[7 21] If we relate these hypotheses to our cases, we can speculate that a chronic low level of muscarinic receptor stimulation occurs in dementia of the Alzheimer type. In such a situation, pilocarpine could induce muscarinic receptor hyperactivity or supersensitivity in some patients with dementia of the Alzheimer type and give rise to mental status changes. This proposed mechanism will have to be verified by future appropriately designed clinical and animal studies.

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Matters arising

Age-specific incidence rates for motor neuron disease

Sir: The recent paper by Li, Swash and Alberman[1] states that they are not aware of previous estimates of age-specific rates in motor neuron disease. We originally reported in 1980[2 3] that age-specific incidence rates for motor neuron disease rise with increasing age. We presently have a paper in press which updates our previous study and confirms this finding.[4] Although the authors report theirs is the first age-specific incidence figure in motor neuron disease, they have been reported prior to our 1980 paper.[5]

The use of hospital admissions as the source of cases implies that the diagnosis of motor neuron disease will always be made and recorded. This may be true for younger patients; however, elderly patients, particularly those in nursing homes, are less likely to be hospitalised and are more likely to have multiple disease involvements, such as cardiovascular, and pulmonary, which may obscure the diagnosis of motor neuron disease. A greater proportion of overlooked diagnoses of motor neuron disease is likely among elderly patients.

In our experience as well as that of Li *et al*, the rise in incidence was not apparent in women aged over 80 years. The numbers are small and the possibility exists that motor neuron disease is more commonly overlooked in elderly women. Thus, the significance of this finding is not now obvious and deserves further study.

We agree that the findings of Li *et al* are important and support our observation that the age-specific incidence rates of motor neuron disease increase with advancing age.

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