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Review Article

Drug Treatments of Dementia

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Present drug treatments for the more common types of dementia are largely palliative or symptomatic, but the promise of drugs to prevent the development of dementia does not seem unrealistic. Neuropharmacological strategies that aim to improve behavioural or cognitive symptoms in dementia are subdivided into drugs that modify central cholinergic, serotonergic, dopaminergic, GABAnergic, and peptidergic transmission. There are no clear clinical guidelines for the management of demented patients who are also hypertensive. The early identification of patients with incipient dementia, the detection of slight but theoretically important beneficial effects, the optimum method of drug administration, more soundly based treatment of behavioural symptoms, and the evaluation of drug combinations are all identified as areas requiring further research.

There is a compelling need for well conducted studies of the treatment of dementia. Major changes in the age structure of our population and consequent increases in the prevalence of all age-related diseases have placed a steadily growing burden on our capacity to provide satisfactory care for increased numbers of old people, particularly those who are demented. Recent advances in understanding the neurochemistry and the molecular biology of dementia are widely reported, and professional and public expectations of the potential benefits of such progress have understandably increased. Occasional reports of patients whose severe and apparently irreversible dementia recovers completely in response to therapy (e.g. Paulson, 1983) strengthen the hope that, eventually, specific treatments will become available for the more common forms of dementia. Among specialists in the care of old people, however, considerable pessimistic reserve about the treatment of dementia remains commonplace, yet it is clear to all concerned just what might be the rewards of even a slight degree of improvement or a moderate slowing of an otherwise relentless decline. For the patient in the early stage of a dementing illness, this might mean the difference between independence and in-patient care, while for the planner of health services it could translate into reduction in demand for hospital beds.

Treatment studies in dementia have not proved easy to design or to interpret. Demented patients often suffer from other medical disorders and, since many are more than 80 years of age, their treatment is complicated by age-related changes in the absorption, distribution, and excretion of drugs. Frequently there is poor compliance with drug regimes, worsened by any cognitive deficits. When other medicines are concurrently prescribed, it is often difficult to judge precisely whether an unwanted effect is a consequence of the new drug or is related to an intercurrent disease or is an unexpected drug interaction.

Attempts to treat dementia are not new and the history of medicine is replete with examples of failed treatment ventures. Recent optimism dates from important advances in the study of brain chemistry, especially those that related the degree of dementia to the extent of post-mortem neuropathological and neurochemical changes (Perry *et al*, 1978). From the outset, it was clear that the relative neglect of dementia as a topic worthy of systematic clinical inquiry meant that many well intended investigators were working without much-needed basic information. Firstly, there was ignorance about the precise nature of the symptoms of dementia, the extent to which the presence of one symptom depended upon another, and the exact progress of the disorder. This type of information was, and remains, crucial to planning treatment studies, especially where it is reasonably expected in the initial stages of drug development that the benefits of treatment may be only slight. Secondly, assumptions were required about the potential value of a specific treatment on a target symptom of dementia when the neurobiological basis of that symptom was unknown or where it seemed unlikely that a simple reductionist model of the nervous system would suffice. Higher-order cognitive abilities, including memory, are likely to involve numerous synapses and transmitters (Black *et al*, 1987) and although much recent research in Alzheimer's disease (AD) has emphasised the role of cholinergic cells, other neurotransmitter systems deteriorate in this condition and may be implicated in the cognitive deficits associated with dementia (Kopelman, 1985).

TABLE I
Neurotransmitter changes in Alzheimer's disease (AD), Huntington's disease (HC), alcoholic dementia (Alc), multi-infarct dementia (MID), Parkinson's disease (PD), and ageing in the absence of dementia

Transmitter	*AD*	*HC*	*Alc*	*MID*	*PD*	*Ageing*
Ach-CAT	↓↓↓	↓	↓	→	↓	↓
ACE	↓↓	↓	↓	→		→
DA	↓	↓	↓		↓	↓
NA	↓		↓	→	↓	↓
GABA	↓	↓	↓			↓
5-HT	↓↓	↑			↓↓	→
CRF	↓↓				↓	
NY		↑				
SS	↓					→
SP		↓				
GLUT	↓					→

ACh: acetylcholin, CAT: choline acetyl transferase, ACE: acetylcholinesterase, DA: dopamine; NA: noradrenaline; GABA: gamma amino butyric acid; 5-HT: serotonin; CRF: corticotrophin-releasing factor, NY: neuropeptide Y; SS: somatostatin; SP: substance P; glut: glutamate.
↓ decreased, ↑ increased, → unchanged or uncertain.
Adapted from Hardy *et al* (1985).

Neurochemical pathology of the dementias

From a neurochemical standpoint, AD is by far the most exhaustively studied of all the dementias, and there is a paucity of information about cerebrovascular or alcoholic dementia. The literature allows few valid comparisons between the subtypes of dementia, largely for technical reasons but also because the brain areas sampled may differ substantially from one study to another. Small study numbers often limit statistical treatments of data and, unfortunately, this is particularly true of cerebrovascular dementia, despite the fact that it is relatively common. Table I summarises major findings to date. It shows that the cortical cholinergic deficit is not unique to AD, that in most respects the subcortical changes in Huntington's disease (HD) are highly specific, and that in AD deficits occur in transmitter systems other than the cholinergic.

Two hypotheses, both relevant to treatment, are derived from studies of the neurochemical pathology of the dementias and these concern the specificity and selectivity of the neurotransmitter changes found in each type of dementia. The *specificity* hypothesis proposes that each dementia has its own characteristic pattern of neurotransmitter abnormalities. Detection of such disease-specific patterns of neurotransmitter changes during life would, of course, substantially improve the accuracy of the diagnosis of dementia, which would be invaluable to treatment studies. The *selectivity* hypothesis postulates that the pattern of neurotransmitter changes found in each type of dementia correlates closely with the exact pattern of neuronal loss. From a therapeutic standpoint, demonstration of a disease process that leads to selective neuronal loss raises possibilities that target neurons could be precisely identified by the pattern of transmitter changes and that a single factor, available to therapeutic manipulation, is responsible for the selective loss of neurons. This thought was certainly uppermost in the minds of clinicians treating the cholinergic deficit in AD.

Diagnosis and the measurement of change

The symptoms and signs of dementia include a mixture of deficits in learning and memory, language, and psychomotor speed. These are accompanied by varying degrees of impairment of reasoning, behavioural problems, attentional difficulties, movement disorders, and disturbances of temperament and mood (Huppert & Tym, 1986). The cognitive symptoms of dementia are central to most concepts of the disorder, and the behavioural and affective changes are seen as complications (Miller, 1981). This has potential relevance to treatment studies, since the alleviation of a primary symptom may lead to the relief of secondary symptoms. Demented patients can vary substantially in the nature and severity of such cognitive symptoms, attributable in part to the exact location of the pathological changes taking place in the dementing brain, and also to the fact that, as the pathology progresses, the dementia may worsen in a non-uniform manner. A sample might contain patients who have some functions well preserved yet others deteriorated seriously. Variability of the nature and severity of clinical features is commonplace in dementia of presumed vascular origin and discrepancies between behavioural and cognitive symptoms are often pronounced. Measures of change in treatment studies of dementia must be sensitive to a wide range of dysfunction and severity (Rosen *et al*, 1984), yet at the same time not demand too much of the cognitively impaired patient who may be unable to co-operate for more than 30 to 40 minutes. There are as yet no measures of change that are entirely satisfactory in these respects.

An important aspect of most if not all of those neurochemical studies of dementia that provided the springboard for much of the current therapeutic optimism is that they have relied (quite properly) on precise neuropathological confirmation of clinical diagnoses. Unfortunately, the same is not true or even possible for the clinical studies that seek to

capitalise on these advances. Since most clinicians are understandably wary of an invasive validatory procedure like cerebral biopsy when the possible gains for a particular patient seem slim, almost all treatment trials are based on diagnostic criteria derived from clinical examination, with well recognised and potentially quantifiable risks of misdiagnosis. In this setting, a novel drug whose actions have been precisely anticipated by careful neurochemical investigations of diagnostically homogeneous groups of demented patients may fail to show an expected effect (especially when the effect is small) because treated patients could not be as reliably ascertained, thereby diluting and rendering statistically non-significant any advantage the new drug may in fact possess. It is among patients with senile dementia, who are the largest group likely to benefit from new treatments, that the problem of misdiagnosis is probably greatest. Cerebrovascular disease so commonly confounds Alzheimer's neuropathological changes in this group that it is often difficult, even when histological findings are to hand, to determine precisely the neuropathological basis of the clinical presentation. It is, therefore, mandatory for all drug treatment trials in dementia to state their diagnostic criteria and to ensure that, whenever possible, diagnoses are validated using neuropathological findings.

A further source of difference between studies in neurochemical pathology of the dementias and current neuropharmacological investigations concerns the stage of illness at which subjects are included. Neurochemical studies are based almost entirely on brain tissue obtained from patients dying in the terminal phase of illness, although it is clear from the few biopsy studies that the same neurochemical changes are present earlier in the course of the disease (Sims *et al*, 1980). However, drug treatments are probably more likely to be effective when used in patients with only a mild degree of dementia, in whom it is thought neurons have survived in numbers sufficient to respond to the treatment. Unfortunately, diagnostic criteria for mild dementia validated by natural history and pathological findings are not yet available, and there are difficulties in distinguishing mild dementia from the effects of coexisting physical illnesses, unrecognised depressive disorders, and 'benign senile forgetfulness' (Bergmann *et al*, 1971; Karl, 1978; Henderson & Huppert, 1984). Preliminary data from longitudinal studies are now beginning to appear in the literature and suggest that mild senile dementia of the Alzheimer type can be distinguished from health. In one recent study, subjects with mild memory impairment frequently progressed to AD, which was sometimes confirmed at autopsy (Rubin *et al*, 1989).

Neuropharmacological strategies

(a) Cholinergic

Alzheimer's disease

Early attempts to enhance the recovery of motor function following destructive cortical lesions often examined the administration of cholinergic drugs (Ward & Kennard, 1942). Although some benefits were detected in primate models, 'cholinergic stimulation therapy' never became an established clinical practice. In the modern era, interest in the possible benefits of cholinergic drugs in dementia dates from the demonstration that blockade of central cholinergic transmission by scopolamine in healthy volunteers causes a dementia-like syndrome, reversible by physostigmine, an anticholinesterase (Drachman & Levitt, 1974; Drachman, 1977). Later, the activities of enzymes associated with central cholinergic function were found to be decreased in brain tissue from AD patients (Davies & Maloney, 1976), and these reductions were found to be closely correlated with the density of senile plaques and deficits in cognitive function (Perry *et al*, 1978). Central cholinergic activity can be enhanced in health by administration of the acetylcholine precursors choline or phosphatidylcholine, which increase brain acetylcholine and cholinergic transmission (Cohen & Wurtman, 1975; Ulus & Wurtman, 1976) and decrease abnormal involuntary movements (Davis *et al*, 1976).

The cholinergic hypothesis has prompted much research, but is now seen to rest with some uncertainty on assumptions that an intact central cholinergic system is a prerequisite of normal memory, and that the signs and symptoms of AD are attributable to decreased central cholinergic function.

Although some early open studies suggested that supplementation of dietary choline (with choline or phosphatidylcholine) was of benefit in AD (Levy, 1978), more systematic studies provided no support for this conclusion (Bartus & Dean, 1982; Bartus *et al*, 1985; Little *et al*, 1985; Hollander *et al*, 1986). Little *et al* (1985) suggested that a subgroup of patients did in fact improve on long-term therapy, and that their improvement may have been more likely if compliance was poor. Their inference from these observations is that there is a 'therapeutic window' for the optimum dose of dietary choline, and this should be taken into account when planning future studies.

Physostigmine produces the most consistent improvements in both healthy volunteers (Davis *et al*,

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TABLE II
Summary of reports on the effects on memory of physostigmine (occasionally used in combination with phosphatidylcholine) in demented patients

Reference	*Subjects*	*No.*	*Dose*	*Effects on memory*
Davis *et al* (1978)	volunteers	19	1 mg.i.v.	enhancement
Davis *et al* (1979)	dementia	6	0.125–0.5 mg.i.v.	modest improvement
Muramoto & Sugashita (1979)	dementia	1	1 mg.s.c.	improved constructional
Peters & Levin (1979)	AD	5	0.008 mg/kgBW s.c.	+lethicin:improved
Smith & Swash (1979)	AD	1	1 mg.s.c.	some benefit
Christie *et al* (1981)	AD	11	0.25–1 mg.i.v.	some improved
Davis & Mohs (1982)	AD	10	0.125–0.5 mg.i.v.	some improved
Davis & Mohs (1983)	AD	13	2–8 mg oral	slight effects
Jotkowitz (1983)	AD	10	10–15 mg oral	nil effect
Thal *et al* (1983)	AD	12	3–6 mg oral	some improved
Welstein (1983)	AD	8	3–10 mg oral	nil
Mohs *et al* (1985*a*,*b*)	AD	12	4–16 mg oral	slight effects
Thal *et al* (1989)	AD	10	2–4 mg oral	some improved

All but one report concerns patients with a presumed diagnosis of Alzheimer's disease. Davis *et al* (1979) included three non-demented elderly patients, one Huntington's disease and two with Alzheimer's disease.

1978) and in AD (see Table II). Although enhancement of attention by physostigmine may partly explain improvements in memory, drugs that only improve attention do not improve memory performance in AD. The incidence of unacceptable peripheral effects, a short half-life and a narrow therapeutic window, the slight degree of improvement, and the fact that only a minority of AD patients improve after physostigmine have tempered enthusiasm for its use in AD, and encouraged the development of cholinesterase inhibitors. Latterly, intense interest centred on tetrahydroaminoacridine (THA) after the report by Summers *et al* (1986) of substantial gains by AD patients after treatment with THA. The study has encountered many methodological criticisms (Pirozzolo *et al*, 1987; Tariot & Caine, 1987) and a follow-up multicentre trial was temporarily halted by the United States Food and Drug Administration for assorted reasons, including reports that 20% of the first-treated patients had some hepatic impairment (Marx, 1988).

The use of cholinergic agonists in AD has not been widely investigated, largely because of their side-effects and lack of selectivity for central neurons. Pilocarpine was found to be ineffective in AD by Caine (1980), but the first study of physostigmine and arecoline in AD (Christie *et al*, 1981) provided some encouragement for further studies. The Sandoz compound RS-86 (a cholinergic agonist) lacked efficacy (Bruno *et al*, 1986), and Davis *et al* (1987) found the muscarinic agonist oxotremorine to be without effect. Tariot *et al* (1988) administered in a double-blind randomised design 1, 2 and 4 mg/h arecoline to 12 patients with AD. As in the study of Christie *et al* (1981), no statistically significant enhancements of cognitive function were detected, but at the lower dose improved picture recognition was found. The study design of Tariot *et al* (1988) is of particular interest because of the care with which the investigators sought to demonstrate that the administered drug in fact produced central cholinergic activation. The authors argued that their observations of a combination of increased heart rate, lowered body temperature, and increased plasma cortisol concentrations with unchanged prolactin secretion were consistent with increased central cholinergic activation rather than the effects of stress.

At present, most available drugs that can be used safely to modify central cholinergic transmission have been tried in AD. The benefits of physostigmine remain the only consistent and relatively uncontroversial finding. Novel, longer-acting, and safer cholinomimetic drugs are confidently promised, and these may soon be available for clinical investigation. Perhaps, as initially suggested by Christie *et al* (1981), future clinical trials will select for inclusion in long-term studies only those AD patients who show a response to a shorter-acting drug, such as physostigmine. The lack of selectivity of available muscarinic agonists for M_1 or M_2 receptors (which exert functionally opposite effects) is currently the focus of some research.

Alcoholic dementia

The cholinergic hypothesis of memory impairment has recently been convincingly extended from AD to include the dementia associated with alcoholism. Among alcoholics there is a spectrum of psychological

deficits that ranges from Korsakov's syndrome (KS) to milder forms of cognitive dysfunction. However, use of the term 'alcoholic dementia' to distinguish some cognitively impaired alcoholics from those with typical KS is not universally accepted. Tarter & Alterman (1984) and Goldstein (1985) concluded that the neuropsychological and presumed causal factors (alcoholic neurotoxicity, malnutrition, hepatic impairment, head injury, etc.) are so diverse in the non-KS group that it is unreasonable to regard alcoholic dementia as a discrete clinical entity. The outcome of cognitively impaired alcoholics is probably non-uniform, and the diagnostic requirements for alcoholic dementia are not simply the criteria for alcohol dependence combined with those for a steadily progressive dementia developing after long-term, excessive intake of alcohol. In the most thorough study so far, Cutting (1978) reviewed the case notes of 183 Bethlem and Maudsley in-patients with a final diagnosis of alcoholic psychosis and used these and interview data to examine the relationships between several categories of chronic organic mental deterioration and KS. He proposed that the spectrum of cognitive impairments in alcoholism included: (a) KS, which arose abruptly in alcoholics who were already mildy impaired, in whom nutritional deficiencies (particularly thiamine) appeared to be causally important and which tended to be irreversible; (b) alcoholic dementia, in which psychological deterioration developed gradually, appeared to be relatively independent of nutritional factors, and tended towards gradual improvement; (c) a mixed group of KS superimposed on alcoholic dementia. This classification should prove to be of value in future treatment studies of related memory impairments.

Thiamine deficiency has been consistently and clearly demonstrated as the important causal factor in the pathology of Wernicke's encephalopathy, even when it is not associated with alcoholism (Sable & Gubler, 1982). These pathological changes most frequently affect the grey matter around the third ventricle and brain stem, where demyelination and glial proliferation are characteristic. In KS, the medial dorsal nucleus of the thalamus, medial pulvinar and mamillary bodies are particularly involved (Victor *et al*, 1971) and, even when KS is not suspected ante-mortem, this type of pathological change is probably common place in alcoholics (Harper, 1983). The neurological signs of Wernicke's encephalopathy respond well to thiamine treatment, but the same is not true of the memory impairment. This may be because the brain has been irreversibly damaged by thiamine deficiency or because the memory impairment is caused by some other factor, such as alcohol neurotoxicity. The neurochemical pathology of KS is yet to be systematically described (McEntee *et al*, 1984) and so does not so far provide a rational basis for the therapy of memory deficits. Early reports of decreased indices of noradrenergic activity in KS (McEntee & Mair, 1978; Mair & McEntee, 1983) led to a study showing memory enhancement after clonidine, an alpha-2 adrenoceptor agonist, but not methysergide or *d*-amphetamine (McEntee & Mair, 1980). The memory deficits of alcoholism are, however, probably not attributable to damage to subcortical noradrenergic systems, but instead point to impaired central cholinergic function (Lishman, 1986).

A recent test of the cholinergic hypothesis of alcoholic dementia has provided evidence that the memory impairment associated with high alcohol intake is associated with decreased cholinergic function (Arendt *et al*, 1988). In this study, working and reference memory errors were induced in rats by high alcohol intake. These memory deficits were reversed about seven weeks after implants of cholinergic-rich foetal cell suspensions, and the extent of improvement correlated closely with the acetylcholine content, but not the noradrenaline content, at the implant site. Histology did not detect lesions in the periventricular grey matter of the alcohol-treated rats typical of KS, and so led the authors to question the widely accepted view that such lesions are causally important in the memory dysfunctions seen in this condition. The results of this study point to the possibility of investigating the effects on cognitive function in alcoholics with memory deficits of drugs that enhance central cholinergic activity (Lishman, 1986).

(b) Dopaminergic

Once the safety and efficacy of antipsychotic drugs had been demonstrated in younger patients, the behavioural problems of dementia were soon treated with the newly discovered antipsychotic drugs. Using a double-blind, cross-over design, Seager (1955) compared chlorpromazine and placebo in a diagnostically mixed sample of female patients (dementia, 29 subjects; schizophrenia, 12 subjects; depression, 6 subjects). Irrespective of diagnosis, nursing problems were much reduced in about 60% of patients on chlorpromazine but not on placebo. Later studies (Hamilton & Bennett, 1962*a*,*b*; Sugerman *et al*, 1964) added to these early findings, and in due course the use of antipsychotic drugs became an established part of clinical practice and their use is now almost routine.

The use of dopaminergic blocking drugs in the elderly is not yet well founded on substantial clinical

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investigations, and there are no clear-cut clinical guidelines. Recent reviewers (Helms, 1985; Risse & Barnes, 1986; Raskind *et al*, 1987; Sunderland & Silver, 1988) have remarked on the paucity of good studies, often finding problems in design, diagnostic criteria, measures of change and duration of treatment. In fact, Helms (1985) considered only three trials met all his methodological criteria, although this is probably too restrictive a view upon which to base clinical practice. The main findings of the study by Barnes *et al* (1982) are of interest. They could detect little difference between thioridazine, loxapine, and placebo after eight week's treatment of behavioural disturbance in 34 demented patients, and concluded "many older demented patients with behavioural disturbances are not significantly helped by ongoing antipsychotic treatment". Similarly, Petrie *et al* (1982) found that only about a third of actively treated (haloperidol or loxapine) demented patients improved. Obviously, such reported lack of efficacy is of some concern, especially since so many of the institutionalised elderly are regularly prescribed neuroleptics, often with anti-Parkinsonian medication (Michel & Kolakowska, 1981; Mann *et al*, 1984). Further, two of these studies (Rada & Kellner, 1976; Barnes *et al*, 1982) reported high placebo responses, strengthening the view (Hanley *et al*, 1981) that behavioural or non-pharmacological treatments should continue to be systematically evaluated in demented patients.

There is also a need for investigations on the effects of antipsychotic withdrawal. Fifty demented patients who had received chlorpromazine for at least seven months were changed to placebo by Barton & Hurst (1966), who noted little deterioration during the following three weeks. Although the authors concluded that some patients may receive neuroleptics unnecessarily, this was not clearly established as three weeks could be too short a period to recover from the effects of long-term administration.

The optimum choice of dopaminergic blocking drug for use in the elderly is not yet established. Reduced central cholinergic transmission in AD could lead to more frequent and severe anticholinergic side-effects of dopaminergic drugs like thioridazine, although this does not appear to be a common clinical problem and the practice of preferring neuroleptics with fewer anticholinergic effects (e.g. pimozide; Kushnir, 1987) has not been widespread. There is also some evidence that the dose range usually associated with the antipsychotic actions of dopaminergic blocking drugs is much higher than the dose range required by demented patients. Steele *et al* (1986) examined the effects of haloperidol and thioridazine on behavioural symptoms in 16 patients with senile dementia of the Alzheimer type, but only six patients completed the open, cross-over design. Both drugs were effective and although thioridazine was better tolerated, increased doses in two patients were associated with cognitive deterioration. Very low doses of haloperidol or thioridazine were used in two patients with dementia who had failed on conventional low-dose regimes but later showed clinical improvement on very low doses (haloperidol 0.125 mg daily or thioridazine 10 mg daily). Although a lower preferred dose of neuroleptic may reduce the incidence of unwanted effects, a survey of tardive dyskinesia studies led Kane & Smith (1982) to conclude that increasing age and female sex are the major risk factors for tardive dyskinesia, and that dosage, duration, and 'drug-free' periods do not reduce their likelihood.

In summary, the typical or 'core' symptoms of dementia (dysmnesia, disorientation, confusion, etc.) are not significantly changed by neuroleptics, and specific behavioural target symptoms must be present if these drugs are to be effective. These symptoms are well described by Reisberg *et al* (1987), who have also devised a rating instrument that may prove useful in future clinical trials.

Animal models of the behavioural problems that follow brain injury (Marotta *et al*, 1977) have prompted the use of dopaminergic agonists in comparable clinical settings, although as yet without success (Gualtieri, 1988). In elderly patients, drugs that potentiate dopaminergic transmission have rarely been considered other than in the setting of Parkinson's disease, where *l*-dopa was found to be ineffective in the treatment of cognitive symptoms in the absence of Parkinson's disease (Jellinger *et al*, 1980). The dopaminergic agonist memantine (20–30 mg i.v. *p.d.*) was thought ineffective by Fleischhacker *et al* (1986) in a placebo-controlled, single-blind study of 20 demented patients.

(c) Noradrenergic

The majority of research reports on the pharmacology of memory function in elderly subjects have involved manipulation of central cholinergic transmission. There is some evidence, however, that loss of catecholaminergic neurons contributes to cognitive decline in AD. Concentrations of noradrenaline, dopamine, and their metabolites are reduced in cortical tissue from AD patients to a greater extent than is found with ageing in the absence of dementia. Pharmacological enhancements of catecholaminergic function may, therefore, improve some of the symptoms of AD when used either alone or, potentially, in combination with cholinomimetic agents.

Arnsten & Goldman-Rakic (1985) conducted careful studies on the effects of ageing on cognitive performance tasks in rhesus monkeys. Clonidine, an alpha-2 adrenoceptor agonist, improved performance in each of five monkeys tested, and although at high doses (0.05–0.07 mg/kg) clonidine's sedative actions impaired performance, once an animal could tolerate this effect, similar improvements were observed. Unlike propranolol, which was without effects, yohimbine worsened performance, supporting the view that alpha- rather than beta-adrenoceptors are involved. Further studies showed that these actions are probably (a) unrelated to the sedative action of clonidine, as they could not be produced by diazepam, (b) mediated through alpha-2 adrenoceptors, as they could be prevented by the receptor antagonist, yohimbine, and (c) required the presence of adrenoceptors in the principal sulcal region. In the light of these results, Arnsten & Goldman-Rakic (1985) argued that since adrenoceptors do not appear to be reduced in AD (Hardy *et al*, 1985), therapy with adrenergic agents might prove of value in this disorder. Chronic therapy at high doses may be required in some subjects if the strategy is to be effective. Patients with KS show some improvement in memory after clonidine (Mair & McEntee, 1986). However, when eight patients with clinically diagnosed AD were studied in a double-blind, placebo-controlled trial of clonidine given orally (0.1, 0.2 and 0.4 mg), the drug was without effect (Mohr *et al*, 1989). Cognitive function was measured using alternative forms of object naming, verbal learning, sentence memory, word fluency, digit span, and visual retention. The authors concluded that "single neurotransmitter replacement therapies increasingly suggest the necessity for consideration of a multiple-system approach for the symptomatic treatment of Alzheimer's disease".

There have been few systematic trials of noradrenergic therapies in dementia. Most studies have examined the value of antidepressant drugs, although the reasoning has rarely been as well argued as in the above animal studies. The possibility that the behavioural problems of dementia may be responsive to monoamine oxidase inhibitors (MAOIs) was first suggested by the efficacy of MAOIs in hyperactive children (Zemektin *et al*, 1985) and discussed by Jenike (1986). Later, Tariot *et al* (1987) administered *l*-deprenyl, a selective monoamine oxidase B (MAO-B) inhibitor, to 17 Alzheimer patients in a double-blind, placebo-controlled, cross-over study in which placebo was followed by active drug (10 mg daily rising to 40 mg daily) later replaced by placebo. Improvement was observed in mean behavioural and cognitive scores, so much so that six of the 17 were thought to be "definitely improved", and this was more marked at the lower dose. Within the limitations of their design, the authors postulated that the greater efficacy at the lower dose pointed to inhibition of MAO-B and not MAO-A, and that selective "improved modulation" might play a neuroprotective role in AD. Their results suggest that *l*-deprenyl may prove of value in dementia.

There have been several reports that propranolol may be useful in the treatment of behavioural disorders associated with chronic organic cerebral disease. Elliot (1977) thought the aggressive behaviour linked to brain damage could be controlled by propranolol, and a few methodologically limited studies have tended to support this view (Schreier, 1979; Yufodfsky *et al*, 1981; Petrie & Ban, 1981; Williams *et al*, 1982). The mode of action of propranolol when used in the treatment of behavioural difficulties is unclear. Many of the patients chosen for study appear to have been unresponsive to more conventional treatments, and their symptoms may have been worsened by anxiety linked to the retention of some insight into their predicament. The efficacy of propranolol may thus be attributable to its anxiolytic effects, although the general lack of efficacy of benzodiazepines when used in this context would not support this view.

(d) Serotonergic

Potentiation of serotonergic transmission has recently been investigated in the treatment of behavioural and cognitive symptoms of dementia. The finding that post-mortem cortical tissue concentrations of serotonin are reduced in AD formed the basis of these studies, but several had been prompted by the clinical observation that the behavioural symptoms can be substantially relieved by antidepressants. O'Neil *et al* (1986) reasoned that since decreased brain concentrations of serotonin and its metabolites are associated with aggression in some animal models, combination treatment with tryptophan and trazodone might be effective. The same combination was later found useful in reducing the screaming and banging of an elderly demented patient (Greenwald *et al*, 1986). Systematic evaluation of this strategy in the management of behaviour disorders in dementia is awaited with interest. Alaproclate, a potent and selective blocker of serotonin uptake in central serotonergic neurons, was found to be ineffective in senile dementia (of either presumed Alzheimer or multi-infarct types) by Dehlin *et al* (1985). Likewise, Cutler *et al* (1985*a*) found zimelidine (also a serotonin uptake inhibitor) to be ineffective.

(e) GABAnergic

The pharmacological treatment of behavioural symptoms associated with dementia has been based on the sedative actions of a wide range of compounds and not on the specific activities of drugs acting on the underlying pathological processes. Optimum clinical management must take into account frequently expressed and persistent anxieties about needless overprescribing and the potential for harm of psychotropic drugs in old people (Castleden *et al*, 1977; Morgan *et al*, 1982; Gilleard *et al*, 1983).

Sedative drugs that are active at GABAnergic synapses are largely contraindicated in the care of demented patients. The induction of tolerance, worsening of confusion, and overall impairments of performance have contributed to this view. Chlormethiazole, which has anticonvulsant, hypnotic, anxiolytic, and sedative properties, is a notable exception to the general rule. It is widely used in the treatment of behavioural problems of old people, whatever the presumed cause. The neuropharmacology of chlormethiazole is not understood, but as it enhances the inhibitory effects of gamma-aminobutyric acid (GABA) and may also potentiate the effects of glycine, these seem the most likely bases of its actions. Because sleep disturbance commonly coexists in the demented elderly with other behavioural problems, the use of chlormethiazole has been extended to include the management of agitated confusional states where there is nocturnal wakening. Chlormethiazole is most often used as an hypnotic when the choice in the elderly is influenced by concern that their use, especially if prolonged, might worsen the cognitive or behavioural problems of dementia. The available literature supports the view that chlormethiazole has distinct advantages over the benzodiazepines (Bayer *et al*, 1986; Pathy *et al*, 1986) but is less helpful concerning other hypnotics. Controlled clinical trials have shown that chlormethiazole has advantages over haloperidol (ter Haar, 1977) and thioridazine (Ather *et al*, 1986), attributable to a lower frequency of side-effects.

Sarter *et al* (1988) suggested that a fresh look at GABAnergic antagonist therapies in AD may well prove fruitful. Firstly, they cite anatomical and pharmacological evidence that inhibitory GABAnergic neurons control the activity of basal forebrain cholinergic cells, thought to be involved in AD. Secondly, they suggest that GABAnergic antagonist drugs may disinhibit surviving cholinergic neurons in AD, and so enhance memory function. In support of their hypothesis they point to animal studies indicating that the amnesic effects of scopolamine can be attenuated by GABAnergic antagonists, which probably improve memory largely by improving acquisition (Gamzu, 1988). Like other hypotheses linking neurochemical changes to cognitive function, the reasoning may appear simplistic but it seems likely to stimulate further examination of the GABAnergic system in AD (Robbins, 1988).

(f) Peptidergic

Most if not all the neuropeptides of the cerebral cortex may coexist with classic transmitters and subpopulations of cortical neurons can be defined by the presence of particular peptides. In AD, there is a consistent decrease in somatostatin and corticotrophin-releasing factor (CRF) in the cerebral cortex, but other peptides are not affected. Importantly, these include neurohypophyseal peptides, vasopressin and oxytocin, putatively involved with memory, and vasoactive intestinal polypeptide that is found with cortical cholinergic neurons. Changes in receptors for somatostatin and CRF are markedly different in AD, somatostatin receptors decreasing by about 40–60% while CRF receptors increase.

Neuropeptides are found in almost bewildering variety throughout the central nervous system, although at concentrations often considerably below those of 'classic' neurotransmitters. Outside the hypothalamic–pituitary system, their functions remain almost unknown, despite more than a decade of intense inquiry. Presently, the non-endocrine actions of neuropeptides are believed to be as neurotransmitters, neuromodulators, and neurotrophic factors. Their relevance to treatment studies in dementia is based on two lines of argument. Firstly, some neuropeptides are thought to be important in the acquisition of adaptive behaviour. Since these involve learning, memory, attention, and motivation, they may be improved by treatment with those peptides. A successful therapy could include a neuropeptide chosen because of hypothesised 'behaviour enhancement' and not simply because it was decreased in post-mortem studies. Trials with analogues of ACTH and vasopressin and opiate receptor blockade are examples of this approach. Secondly, selective loss of neurons, believed to occur in some types of dementia, may be caused by a deficiency of a single peptide, especially if that peptide had a key part to play in the trophic functions of those neurons. Attempts to correct such an hypothesised deficiency with a somatostatin analogue (e.g. L363,586) as reported by Cutler *et al* (1985) exemplify this approach. Likewise, thyrotrophin-releasing hormone (TRH) is reported to enhance central cholinergic function (Yarbrough, 1979; Yarbrough & Pomara, 1985), and its use in

motor neuron disease prompted its advocacy in AD. Subsequently, Peabody *et al* (1986*a*) assessed 300–500 μg TRH i.v. in four demented patients and found no effect.

Potentially, the neurotrophic protein nerve growth factor (NGF) is of considerable relevance to treatment studies in dementia. Elegant animal studies had already demonstrated the treatment potential of NGF following lesion experiments, and septo-striatal cholinergic neurons were known to be responsive to NGF before Fischer *et al* (1987) found that continuous NGF intracerebral infusions over four weeks were partially able to reverse cholinergic cell body atrophy and to improve spatial memory performance in aged rats. Previously, Hefti & Weiner (1980) had hypothesised that in AD, the loss of forebrain cholinergic neurons may be caused by a disorder of the trophic functions of these cells, reversible by treatment with NGF, and that this treatment may lead to clinical improvement. Cholinergic cell bodies in brain areas known to be affected in AD have cell surface receptors that can recognise NGF (Rosenberg *et al*, 1987), and this may be related to the selective vulnerability of these neurons in AD (Perry, 1988). Studies on the effects of NGF in AD are awaited with interest.

Vasopressin

Vasopressin and some of its synthetic analogues improve animal learning and memory (de Wied, 1976), and this may be related to the involvement of vasopressin in the integration of behavioural, neural, and hormonal components of stress responses (Koob *et al*, 1984). Vasopressin nasal spray improves memory in non-demented adults (Legros *et al*, 1978), effects that are probably independent of the endocrine actions of vasopressin since they can also be produced by its synthetic analogue 1-desamino-8-D-arginine vasopressin (DDAVP) that is largely devoid of its endocrine actions (Weingartner *et al*, 1981*a*). Early studies in dementia (Weingartner *et al*, 1981*b*; Durso *et al*, 1982; Tamminga *et al*, 1982) and cognitive impairments after head trauma (Oliveros *et al*, 1978; La Boeuf *et al*, 1978) were fairly encouraging. However, the most systematically conducted study to date (Peabody *et al*, 1985) failed to detect any clinically significant effects of desglycinamide arginine vasopressin (DGAVP) in either alcoholic or Alzheimer-type dementia, and raised the possibility that the beneficial effect of vasopressin on performance was a non-specific stimulatory action that indirectly improved scores on memory tests. A later study by Peabody *et al* (1986*b*) found similar results using DDAVP (30–180 μg/day over three weeks). Such variability in outcome could be attributed to one of several factors, including the width of the 'therapeutic dose window', individual pharmacokinetic differences, variation in duration of therapy, and the inclusion of too many patients at a late stage of illness. As more potent, longer-acting vasopressin analogues become available, they too may be systematically evaluated, and most interest will focus on the effects of their chronic administration in patients with mild dementia.

ACTH

Although there are no reported abnormalities in the synthesis or release of adrenocorticotrophic hormone (ACTH) in dementia, there has been considerable interest in the treatment of cognitive disorders using ACTH analogues with the behavioural effects of ACTH but without its peripheral endocrine actions. This interest arises because of the stimulatory effects of ACTH on behaviour, recognised at least since 1955 (Quarton *et al*, 1955) but not distinguished from the hormonal actions of ACTH until synthetic analogues of ACTH fragments became available about 20 years ago (de Wied, 1969). The human psychopharmacology of ACTH peptides is now extensive (for reviews see Pigache & Rigter, 1981; Pigache, 1983). In summary, ACTH-like peptides may be involved in the acquisition of adaptive behaviour, and this involvement does not depend upon the ability of ACTH to release steroids since the same effects can be produced by ACTH $^{4-10}$, which is devoid of steroidogenic activity. Oral ACTH$^{4-9}$ with a glycine residue at position 10 (ORG 2766) has been most extensively studied in demented patients. Martin *et al* (1983) found ORG 2766 (40 mg daily *p.o.* for four weeks) had little effect in a double-blind cross-over placebo trial in 38 severely deteriorated female patients. Kragh-Sorensen *et al* (1986) found that ORG 2766 produced "clinically significant" effects in about 25% of 156 demented patients. Partanen *et al* (1986) examined both the symptomatic and EEG responses to ORG 2766 (40 mg daily *p.o.* for six months) or placebo. When the effects of other psychotropic drugs were taken into account, ORG 2766 did not prevent the deterioration in the EEG associated with the progress of AD. Analogues of ACTH are therefore without beneficial effects in AD.

Opiate antagonists

Although no abnormalities in central opioid systems have been detected in AD, several research groups have examined the effects of opiate receptor blockade

in this disorder. This approach is based on the observation in healthy subjects that naloxone (1–10 mg i.v.) may improve some of the electrophysiological parameters associated with attention (Arnsten *et al*, 1983), although this is an inconsistent finding, especially at low doses. In a preliminary study in AD, Reisberg *et al* (1983) reported that low doses of intravenous naloxone produced clinical improvements. Later studies failed to reproduce these early findings (Steiger *et al*, 1985; Tariot *et al*, 1985). Longer-acting opiate antagonists do not appear to be more efficacious: naltrexone (Pomara *et al*, 1985; Hyman *et al*, 1985; Serby *et al*, 1986) and nalmafene (Weiss, 1987) were without significant clinical effect. The beneficial effects of opiate receptor blockade in dementia appear to be unpredictable; the study by Tariot *et al* (1986) suggests that the cognitive and behavioural actions of naloxone occur at about 5% of the dose required in younger, non-demented subjects. At present there is no indication for further studies on the endogenous opiate system in AD. However, opiate antagonists may prove to be of value in the treatment of dementia of presumed vascular origin. Naloxone can protect against the sequelae of cerebral ischaemia in some animal studies (e.g. Avery *et al*, 1983) and after acute stroke in clinical studies, especially when administered within the first 24 hours. In conjunction with the control of other risk factors for stroke, opiate antagonism may prove of value in the long-term treatment of cerebrovascular dementia when it is proposed that cognitive decline is caused by a succession of cerebral infarcts.

(g) Antiviral agents

Creutzfeld–Jakob disease (CJD) is a rapidly progressive dementia with an almost invariably fatal outcome (May, 1968; Manuelidis *et al*, 1978). Its features include abnormalities of muscular tone and movement, all attributable to a spongiform encephalopathy caused by an unconventional virus (Gajdusek, 1977). The infectious pathogen is believed to be similar to the infective agent in murine scrapie, which is often used as an animal model of transmissible dementia. Although antiviral drugs are without benefits in the animal model, in the absence of any other effective treatment these are thought justified in the terminal care of CJD patients. Initial single-case studies with idoxyridine were unsuccessful (Goldhammer *et al*, 1972; Herishanu, 1973) but several case reports of experience with amantidine are more encouraging (Braham, 1971; Sanders & Dunn, 1973; Sanders, 1979). The largest therapeutic trial reported to date included nine CJD patients in whom the diagnosis was confirmed at autopsy in seven subjects (Terzano *et al*, 1983). Four patients received amantadine (3.5–15 mg daily for an average of 32 days) and five others continued to receive supportive therapy. Although death appeared a little delayed in those receiving amantadine (seven months compared with three months for those on supportive therapy) this was not significant. The authors felt, however, there were some transient therapeutic benefits associated with amantadine (improved EEG, improved wakefulness, and reduced motor impairment) and they thought these effects might indicate some therapeutic potential, especially if amantidine were administered at an earlier stage. Other antiviral agents have been introduced late in the course of illness: interferon therapy was ineffective in two women with CJD (Kovanen *et al*, 1980) and acyclovir was likewise without effect (David *et al*, 1984; Newman, 1984). However, the course of illness in one patient with an histopathologically confirmed CJD diagnosis was repeatedly suppressed by vidarabine, which had little or no action in two other subjects (Furlow & Whitley 1982).

(h) Antihypertensive agents

Although AD is the commonest type of primary degenerative dementia, about one in eight dementias examined at autopsy have cerebrovascular disease without significant Alzheimer pathology (Jellinger, 1976; Katzman & Terry, 1983). Hypertension is associated, in most studies, with the development of cognitive impairment and, among the elderly, it is importantly linked with subsequent deterioration of cognitive performance (Scheinberg, 1988). However, the incidences of both hypertension and cognitive impairment increase with age and the association may be explained, at least in part, by chance. Further, it would not be surprising if hypertension, which is known to cause or exacerbate vascular disease, were to lead in turn to impaired cardiovascular performance, cerebrovascular accidents and, eventually, coarse brain disease and reduced mental efficiency. Although the majority of studies have detected an association in the absence of stroke between hypertension and impaired cognitive performance, the largest and most systematic to date found that among 2032 hypertensives neither blood pressure nor antihypertensive treatment was significantly associated with cognitive performance (Farmer *et al*, 1987).

It is clear from studies of the elderly that control of hypertension significantly reduces mortality and morbidity due to cardiovascular and cerebrovascular disease, but it is not yet established that the reduction

of blood pressure in demented hypertensives contributes to improved life expectancy or is in fact desirable. One view, which was once widely held, is that the prognosis for all dementias is uniformly poor, their courses are unremittingly progressive and, on the assumption that the complex functions of dead or dying neurons cannot be restored, any attempt at treatment is doomed. Another view is that as cerebrovascular structures age, greater systemic blood pressure is required to maintain optimal cerebral perfusion (Strandgaard, 1976). If there were evidence to support this last hypothesis, then lowering of blood pressure in demented hypertensives would be contraindicated, as it would further compromise cognitive function.

Until recently, most clinical practice would have been based on the second view. Experience in the care of the demented elderly suggested that worsening of psychological and physical status was commonplace when hypertension was treated in demented patients. Such opinion, however, was based on experience with a wide range of antihypertensive agents, many of which are now known to exacerbate rather than relieve memory impairment and may have harmful effects on the autoregulation of cerebral blood flow. If it is assumed that the pathogenesis of vascular dementia involves progression from sustained hypertension to atherosclerotic cerebrovascular disease to a succession of cerebral infarcts to impaired cognitive performance, then the removal or control of factors predisposing to such a progression could possess distinct advantages for the hypertensive demented patient.

Meyer *et al* (1986, 1988*a*, 1988*b*) have completed the most extensive series of investigations on this topic. In summary, their studies have examined (a) the pathology of cerebral blood flow (CBF) during the course of vascular or Alzheimer-type dementias, (b) the relationship between cortical blood flow and reduced cognitive function in dementia, (c) incidence of 'risk factors', including hypertension, for stroke in multi-infarct dementia, (d) the question of whether hypertension should be treated in demented patients, and (e) the possibility that there is an optimum blood pressure (a 'therapeutic window') for demented hypertensives. They found a significant relationship between reduced cognitive test scores in multi-infarct dementia and mean local CBF (Kitagawa *et al*, 1984). This research group has provided data to support the contentions that while CBF is lower in both AD and vascular dementia, it decreases at least two years before the onset of vascular dementia but falls in step with the decline in cognitive function in AD (Rogers *et al*, 1986). They have also examined the effects of controlling blood pressure in two groups of hypertensive demented patients with presumed cerebrovascular dementia. In one group, blood pressure was reduced to within the upper normal range, and in the other group was reduced below this range. The findings were striking: improvements in cognitive function were clearly associated with the maintenance of systolic pressure within the upper normal range, but if systolic pressure was reduced below this range, patients showed a marked deterioration. This is the first study to examine systematically the effects of lowering blood pressure on cognitive function in dementia, and requires replication. It also raises important questions about the optimum choice of antihypertensive medication.

Non-demented, hypertensive old people were carefully investigated by Gurland *et al* (1988). Effective treatment of isolated systolic hypertension neither worsened nor improved cognitive function or behaviour. In this study, adequate control of blood pressure was achieved with diuretic alone (chlorthalidone) in 88% patients, and only a minority required alternative treatment (reserpine or metoprolol or hydralazine). The finding that lowering blood pressure in this group of non-demented subjects is probably safe is of potential relevance to the use of antihypertensives in multi-infarct dementia.

The Medical Research Council Working Party (1985) reported a trial of the treatment of mild hypertension, and raised the question of the optimum choice of antihypertensive agent for protection against strokes. If a succession of cerebral infarcts is presumed to be the essential component of vascular dementia, the results are pertinent here. The trial showed that bendrofluazide was almost three times as effective as propranolol in protecting against strokes and that this difference was even more marked between smokers. Previously, it had been assumed that most antihypertensives currently in use were equipotent in this respect, simply because of their ability to reduce blood pressure.

Centrally acting sympathetic blocking agents are associated with impairment of psychological functions when used to treat hypertension. In the demented elderly, these effects are not straightforward to interpret. In fact it would not have been surprising if Meyer *et al* (1986) had chosen to explain deterioration of some of their patients on the basis of the type of drug used rather than to implicate the final blood pressure. Antihypertensive treatment can have beneficial and harmful effects, capable of both slowing or reversing cognitive decline or producing new symptoms. In health, beta-blockers impair flicker fusion threshold, simple reaction time, and digit copying in some reports (McDevitt, 1985) but not others (Betts *et al*, 1985; Madden *et al*, 1986).

In hypertensives, memory impairment is linked to treatment with beta-blockers (Solomon *et al*, 1985) but not to angiotensin-converting enzyme (ACE) inhibitors (Lichter *et al*, 1986). Similarly, the ACE inhibitor captopril was associated with better performance at work and better 'life satisfaction' than either propranolol or methyldopa (Croog *et al*, 1986). In a study of adult hypertensives, nicardipine, a calcium channel antagonist, did not differ from propranolol (Callender *et al* 1986). Most studies of the cognitive effects of antihypertensives have linked methyldopa or the beta-blockers to cognitive impairment in treated hypertensives but the same does not appear to be true of the ACE inhibitors or the thiazide diuretics.

A potentially informative approach to the choice of antihypertensive drug is provided by studies on the effects of these drugs on CBF. Autoregulation of CBF is defined as the maintenance of a constant CBF in the face of normal changes in systemic blood pressure. In health, CBF is maintained by auto-regulatory adjustment of resistance calibre during activities such as postural change, defaecation, etc. In both normotensive and hypertensive individuals the range of pressures within which autoregulation is effective may vary substantially. However, because cerebral flow is the same in both conditions, there must be increased cerebrovascular resistance in hypertension. Structural changes in the cerebral vasculature thus represent adaptations to sustained high blood pressure but have an important con-sequence for the hypertensive patient (Strandgaard *et al*, 1973). The chronically adapted resistance vessels are much less able to respond to hypotension, probably because their thickened vessels are less able to dilate than are healthy ones. The outcome for the demented hypertensive patient may well be catastrophic: if blood pressure is rapidly lowered then CBF will fall and ischaemic brain damage may ensue. Additionally, if the brain of the demented patient contains areas of normal tissue, which have retained their ability to autoregulate, these will maintain perfusion at the expense of adjacent damaged areas.

Patient studies support the view that ACE inhibitors have unique actions on CBF. For example, Britton *et al* (1985) showed that in ten patients with cerebrovascular disease, in spite of a fall of mean systemic blood pressure from 123 to 109 mmHg, the average CBF to an affected hemisphere tended to increase (by about 10%). In nine hypertensive control subjects receiving conventional antihypertensive therapies, mean systemic blood pressure fell from 118 to 114 mmHg, but CBF to an affected hemisphere tended to decrease (by about 11%). Unfortunately, the numbers of patients involved in this study were too few to have detected a statistically significant difference between groups given the size of the effect reported. Rajagopalan *et al* (1984) reported a similar result in a study of nine patients with severe congestive heart failure. After treatment with an ACE inhibitor (captopril) for between 4 and 15 days, mean diastolic blood pressure fell from 95 to 85 mmHg, while CBF increased significantly (from 61 to 74 units). Although it may be simplistic to equate CBF with cognitive performance (but see Meyer *et al*, 1988*a*), it is reasonable to take it into account when deciding upon the optimum hypotensive agent for a hypertensive demented patient.

Conclusion

There are no consistently effective drugs for the prevention of relief of dementia, but there is no lack of enterprise in the search for new treatments. This review has summarised how interest in neurochemical pathology has generalised from Parkinson's and Huntington's diseases to AD and on to other types of dementia, and how a better understanding of this pathology has led to novel therapeutic approaches.

The cholinergic hypothesis, which was the stimulus for much recent research activity, is no longer linked solely with Alzheimer's neuropathological changes, but is now confidently incorporated in several other hypotheses of memory dysfunction, whatever the associated neuropathology (e.g. the dementias associated with alcoholism (Lishman, 1986) and Parkinson's disease (Perry *et al*, 1985)). At the same time, initial emphasis on cholinergic deficits in AD has yielded to the more considered view that changes in non-cholinergic transmitter systems are also important in the pathogenesis of the cognitive and behavioural symptoms of AD, and may be amenable to therapeutic modification.

The problems of behavioural disturbances associated with dementia are worth intense research efforts, despite the fact that they have been relatively neglected. Community-based studies in this area may prove especially informative. More effective management of behavioural problems of demented patients in the community could substantially reduce the need for admission to a psychiatric hospital. The recognition that multiple transmitter deficits occur commonly in most types of dementia is now influencing the choice of treatment strategies to be evaluated in memory impairment and behavioural disturbances associated with organic brain disease. Proposals to modify simultaneously the function of several neuro-transmitter systems are based on such observations.

The problems of ensuring that new drugs are indeed active at central sites putatively involved in

the symptoms of dementia are important. Although most attention has been given to infusions of cellular preparations in the treatment of chronic neurodegenerative disorders, more conventional drugs have been administered by such direct routes. Harbaugh *et al* (1984) have demonstrated that it is practical to implant chronic intrathecal infusion devices in AD patients. Their use of the muscarinic agonist bethanechol yielded largely negative results, but similar techniques could prove crucial when used with other drugs. There may also be advantages to be gained from the use of agents in combination with already tested cholinomimetic drugs. Preliminary studies of combinations of physostigmine and phosphalidylcholine or piracetam have been largely negative (Growden *et al*, 1986), but other combinations may prove beneficial.

As knowledge has accumulated about the treatment of AD, so a fresh look has been taken at other dementias. Although it is probably naïve to equate cerebral blood flow and cognitive function, further studies of the potential benefits of controlling hypertension in patients with early features of cerebrovascular dementia should prove rewarding. Certainly, the results of Meyer *et al* (1986) require replication, and future studies of the treatment of hypertension in old people should include the detection of cognitive decline among the more usual measures of morbidity such as stroke or myocardial infarction.

Looking to the future, advances in understanding the pathogenesis of cerebrovascular disease will lead to novel therapies for dementias of vascular aetiology (following an argument already made, for example, on behalf of tissue plasminogen activator (Zivin *et al*, 1985)). Present knowledge, however, provides a substantial and sufficient basis for the investigation of many currently available treatments, and much could now be done to establish the value of controlling the harmful effects of acknowledged risk factors for multi-infarct dementia (Scheinberg, 1988). Studies on the memory impairments associated with Huntington's disease, alcoholism, and Parkinson's disease should benefit from experience of therapeutic efforts in AD. Specifically, the impetus given to dementia research by progress in AD is generalisable to other dementias. Creutzfeldt–Jakob disease, alcoholism, and brain injury have been discussed in this review, but Huntington's disease has been largely neglected. A literature search showed that almost without exception, treatment studies in Huntington's disease have examined only the abnormal movements, and a consensus did not exist concerning the exact nature and progress of the cognitive deficits in this condition. Selective neuronal loss is a characteristic feature of Huntington's disease, and one hypothesis attributes such loss to the toxic effects of neuroexcitatory amino acids, especially quinolinic acid (Schwarcz *et al*, 1982). Agents that specifically antagonise excitatory amino acids may provide a fertile source of novel drugs that prevent selective neuronal loss in AD and Huntington's disease (Schwarcz & Meldrum, 1985). Potentially, advances in understanding the molecular pathology of chronic neurodegenerative conditions may provide the most informative approach to the selection of such compounds. There is, therefore, certainly a strong case to be made for extending treatment paradigms to include new subgroups of dementia, among which alcoholic dementia will probably be the first.

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