Clinical strategies in the treatment of Alzheimer’s disease

D. F. Swaab and E. Fliers

Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam Zuidoost, The Netherlands

Introduction

Every culture has tried to obtain life extension. A 2400-years-old example is the Babylonian-Assyrian epos of Gilgamesh, who tried in vain to escape the aging process by bathing in the fountain of youth and by eating the herb of life. The latter endeavor makes clear that ‘research’ in the pharmacological prevention of the symptoms of aging has a long history. From the pharmacological literature of the last century it is evident that hypotheses concerning the causal factors of aging and Alzheimer’s disease as well as the therapies for treating them were often changing parallel to neurobiological interests and fashions. Clinical strategies were not specific for Alzheimer’s disease, but passively followed new developments in medicine and research by trying out nearly every new compound or idea relevant to this condition. This may also explain why therapies that were considered to be ‘rational’ in the light of a new development, appeared nonsensical as soon as new insights developed.

The approach of trying out everything that is new in neurobiology on Alzheimer patients does not preclude of course the possibility either that an effective substance will be found, or that its proposed mechanism of action will indeed turn out to be correct. However, the chance of success of this strategy is very small. Repeatedly, ideas about the etiology of Alzheimer’s disease have been adapted immediately to new disciplines or insights that developed in neurosciences. Thus changes in hormone levels, blood supply, metabolism, and transmitters have been pinpointed as possible causes of brain aging and Alzheimer’s disease. Subsequently, a ‘new and promising’ therapy was claimed to have a ‘rational’ basis and was tried out on Alzheimer patients. This history might make us less optimistic about all the ongoing clinical trials, and even more convinced about the necessity of fundamental research in Alzheimer’s disease before a therapy with a reasonable chance of success will ever succeed in being developed.

Experimental endocrinology started in 1848 when Berthold, professor of medicine at the University of Göttingen, showed that the atrophy of the comb and the changes in behavior following castration of cockerels, could be prevented by transplantation of testis (cf. Tausk, 1976). Endocrine experiments in animals were followed by series of observations on the possible effects of gonadal hormones on the process of aging and dementia in man. Brown-Séquard (1889), at the age of 72, injected himself with extracts prepared from crushed testicles of guinea-pigs or dogs. We may wonder now how little of the active steroids these aqueous extracts must have contained. Yet he claimed that both his physical and intellectual powers increased. Lorand (1913) reviewed the ‘marvelous effects’ of ovarian extracts, thyroid extracts and extracts of testicles on the prevention and treatment of the symptoms of old age. Lorand too (‘for experimental purposes’, as he explained, apparently being in need of an apology) subsequently tried out testicular...
extracts from the pig on himself and confirmed the increase in 'muscular and mental' powers. In the line of thought of that period, transplantation of animal testicular tissue to the testis of aged men was quite logical. This treatment, with monkeys as donors was indeed reported to be very successful in old animals including man (Voronoff, 1925).

In the same period an indirect way of increasing gonadal hormone levels was proposed by Steinach. He claimed to have experimental evidence for 'hormone accumulation' by ligation of the vas deferens, an operation that would result in 'reactivation'. He subsequently asked the Viennese surgeon and urologist Dr. Robert Lichtenstern 'to perform vasoligature on suitable patients for reactivation purposes'. Lichtenstern carried out the first 'Steinach' operation on November 1, 1918 on the vas deferens of an 'exhausted and prematurely old man'. This operation was followed by 'many thousands — perhaps even tens of thousands — of successful repetitions'. Steinach called the operation 'a means of enriching our stock of remedies against pre-senility, inasmuch it removes disturbances of the central nervous system' (Steinach and Loebel, 1940). Reading through their case histories labelled as 'premature senility', 'moods of depression' are mentioned remarkably often. In those days, the differential diagnosis between depression and dementia will already have been a difficult one, and a beneficial effect of this operation upon depression might be the explanation of the astonishing high success rate of some 80%. It is a pity that Steinach's misconception may have contributed to preventing serious study on the effects of testosterone treatment on aging subjects, since, at present, we know that testosterone levels are indeed decreasing during senescence (Deslypere and Vermeulen, 1984; Warner et al., 1985). Although we do not have any data on testosterone levels in dementia, changes would probably have strong effects on several transmitter systems in the brain. In the old rat, decreased testosterone levels seem to be the most probable explanation for the diminishment of vasopressin-containing fibers originating, e.g., from the bed nucleus of the stria terminalis (Fliers et al., 1985a), although experimental confirmation has still to be performed. Whether or not similar testosterone-dependent fiber systems do also exist in the human brain is not known.

In the subsequent period in our story, the condition of the blood vessels was put central, as appears from the slogan 'a man is as old as his blood vessels' (e.g. Foley, 1956). The idea that dementia was caused by arteriosclerosis of the cerebral vessels led to the development of 'vasodilatators' (see below). Hyperbaric and normobaric oxygen therapy also fit into the vascular hypothesis of aging (McFarland, 1963) and dementia. The initially reported improvements obtained with the use of these therapies were not confirmed in later studies (Wittenborn, 1981; White et al., 1975).

In the meantime, psychotropic drugs had been developed that appeared to be effective, e.g., in treating schizophrenia and depression. They were subsequently applied, without any beneficial effects, in dementia. Such medicines were followed by the 'geronto-psychiatric drugs' that would be 'specifically' beneficial for the elderly patient with mental impairments, again without great success, however.

The recent boom in our knowledge concerning neurotransmitters has resulted in a new direction in gerontological treatments viz. transmitter substitution therapies. In addition, possibly under the influence of social sciences on medicine, increasing attention is currently being paid to non-pharmacological therapies, such as the effects of food or environment (Lieberman and Abou-Nader, 1986; Roth et al., 1986). However, in spite of all these efforts, we still have no effective therapy for
Alzheimer's disease, which is perhaps not surprising, since its etiology has not yet been elucidated. There may in fact not even exist any such thing, in view of the possibility that Alzheimer's disease may represent an accelerated form of the normal aging process. Such ignorance merely stresses the importance of more fundamental research into the process underlying normal aging of the brain, and Alzheimer's disease in particular. The modest beneficial effects that have been reported for various pharmacological and non-pharmacological therapies and that are reviewed in the present paper might provide some clues for effective further research.

**Cerebral vasodilators**

The use of cerebral vasodilators was based upon the assumption that dementia was largely caused by cerebral arteriosclerosis. The justification for the use of such drugs in Alzheimer's disease is at present weak. Moreover, even if AD were to have a vascular cause and vasodilators were effective, one could wonder how arteriosclerotic arteries would be able to dilate (Branconnier and Cole, 1977; Yesavage et al., 1979).

*Carbon dioxide* and *carbonic anhydrase inhibitors* (e.g., acetazolamide) have been used in dementia without effective therapeutic consequences (Ban, 1978; Cole and Liptzin, 1984).

*Papaverine*, an ancient drug found in opium and having morphine-like analgesic activity, and the related drug *cyclandelate* have been among the most widely prescribed categories of agents in the treatment of 'arteriosclerotic' dementias. It is questionable, whether the reported therapeutic effects, e.g. in elderly volunteers (Branconnier and Cole, 1977; Wittenborn, 1981), were indeed due to improved cerebral blood flow or alternatively; the improved cerebral blood flow is more likely to have been secondary to increased brain metabolism. There is no conclusive evidence that *nicotinic acid, tocopherol* (vitamin E) or any of the numerous other 'vasodilating agents' improve either cerebral blood flow or the condition of the Alzheimer patient (Ban, 1978). *Hydergine*, that was developed as a vasodilatator will be discussed in the section on CNS stimulants.

*Dicumarol, warfarin* and other *anticoagulants* have been employed because of the theory that cerebral emboli could contribute to the development of dementia. The studies reported with this therapy were usually uncontrolled and very limited, so that useful conclusions are hard to draw. The risk of bleeding with this therapy is substantial (Ban, 1978; Wittenborn, 1981).

**Classical psychotherapeutic drugs**

The success of psychotherapeutic drugs in psychiatry has led to their prescription in aging and dementia, where they have to be considered as merely symptomatic agents (Hollister, 1985). Yet, some 36% of the US subjects over 60 years of age have used such drugs (Epstein, 1978). During the last few years, the number of studies on the effect of major tranquilizers on senile patients seems to have diminished (Wittenborn, 1981), presumably because it has become apparent that they have no unequivocally favorable effects on the condition, although the symptomatic improvements may be highly valued by those charged with the care of such patients (cf. Hollister, 1985). On the other hand, this population is certainly at risk for iatrogenic illness secondary to the action of psychotherapeutic drugs.

**Antidepressants, neuroleptics and anxiolytic agents**

The fact that depression may easily be confused with dementia does of course not mean that *antidepressants* have a favorable action on the clinical condition in Alzheimer's disease. Negative effects have been obtained with such compounds as *neuroleptics*: compounds that even frequently have been the cause of pseudodementia in aged patients (De Beer and Simons, 1977).

*Benzodiazepines, propanediols* and *barbiturates* are frequently used in the elderly and are clearly effective in treating such symptoms as anxiety,
tension, restlessness and agitation. However, there is no indication that tranquilizers improve impaired functioning in old people (Wittenborn, 1981). Moreover, benzodiazepines are among the most frequently misused drugs (Epstein, 1978) and may induce similar amnestic performance deficits as found in Alzheimer’s disease (Wittenborn, 1981; Bartus et al., 1982). Long-term use of benzodiazepines might possibly even cause some degree of brain atrophy, since it has been reported to be accompanied with an increased ventricle/brain ratio. However, a causal relationship between drug use and brain atrophy in human has not yet been proven (Lader and Petursson, 1983).

Alcohol is most probably the most widely used anxiolytic compound. Wine or beer in modest amounts improved the condition of old subjects, also in chronic brain syndromes, whereas no difference was found when drinks were given either in a pub or a ward setting (Chien, 1971; Chien et al., 1973). Yet, in the long run, alcohol has serious negative effects, e.g. on gnostic functions (Freund, 1982; Freund and Butters, 1982) and may cause brain atrophy (Lader and Petursson, 1983). Therefore, it cannot be recommended as a safe alternative therapy.

Central nervous system stimulants

Because of the changing ideas about the etiology of dementia through the years and the technical improvements that have enabled the measurement of brain metabolism, pharmacotherapeutical interest shifted from the improvement of cerebral circulation to the improvement of brain metabolism in the elderly. This development has led to many claims regarding new gerontopsychiatric drugs. However, only few weakly effective compounds were in fact produced, presumably because the diminished metabolism in the Alzheimer brain is an effect rather than a cause of the condition (Frackowiak, 1986).

Piracetam (2-oxy-1-pyrrolidine acetamide), originally developed as a compound against motion illness, was later claimed to protect the brain against oxygen shortage and to improve learning. It is a GABA-derivate without GABA effects (Cole and Liptzin, 1984). It was considered to be the first compound of a new class of ‘nootropic’ drugs (Ban, 1978), i.e., able to enhance memory and learning, and thus of possible importance for the treatment of Alzheimer. This idea was confirmed by a number of methodologically imperfect clinical trials. Careful studies, using a standardized factor-analyzed rating scale for elderly patients (BOP), psychometric tests and a double-blind crossover design did not show any significant effect as compared to placebo, upon psychometric performance of Alzheimer patients (Diesfeldt et al., 1978; Wittenborn, 1981). The drug is currently advertised as Nootropil® for transient ischemic attacks and would — according to the advertisement — improve the disturbed microcirculation and the oxygen and glucose utilization. It has been claimed to be effective in Alzheimer’s disease in combination with choline (see below).

Magnesium pemoline (Cylert®) was originally introduced as a compound that would increase the synthesis of ribonucleic acid and, consequently, the consolidation of memory. This finding was, however, shown to be in error (Eisdorfer et al., 1968). The favorable results on memory could not be confirmed in subsequent clinical investigations using tests involving learning, memory, and performance. The compound is now marked for use in children suffering from minimal brain dysfunction and/or hyperkinetic behavior (Branconnier and Cole, 1977; Ban, 1978; Wittenborn, 1981).

Yeast RNA taken orally was supposed to affect memory but — perhaps not too surprisingly — had no better effect than did placebo in old impaired or demented patients (Wittenborn, 1981).

Anabolic agents, such as fluoxymesterone, isopri-nosine and related hormone preparations, have been administered to gerontopsychiatric patients in the hope of correcting the disturbance of protein synthesis encountered in aging, however, without any clear-cut effect on memory function (Ban, 1978).

Pentylenetetrazole and methylphenidase do not
seem to have an apparent value in improving mental functions (Ban, 1978; Wittenborn, 1981; Cole and Liptzin, 1984). The results with pipradol seem to be favorable only in the first weeks of the treatment, but not at subsequent assessment periods (Wittenborn, 1981).

**Procaine** was introduced in 1956 as 'a new method for prophylaxis and treatment of aging' by Dr. A. Aslan from Roumania supposedly having 'eutropic and rejuvenating effects'. In 1958 she started treatment with Gerovital H3 (2% procaine-HCl combined with a preservative plus an antioxidant) a preparation which she called Aslavital® and for which novel pharmacological properties were claimed. Expensive trips to Roumania are still advertised emphasizing the "remarkable value of Dr. Aslan's cure" that "is efficient in the prophylaxis and cure of the phenomena that appear in the affections of the central nervous system...". In addition, "...it has a favorable effect in...memory, attention and concentration capacity troubles...in the decline of intellectual and physical ability". However, most studies provide little support for the claim that this drug improves the mental status of geriatric patients (Wittenborn, 1981; Millard, 1984). An exception is a study by Hall et al. (1983), that reported an effect on consolidation of new learning and muscle strength, but also documented several adverse reactions. Gerovital H3 probably acts, however, as a mild antidepressant drug, because it is a weak, reversible and competitive inhibitor of MAO (Zung et al., 1974; Branco and Cole, 1977).

**Hydergine®** is composed of the methylates of four dihydrogenated ergot derivatives. In the period that the decline of cognitive function in aging and Alzheimer's disease was thought to be due to vascular changes, hydergine was developed and advertised as a vasodilator. Evidence for such an effect is totally lacking. Yet, it is still used in various countries even for the treatment of hypertension (Hollister and Yesavage, 1984) in the belief that it possesses a vasodilatory action. Hydergine was subsequently classified as 'a metabolic enhancer', since in some pharmacological tests it induced a changing in cyclic-AMP levels. How such effects relate to Alzheimer's disease is not at all clear (Hollister and Yesavage, 1984). Recently, the action of hydergine has been explained by its binding to dopamine, serotonin and noradrenaline receptors, or was simply called 'a rational approach' (cf. Ermini and Markstein, 1984). This clearly illustrates how time after time the commercial machinery gets its hand on whatever neurobiological approach is in fashion at the moment. It is no less than amazing that the interesting observation of Nandy and Schneider (1978) that hydergine causes a decrease in lipofuscin content as well as an increase in neurite formation in mouse neuroblastoma cells kept in culture, has not been used in advertisements, since on theoretical grounds such a general effect might prove to be beneficial in the treatment of Alzheimer's disease (cf. Coleman and Flood, 1986). This observation may point to a non-specific metabolic activation of neurons and might as such be an alternative explanation for its effects (see below). Regardless of the validity of the various explanatory proposals, double-blind studies of hydergine versus papaverine-hydrochloride or other controls indeed favored the former, also in cognitive tests, although the improvements were relatively modest. Alzheimer patients were those who benefited the most, provided their condition was not too far advanced, while patients with multi-infarct dementia improved less (Loew and Weil, 1982). The generally reported improved mood and feeling of well-being resulting from hydergine are more pronounced than are the reported cognitive improvements. One may wonder, therefore, whether its effects might not best be explained by an antidepressive action (Fliers, 1982), although some correlations plead against this possibility. As an alternative mechanism of action the induction of decreasing prolactin levels by hydergine are mentioned (Loew and Weil, 1982). Although statistically present, the reported improvements with hydergine are clinically marginal and lacunar, while great improvement in memory has never been observed (e.g., Pomara et al., 1983; Cole and Liptzin, 1984). This consider
ation puts question marks to the clinical usefulness of this drug in the treatment of Alzheimer’s disease (Meier-Ruge, 1983; Hollister and Yesavage, 1984). The combination of hydergine with lecithin was not effective in Alzheimer’s disease (see below).

**Nafronyl**, a new compound that would increase metabolic activity and was claimed to have beneficial clinical effects on dementia patients, is currently under further investigation (Yesavage et al., 1982).

**Neurotransmitter substitution therapies**

At present, the study of specific neurotransmitter systems is a hot topic in neurobiology. No wonder, thus, that various neurotransmitter substitution therapies are currently being proposed for Alzheimer’s disease. Neurotransmitters may be subdivided into acetylcholine, monoamines, amino acids and neuropeptides. All four classes of transmitter systems undergo changes during aging and in Alzheimer’s disease; findings that have stimulated clinical trials aimed at their substitution in Alzheimer’s disease.

**Cholinergic system**

The ‘cholinergic hypothesis’ concerning the etiology for the decrease of cognition in the elderly and in Alzheimer’s disease has gained considerable attention during the last years (for review see Bartus et al., 1982). Indeed, choline acetyltransferase (CAT) activity and acetylcholine production is markedly reduced in Alzheimer’s disease. Moreover, a severe loss of neurons was found in this condition in the nucleus basalis of Meynert, the main source of neocortical cholinergic innervation. Yet it is questionable whether this is indeed an adequate explanation for the etiology of Alzheimer’s disease, since disruption of this cholinergic system in the rat causes only a temporary cognitive impairment (Bartus, 1986), whereas lesions in the rat cerebral cortex induce degenerative changes in Meynert’s nucleus (Sofroniew et al., 1986). In addition, many other transmitter systems are affected in Alzheimer’s disease (Gottfries, 1986; Swaab et al., 1985, 1986; Fliers and Swaab, 1986; Francis et al., 1985).

Clinical studies, aimed at substituting the cholinergic deficit in Alzheimer, have attempted (1) to enhance the synthesis and release of acetylcholine by providing abundant amounts of precursor substances, such as lecithin and choline, and (2) to enhance cholinergic activity by giving drugs that interfere at the synaptic or postsynaptic site or (3) by inhibiting acetylcholine breakdown of the endogenous transmitter using *physostigmine*. The reported effects of precursors on cognition are generally far from impressive or sometimes even completely negative. There are, however, a few more optimistic reports (Bartus et al., 1982; Drachman et al., 1982; Hollister, 1985). In addition, the dose range seems to be very narrow and to vary considerably among individual subjects (Bartus et al., 1982). The muscarinic agonist *arecoline* may enhance performance on a memory task in Alzheimer’s disease, although not to the extent of achieving any significance (Palacios and Spiegel, 1986). Combinations with central nervous system stimulants have also been tried: cholinepiracetam and lecithin-piracetam combinations were reported to be effective in an open trial and in preliminary results of a double-blind cross-over study, respectively (Bartus et al., 1981; Samorajski et al., 1985), but a *hydrgine-lecithin* combination was not (Pomora et al., 1983).

In conclusion, although “some clinical improvement can occasionally be seen” (Barbeau, 1978), a satisfactory treatment of the cognitive impairment of Alzheimer’s disease by means of pharmacological substitution for deficits in the cholinergic system seems, at present, not to be feasible.

**Amines**

Recent evidence for considerable cell loss in the locus ceruleus with normal aging and in Alzheimer’s disease (Bondareff, 1982), and data on monoamines in brain and CSF, point to catecholamine impairment in the cognitive disturbances
(Gottfries, 1986). Noradrenaline concentrations in the temporal cortex of Alzheimer patients are reduced, as is the serotonin concentration in the frontal cortex, temporal cortex and limbic areas (Francis et al., 1985).

_Bromocryptine_, a dopamine agonist, has no demonstrable effect on intellectual functioning in Alzheimer patients (Smith et al., 1979). _L-Dopa, tyrosine, 5-hydroxy-tryptophan_ and _L-tryptophan_ have all been tried in small samples of patients, occasionally leading to a mild improvement (Cole and Liptzin, 1984). In general, however, compounds influencing the aminergic system have not shown any beneficial effect on cognition or mood superior to that of antidepressants (Reisberg et al., 1983a). For a discussion of the proposal that hyd ergine is effective by virtue of its action on aminergic systems the reader is referred to Ermini and Markstein (1984) and to p. 418 of the present paper.

_Amino acids_

Drugs influencing this class of transmitters, e.g. the _benzodiazepines_, do not seem to have a favorable action on cognitive functions (see above). Recently, the Japan Economic Journal reported that Chugai Pharmaceutical Co. researchers are testing dibenzoxazepine. It would improve learning in aged rats. They predict that this substance will be effective against Alzheimer’s disease. We shall wait and see.

_Neuropeptides_

Various neuropeptides were first known as hypothalamic hormones (vasopressin, oxytocin, LHRH, TRH, CRF) or pituitary hormones (peptides of the opiomelanocortin family). Their endocrine history and the data on their central effects have led to the concept that the brain, like the peripheral endocrine glands, is an endocrine target organ. Many of the peptides in the brain show changes with aging (De Wied and Van Ree, 1982; Swaab, 1982; Facchinetti et al., 1984; Fliers and Swaab, 1986). Moreover, since functions that are influenced by neuropeptides such as motivational, attentional and memory processes tend to decline during aging (Jolles, 1986a), it was postulated that a decreased bioavailability of neuropeptides in the brain of elderly people is associated with specific disturbances in their mental performance (De Wied and Van Ree, 1982). However, neuropeptides appeared not to act centrally as hormones but rather to be transported throughout the brain by extensive fiber systems which terminate on other neurons by means of synapses that cannot be distinguished from those containing the classical neurotransmitters (Buijs and Swaab, 1979; Swaab, 1982). In spite of the relatively short period of research devoted to them, many neuropeptides already fulfill quite some of the accepted transmitter criteria (Buijs, 1982).

Because of the presumed effects of _vasopressin_ on memory consolidation in animal studies, the memory disorders commonly observed in the elderly, and a presumed deficiency of neurohypophyseal hormone release into the periphery during aging, Legros (1975; Legros et al., 1978) studied the influence of vasopressin in men aged 50–65 years and reported a positive effect in memory tests. In later studies, however, less favorable results were obtained (cf. Jolles, 1986b).

From our measurements at the hypothalamic sites of production of vasopressin, the supraoptic (SON) and paraventricular nucleus (PVN), and from the recently reported increased vasopressin blood levels in the aged (cf. Fliers et al., 1985b; Hoogendijk et al., 1985), it has become clear that the vasopressin ‘substitution’ therapy in elderly, and maybe even in Alzheimer patients, has probably been given to subjects in whom neurohypophyseal function was not deficient at all. On the contrary, vasopressin cells were found to be activated in these conditions, probably by way of compensation for decreased renal sensitivity to vasopressin (E. Goudsmit et al., personal communication; Swaab et al., 1986). This might at least partly explain the inconsistent results obtained using this therapy (see Jolles, 1986b).
There are also some general considerations that make ‘neurotransmitter substitution’ an enterprise with only a limited chance of success, one of them being the heterogeneous way cells of a given transmitter type change during aging and in Alzheimer’s disease. As has been reported for other putative neurotransmitter systems, the vasopressin ‘system’ in the brain does not react as a unity: homogeneous while the SON and PVN are activated under these conditions (Fliers et al., 1985b; Hoogendijk et al., 1985), the suprachiasmatic nucleus (SCN) cells degenerate to a large extent after the age of 80 and even more strongly in Alzheimer’s disease (Swaab et al., 1985). Also in 34-months-old rats, the different extrahypothalamic sites of vasopressin-fiber terminations do not show overall changes with age. Areas of termination that have the bed nucleus of the stria terminalis as a source show diminished fiber densities, while other areas remain unaltered (Fliers et al., 1985a). Such differential changes in the vasopressin innervation make it very difficult to substitute vasopressin levels in one area without interfering with normal vasopressin levels in other areas. In addition, deficits have been found in many different transmitter systems in Alzheimer’s disease (see above; also Francis et al., 1985), so that normalization of all the different deficits of all the different neurotransmitters throughout the brain would not seem to be a simple task to accomplish.

Apart from the above-mentioned considerations, it is not realistic to expect that one can mimic the complex and naturally occurring spatiotemporal fluctuations of a local transmitter release by means of global administration of chemical substances. In addition, one can never replace the complete integrating function of a neuron by straightforward administration of transmitter. These are some of the considerations (e.g. Swaab et al., 1986) which call for skepticism regarding the potentialities of neurotransmitter ‘replacement’ therapy, whether in the case of neuropeptides or for other putative neurotransmitters.

In spite of the theoretical reservations which we have concerning neurotransmitter substitution therapies, we should realize that neuropeptides may act by different mechanisms and that some positive results have been reported in Alzheimer’s disease following manipulating peptidergic systems. This holds true for trials with vasopressin or its analogs, analogs of ACTH (cf. Jolles, 1986b) and the opiate antagonist naloxone, that appears to improve cognition (Reisberg et al., 1983b). On the other hand, other peptide trials have turned out negative (cf. Jolles, 1986b) and the possibility of side-effects can not be excluded. For instance, an excited state characterized by paranoid delusions, agitation, elevated pulse rate and blood pressure was induced by DDAVP in a young woman with profound Alzheimer’s disease (Collins et al., 1981). The interesting observation that oxytocin increases life-span in rats (Bodanszky and Engel, 1966) has, so far, not been followed up in the literature.

Miscellaneous therapies

Numerous investigations deal with the possible effects of vitamin preparations in the treatment of geriatric patients with mental impairment.

Nicotinic acid has not proved to be of value (Wittenborn, 1981).

On the basis of the presumptions that zinc deficiency would result in a vitamin B12 deficiency, which in turn would lead to dementia, a combined parenteral therapy of vitamin B12 with zinc-DL-aspartate has been administered to Alzheimer patients and has been claimed to be effective in preventing senile dementia (Van Tiggelen et al., 1983). There is at present neither a theoretical framework for such a presumption nor any well-designed clinical trial giving support to this idea (Wittenborn, 1981; WHO, 1981; Ned. T. Geneesk., 1983). However, sellings of the vitamin preparations have gone up following Van Tiggelen’s claim.

Vitamin E (alpha-tocopherol) would lower lipofuscin concentration in the mouse brain (Kruk and Enesco, 1981). There is, however, no indication that this compound, that also would act as
vasodilator, is effective against dementia (Ban, 1978).

Assuming a causal relationship between Pick’s disease, Alzheimer’s disease and a disturbance of zinc metabolism, EDTA has been given to demented patients (Richard et al., 1978). This therapy is also of interest since aluminum has been implicated in the etiology of Alzheimer’s disease (Crapper McLachlan and Van Berkum, 1986). However, aluminum is tightly bound to DNA in neuronal nuclei, a binding that cannot readily be reversed. Anti-aluminum treatments should thus ideally be directed towards coupling aluminum before it gains access to neuronal nuclei in the first place. There are, in addition, at present no compounds that specifically bind aluminum. Although some practitioners claim beneficial effects of ‘chelation’ in Alzheimer patients, these have been anecdotal reports (with one exception), which may therefore be misleading (Shore and Wyatt, 1982). We thus have to wait for some methodologically sound studies.

**Conclusion**

In conclusion, ‘therapeutic’ drugs are at present more often the cause of pseudodementia than they are the cure of Alzheimer’s disease. Consequently, there seems to be some truth in the cynical point of view concerning the treatment of old, mentally impaired patients in Shem’s ‘The House of God’ (1984): “the cure is the disease” and that “to deliver no medical care is the most important thing you can do”. If a patient develops symptoms of dementia, the doctor should first see whether he is not prescribing something that in fact may be causing it. A subsequent thorough clinical investigation should reveal possible pseudodementia (Millard, 1984; Van Crevel, 1986). It is characteristic for the current state of therapeutics that the only dementias for which clinically significant therapeutic results can be obtained, are the pseudodementias. For Alzheimer’s disease the conclusion, surely, must be that although some of the available pharmacological therapies may improve the condition a little, there is no indication that any of these treatments can really stop or reverse the disease process. If (as has often been claimed, but so far never proven) a treatment were merely to slow down the progressive deterioration rather than ‘cure’ the patient, one might even ask if a prolonged suffering is really what we should aim for. Changes in the nutrition and social environment of the Alzheimer patient may be just as effective as pharmacological therapies (Held et al., 1984; Mirmiran et al., 1986). Indeed, beneficial effects from mere participation in the clinical trials are often found, but never emphasized in the placebo group of a clinical trial (e.g. Chierchetti et al., 1981). Pharmacological therapies may, in addition, produce considerable side-effects (cf. Millard, 1984) that have not been scrutinized so far.

A specific strategy for developing therapeutic tools in the Alzheimer’s disease treatment has not been available until now. On the contrary, new insights and developments in brain research have simply been applied to Alzheimer patients. Many such therapies have statistically significant but clinically insignificant effects. One may wonder whether the small effects produced by quite different drugs and non-pharmacological therapies cannot best be explained, not so much by specific effects, but rather by a generalized stimulation of the brain. Recent observations, both from our own group and from others give support for such a possibility. The vasopressin neuron in the SON and PVN, probably osmotically stimulated secondary to a loss of binding sites in the kidney, remains capable of increased neurosecretion in senescence, both in rats and in human subjects (Fliers and Swaab, 1983; 1986). In contrast, the vasopressin cells of the SCN degenerate after the age of 80, and even more pronounced in Alzheimer’s disease (Swaab et al., 1985).

The idea that symptoms of aging (and dementia) may be due to a decrease in neuronal stimulation, is not a new one. Lorand (1913) already stated: “work of any kind, even mental work alone, is means of preventing precocious senility”. Dietary restriction, an effective way to increase the life-
span of rodents, might also work by stimulating the animals in a generalized way (Zoler, 1984). ‘Compensatory’ dendritic outgrowth is normally occurring in senescence (Buell and Coleman, 1979, 1981). A similar process is stimulated by environmental factors in the adult rat (Uylings et al., 1978; Mirmiran et al., 1986). Since no such ‘compensatory’ dendritic outgrowth occurs in Alzheimer’s disease, a key-question for an effective prevention or therapy in Alzheimer’s disease may thus be how to effectively stimulate the various neuronal systems that are most vulnerable in this condition. On the other hand, if Maurice Ravel really had Alzheimer’s disease (Dalessio, 1984), then neither a productive life, nor a family stimulating him (e.g., by taking him on frequent trips) prevented or cured him from the disease. Moreover, not every change in environment needs to be beneficial for the Alzheimer patient. These patients may, in fact, be so vulnerable to changes in the environment that the effects of the preparatory workup before inclusion of such patients in a trial might already have adverse effects on them (Etienne et al., 1981).

For the time being, Millard’s advice (1984) might be the best: “Until better evidence is available I think I shall tell my mother to go on doing the crossword: like other organs may not brains deteriorate with disuse?” The lack of therapeutic success clearly underlines the need for fundamental research on aging of the brain and on Alzheimer’s disease. At present, this seems to be the only way ever to arrive at a rational strategy for the treatment of this condition.

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Discussion

J. M. RABEY: It still needs to be established if the dying system of the brain works by the principle of all or nothing or there is still a period when the cells are still alive but sick and therefore can be helped by manipulation at the presynaptic level. A good example is the treatment of Parkinson’s disease. For years we may have succeeded in treating Parkinson patients, improving their performance until there is a complete failure of the system.

ANSWER: That is true, but I think that also these therapeutic effects in Parkinson’s disease are in support of my thesis that little may be expected if transmitters are used to substitute for cell loss. Therapy in Parkinson’s disease, although initially effective, becomes at a certain moment ineffective. That means that the precursor (L-dopa) cannot replace the death neurons. It can only help the surviving neurons. However, the biochemistry of the dopaminergic neuron has the advantage of being able to profit from precursor that is administered. This cannot be expected to a similar degree from other transmitter systems (e.g. peptides). Cell loss is the hallmark of dementia and it affects many different brain neurotransmitters, so that I am sceptical about the substitution potentialities.

F. BROWN: Please clarify the statement about neuroleptic therapy causing ‘dementia’.

ANSWER: Quite frequently old subjects are brought into the clinics with the diagnosis ‘dementia’. The condition appears, however, to be due to misuse of medicines. When the various medicines they got, often from different physicians, are stopped, they are cured within a short time. Neuroleptics are often the cause of such pseudodementias (De Beer and Simons, 1977).

D. M. GASH: In trying to interpret the significance of the loss
of small vasopressin neurons in the suprachiasmatic nucleus (SCN) in human aging as compared to the relative stability of large magnocellular supraoptic and paraventricular neurons (SON and PVN) could other principles be operating than those suggested? For example, could those neurons generated earlier in development be more stable during aging? One could also suggest other possibilities, such as the phylogenetically older neurons being the last to undergo aging. Have you evaluated these alternate explanations?

R. M. TERRY: Comment: Dr. Gash suggested small neurons particularly lost in normal aging neocortex. Although Brody claimed that in 1955, data from Haug's lab. and my own are quite opposite (cf. Terry, 1986). Large neurons decrease, small neurons are preserved.

ANSWER: Our own work shows also that one cannot simply predict cell death from cell size. In the human hypothalamus the SON and PVN cells are the largest and the most stable (Fliers et al., 1985; Fliers and Swaab, 1986). The SCN cells start to degenerate after the age of 80. These cells are the smallest. However, intermediate in size, the cells of the sexual dimorphic nucleus of the preoptic area (SDN) show the earliest degeneration. A cell loss was found from the age of 40 onwards in this nucleus (Swaab and Fliers, 1985). But, concerning the cause of cell death and cell stability all possibilities are still open. The only way to give a real answer to Dr. Gash's questions is to do the type of experiments we plan to do in the near future, i.e., activate or inhibit the neurons for a long time during aging and see whether we will influence in that way cell stability or degeneration.

A. GOWER: Could you comment further on the use of the 'nootropic' piracetam in Alzheimer's disease, particularly as several drug companies are busy developing similar compounds.

ANSWER: In controlled studies it was inactive in Alzheimer patients (Diesfeldt et al., 1978; Wittenborn, 1981) and it is currently marketed for use in transient ischemic attacks.

J. E. PIETSKY: Have antiviral agents been used? Has nicotinic acid not been used as vasodilator but to reduce cholesterol?

ANSWER: To my knowledge nobody has used antiviral drugs in Alzheimer patients, and there is no positive effect on dementia reported from nicotinic acid (Ban, 1978; Wittenborn, 1981).

References


