Coenzyme Nicotinamide Adenine Dinucleotide

New Therapeutic Approach for Improving Dementia of the Alzheimer Type*

JÖRG G. D. BIRKMAYER, M.D., Ph.D.

Forschungs-und Lehreinrichtung
des Birkmayer Instituts
für Parkinsontherapie
Vienna, Austria

ABSTRACT

The Coenzyme nicotinamide adenine dinucleotide (NADH) has been used as medication in 17 patients suffering from dementia of the Alzheimer type in an open label trial. In all patients evaluated so far, an improvement in their cognitive dysfunction was observed. Based on the minimental state examination, the minimum improvement was 6 points and the maximum improvement 14 points with a mean value of 8.35 points. The improvement on the basis of the global deterioration scale (GDS) was a minimum of 1 point and a maximum of 2 points with a mean value of 1.82. The duration of therapy was between 8 and 12 weeks. No side effects or adverse effects have been reported from the patients or their caregivers during the observation period which is, in some patients, more than a year. This open label trial represents a pilot study from which no definitive conclusion can be drawn. A double-blind placebo controlled study is necessary to demonstrate the clinical efficacy of NADH. The planning and the fulfillment of all requirements for such a study are in progress.

Introduction

Dementia can be defined as loss of intellectual functions such as thinking, remembering, and reasoning of sufficient severity to interfere with the person's daily functioning. It cannot be defined as a disease itself but rather a variety of symptoms which may accompany the physical conditions or diseases. The cause and rate of progression of dementia varies. The most well-known disease accompanied with progressing dementia is Alzheimer's disease. However, there are other diseases which are accompanied with dementia, such as Huntington disease, Pick's disease, Parkinson disease and multi-infarct dementia. Further conditions which may induce dementia are head injuries, hydrocephalus, meningitis, brain tumors, nutritional deficiencies, and drug reactions. The most common of the dementing disorders is Alzheimer disease affecting as many as four million Americans. Approximately 5 percent of the population over 65 years is affected. The symptoms begin slowly, then progress until the patient is completely dependent on his or her family or cargiver[1]. This dependence becomes an emotional, physical, and financial burden.

These burdens have generated tremendous interest in the definition of the etiological, biochemical, pathological, diagnostic, and treatment possibilities associated with this condition. Many labels have been attached to the clinical profile of dementia. The clinical profile of dementia consists of (1) loss of memory, (2) deterioration of intellectual functioning, and (3) impairment in the activities of daily living.[2] Symptoms of this disease include a gradual memory loss, decline in ability to perform routine tasks, disorientation in time and space, impairment of judgment, personal change, difficulty in learning, and loss of communication skills.

A Work Group established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's disease and Related Disorders Association (ADRDA) published clinical criteria for the diagnosis of Alzheimer's disease, a brain disorder marked by progressive dementia, in 1984. The NINCDS-ADRDA Work Group's diagnostic criteria have become the criteria most universally accepted. There is general agreement on the pathology and biochemistry of Alzheimer's disease.[3] Unfortunately, the pathology can be determined only after death by means of a brain autopsy. A brain autopsy of an Alzheimer's patient will show the presence of (1) cortical atrophy, (2) neuron loss, and (3) senile plagues and neurofibrillary tangles. A definitive diagnosis of Alzheimer disease is therefore possible only through histopathological examination of the brain tissue. As this cannot be done during the treatment period when patients are still alive, the term senile dementia of the Alzheimer type (SDAT) will be used in the following.

The major biochemical changes identified in SDAT is a deficiency of cholinergic neurotransmitters owing to the progressive loss of cholinergic presynaptic neurons located in the basal forebrain.[4] There are similarities between the biochemical changes found in normal age and in SDAT. However, there are also functional disturbances of the catecholaminergic activity in the aged rat brain is reduced.[5,6,7] The enzymatic activity of tyrosine hydroxylase (DOD) has been found significantly decreased in post-mortem samples of humans.[8] Other post-mortem studies in humans have shown reduced levels of dopamine (DA) and noradrenaline (NA) related to age.[9,10] These observations indicate that there is a decrease of the concentrations of catecholamine in the normal aged brain.

*Address reprint requests to: Jörg G. D. Birkmayer, M.D, Ph.D., Professor of Medicine and Clinical Pathology, Schwarzpanierstr. 15, A-1090 Vienna, Austria.

In senile dementia of the Alzheimer type (SDAT), it was well shown already in 1969 that the metabolites of dopamine (DA) homovanilinic acid (HVA) was decreased in the cerebral spinal fluid (CSF) of the patients.[11] Furthermore, a study in Sweden revealed that the dopamine concentration was significantly reduced in the caudatus nucleus and in the hypothalamus, hippocampus, and gyri cinguli. Even more significantly reduced was 5-hyroxy-tryptamine (5-HT), also called serotonine in the same brain regions.[12] These findings were confirmed and extended in showing that dopamine and noradrenaline deficiency do not only occur in nucleus caudatus, hypothalamus, and gyri cinguli, but also in other brain regions such as globus pallidus, putamen, nucleus amygdale, substantia nigra, and basal ganglia.[13] The levels of serotonine (5-HT) were reduced in nucleus caudatus, putamen, globus pallidus, substantia nigra, raphe and nucleus amygdale.

Reinikainnen[14] and coworkers found noradrenaline deficits in locus coeruleus, frontal cortex, temple cortex, hippocampus, and putamen. Dopamine deficits were found by Allard et al15 in thalamus, hippothalamus, nucleus caudatus, and putamen in ponds. Deficit of 5-HT could be detected in putamen, cingular cortex, and raphe by Marcusson et al.[16]

All these findings provide evidence that the biochemical cause of cognitive dysfunction and dementia in SDAT is not only confined to the acetylcholinergic system but also to the catecholaminergic system. This view is further supported by the clinical observation that in SDAT not only intellectual but also emotional and motoric impairments are observed. In particular, the motoric impairments accompanied with other Parkinsonian-like symptoms are observed in 50 percent of the Alzheimer patients.[17] On the other hand, Parkinsonian patients develop symptoms of dementia.[18] These similarities between Parkinson and Alzheimer disease instigated us to apply nicotinamide adenine dinucleotide (NADH) with patients suffering from senile dementia of the Alzheimer type. As shown by us in various clinical trials with more than 2000 Parkinsonian patients, NADH does not only alleviate the motoric impairment but also the cognitive dysfunction of these patients.[19,20,21]

Nicotinamide adenine dinucleotide, in its reduced form abbreviated NADH, is also known as Coenzyme I. This coenzyme is present in all living cells and plays a central role in the cellular energy production. The NADH itself is a very energy rich compound. The reactive hydrogen atoms of NADH are oxidized to water yielding energy. In mammalian cells, this process takes place in the energy producing compartments, the mitochondria, and is performed by a mixture of enzymes called Complex I, NADH ubiquinon reductase, Complex II (Succinat. Dehydrogenase), Complex III (Ubiquinone cytochrome C-reductase), and Complex IV (cytochrome C-oxidase). The driving force in this energy production cascade is NADH. The more NADH a cell has available, the more energy it can produce, presupposing that all the enzymes of Complex, I, II, III, and IV are working properly. If one of these enzymes of Complex I, II, IV does not reach full activity, energy production in the mitochondria decreases.

According to Corbisier and Remacle,[22] alterations of mitochondria lead to their uncoupling which is harmful to the cells and can induce degeneration and cell death. In 1934 NADH was first extensively described by Kaplan and has been used in pure form as diagnostic tool in clinical laboratories for the last 30 years. No therapeutical application had ever been considered until 1988. With the new concept of stimulating the endogenous L-Dopa biosynthesis, it has been successfully applied to Parkinsonian patients.[13,19,23] In 90 percent of 161 patients, an improvement in their disability was observed. Concomitantly, with the clinical approvement of the disability, the urine HVA-level increased significantly indicating a stimulation of the endogenous L-Dopa biosynthesis. These first observations were confirmed and extended in 1990 with 415 Parkinsonian patients.[24,25]

More extensive clinical studies compared the effect of the oral form of NADH with intravenously applies NADH. A total of 885 Parkinsonian patients were included in an open label trial, 415 received NADH intravenously, to 470 NADH was given orally. In 80 percent of the patients, a beneficial clinical effect was observed.[21] This new therapeutic concept was based on the assumption that NADH stimulates the endogenous dopamine biosynthesis. This assumption was first proved in tissue culture by showing that the dopamine production in pheochromocytomacells (PC12) could be increased up to six times by adding NADH to the medium.[26] Furthermore, it was found in this study that the rate limiting enzyme of dopamine biosynthesis tyrosine hydroxylase (TH) is stimulatory effect of NADH on the biosynthesis of dopamine and noradrenaline was obtained in animal studies. It was found that NADH stimulates the biosynthesis of dopamine in the striatum of rat brain by more than 40 percent after 14 days of intraperitoneal injecting of NADH. On the basis of our new therapeutic concept of stimulating the endogenous catecholamine biosynthesis by NADH, patients with dementia of the Alzheimer type are being treated.

Subjects and Methods

In an open label trial, 17 patients were studied, all of whom have been diagnosed at various neurological clinics as presenile and with senile dementia of the Alzheimer type. Before they were included into the study, the severity of the cognitive and functional impairment was assessed at our institute using the Mini Mental State Examination (MMSE)[27] and the Global Deterioration Scale (GDS).[28,29,30] In addition, all the subjects underwent physical, neurological, and psychiatric examinations performed before and after the treatment period; NADH (Synonyms: β-NADH, reduced DPN, Coenzyme I reduced form) was given in oral form as a tablet containing 5mg NADH. The total dosage was 10mg NADH per day, which was given in the morning 30 minutes before the first meal.

Material

Nicotinamide adenine dinucleotide, reduced form (NADH) was obtained as disodium salt.*

Table I
List of Patients with the Examination Parameter Before and After Treatment with Coenzyme Nicotinamide Adenine Dinucleotide

Patient No.	Initials	Sex M/F	Age (years)	MMSE Before	MMSE After	Improvement	GDS Before	GDS After	Improvement	Weeks of Therapy
1	FP	F	79	7	20	13	6	4	2	12
2	SD	F	61	12	21	9	6	4	2	10
3	ML	M	63	12	20	8	5	4	1	10
4	BW	M	84	4	18	14	6	4	2	12
5	LW	M	72	24	30	6	3	1	2	8
6	GE	F	66	24	30	6	2	1	1	8
7	LT	F	69	20	28	8	3	1	2	8
8	AG	M	63	24	30	6	3	1	2	8
9	KA	F	68	24	30	6	3	1	2	8
10	PR	M	71	24	30	6	3	1	2	8
11	GA	F	82	6	16	10	6	4	2	10
12	VV	M	84	10	18	8	6	4	2	12
13	NR	F	53	24	30	6	3	1	2	8
14	PD	M	61	8	18	10	6	4	2	10
15	FR	M	76	10	20	10	5	3	2	12
16	PG	M	33	16	24	8	3	2	1	10
17	RW	M	67	20	28	8	4	2	2	10
MMSE = mini mental state examination (minimum of 6; maximum of 14).										
GDS = global deterioration scale (minimum of 1; maximum of 2).										

It is produced of NAD by enzymatic reduction. NAD is extracted from yeast. The yeast extract is purified by ion exchange chromatography and preparative high performance liquid chromatography. The separation of β-NAD and α-NAD is performed by chromatography. The reference standard is NADH-NA2, grade 1, with a purity of over 99.5 percent.

Results

Results from all the patients who have been evaluated are given in table I. In this table, each patient's initial, sex, age result of the MMSE and the GDS before and after the treatment as well as the improvement are listed.

The minimum improvement after NADH treatment was 1 point in three patients, the maximum 2 points in 14 patients. This yielded a mean value of 1.82. The duration of therapy lasted from a minimum of eight weeks to a maximum of 12 weeks, with a mean value of 9.65.

The statistical analysis of the results as listed in table I, and the evaluations are given in table II.

The age of the patients ranged from 33 to 84 years, with a mean value of 67.71 and a medium of 68. The MMSE before NADH treatment revealed a minimum value of 16 was observed in one patient and a maximum value of 24 in six patients yielding a mean value of 15.82.

After treatment with NADH in the MMSE score a minimum value of 16 was observed in one patient, and a maximum score of 30 was found in six patients with a mean value of 24.18. Considering the improvement after NADH treatment based on the MMSE, the minimum was 6 and the maximum 14 with a mean value of 8.35.

In addition to the MMSE, the GDS was used to examine the dementia patients.

The minimum in the GDs was 2 in one patient, the maximum 6 in six patients yielding a mean value of 4.29. After application of NADH, the minimum in the GDS rating was 1 in seven patients, the maximum 4 in seven patients. The mean value of all patients was 2.47.

All the patients examined by the MMSE and the global deterioration scale showed a distinct improvement after NADH therapy. This holds not only for patients with mild symptoms of cognitive decline (MMSE = 24 and GDS = 3) but also for patients with moderately severe or severe dementia (MMSE = 4-20, GDS = 5-6).

Discussion

Using NADH as therapeutic regimen for demented patients is based on the hypothesis that the stimulation of the endogenous biosynthesis of certain neurotransmitters, in particular dopamine and noradrenaline, should improve the mental performance of patients with cognitive dysfunction and/or dementia as these neurotransmitters are reduced in certain brain areas of Alzheimer patients.[12,13,14]

As shown in in vitro studies using pheochromocytoma cells, NADH increases the biosynthesis of dopamine up to sixfold.[26] Furthermore, it has been shown that NADH increases the level of dopamine in the

Table II Summary Statistics of Evaluated Parameters							
Variable	Number	Mean	St. E.	St. D.	Minimum	Maximum	Median
Age	17	67.71	3.05	12.58	33.00	84.00	68.00
MMSE before NADH	17	15.82	1.83	7.54	4.00	24.00	16.00
MMSE after NADH	17	24.18	1.32	5.46	16.00	30.00	24.00
MMSE improvement after NADH	17	8.35	0.59	2.45	6.00	14.00	8.00
GDS before NADH	17	4.29	0.36	1.49	2.00	6.00	4.00
GDS after NADH	17	2.47	0.34	1.42	1.00	4.00	2.00
GDS improvement after NADH	17	1.82	0.10	0.39	1.00	2.00	2.00
Weeks of therapy	17	9.65	0.39	1.62	8.00	12.00	10.00
MMSE = mini mental state examination (minimum of 6; maximum of 14).							
GDS = global deterioration scale (minimum of 1; maximum of 2).							
NADH = coenzyme nicotinamide adenine dinucleotide.							
St.E. = standard error of the mean							
St.D. = standard deviation							

striatum of the rat brain after peritoneal injection of NADH. These observations provide possible explanations for the mechanism of the action of NADH. From the studies with more than 800 patients with Parkinson disease, it was learned that the dopamine concentration increases in the serum after NADH treatment.[20] As the short term memory as well as certain other cognitive functions of Parkinsonian patients improved simultaneously, it was tempting to use NADH with patients suffering from dementia of the Alzheimer type. In a number of our patients, it was possible to measure dopamine and noradrenaline concentration in the plasma before and after treatment with NADH. Both of these neurotransmitters showed an increase after the NADH treatment period in these patients.

Furthermore, measurement was made of the enzyme NADH Ubiquinone reductase (Complex I of the respiratory chain) in platelets before and after treatment with NADH. Before therapy, the values of the enzymatic activity were between 30 and 60 percent lower than that of age matched controls. After NADH treatment, the activity of Complex I increased. These preliminary findings indicate that NADH stimulates not only endogenous biosynthesis of dopamine and noradrenaline, but also the energy production in the cells, at least in the platelets. Whether or not this positive effect on the cellular energy production is one of the molecular mechanisms by which NADH improves the dementias systems remains to be elucidated. However, it seems reasonable to assume that cells which have more energy available can perform processes more efficiently. They may also survive longer because the state of energy of the mitochondria does play a role in the life time of a cell. Cells injected with mitochondria from very young cells live longer than cells injected with mitochondria from older cells.[22]

For the time being, two main strategies are followed in the treatment of dementia. One approach is to increase the concentration of the neurotransmitter acetylcholine, a substance which is assumed to play an important role in cognitive processes and which is reduced in certain brain areas of dementia patients. As acetylcholine is degraded by the enzyme acetylcholinestrase, it is assumed that inhibitors of these enzymes may lead to an increase in acetylcholine concentration in the brain.

All acetylcholinesterase inhibitors in therapeutic trials, such as Tacrine, follow this strategy. However, as the enzyme itself is reduced in the brain of Alzheimer patients,[12] the question is whether or not a further inhibition may have a beneficial effect. As already outlined, not only acetylcholine but also other neurotransmitters, such as dopamine and noradrenaline, are considerably reduced in the brain of dementia patients. Therefore, only the inhibition of acetylcholine degradation may not be sufficient to alleviate the symptoms of dementia.

A different therapeutic approach is to stabilize the membrane of nerve cells in order to prevent its breakdown and, owing to this, the degeneration of certain brain areas. This concept seems reasonable in terms of preserving certain brain regions and may stop the progression of the dementia. Substances used in that direction are the phospholipids phosphatidycholine and phosphatidylserine. Phospholipids are involved in the transport of biological information across membranes as well as in the production and release of locally acting messenger molecules.[31]

The concept of using NADH as an anti-dementia agent follows a strategy which differs from the approaches mentioned previously. The NADH seems to act in two

ways. One is the stimulation of the endogenous biosynthesis of dopamine and noradrenaline.[26] The other is an increase in energy may lead to a higher capacity in the metabolic performance. In addition, NADH can be regarded as an energy substitute. It is itself a very energy rich compound. One mol of NADH will form 3 moles of adenosine triphosphate (ATP) which is equivalent to an energy of 36 kilocalories. In order to provide the cell with additional energy, NADH has to enter the cell and the mitochondira to reach the target of its actions. Preliminary experiment with radiolabeled NADH indicates that this seems to be the case. It should be noted that NADH, known also as Coenzyme I, in its reduced form is a physiological substance which not only occurs in all cells of the human body but in all living cells whatsoever.

For example, human red blood cells contain 3.5 μg/g skeletal muscles and brain tissue contain 50 μg/g of tissue. Our patients were treated with 10 mg of NADH daily. This is only a very low percentage of the total NADH content of the body. Nevertheless, the safety of NADH should be considered with priority. In this regard, extensive toxicology studies performed at the Corning Hazelton laboratories in England before starting this clinical pilot study revealed that the maximum tolerated dosage of NADH is 500 mg/kg bodyweight per day. Dogs were treated with an intravenous dose of 500 mg/kg for 14 days. There were no deaths. Some of the treated animals were frequently subdued and had pale gums. Some of them had warm ears and dry noses. In some animals the blood pressure was lower than before dosing which indicated that at this high dose level the cardiovascular system is influenced.

The dosage given to our patient is 10 mg per patient per day. With an average weight of 70 kg per patient, a dosage level of 0.14 mg NADH per kg of bodyweight is obtained, which is our therapeutic dosage. Hence, the maximum tolerated dose in dogs is a more than 7,000 times higher that the dose being given to our patients. In a further subacute toxicity study, beagle dogs received 150 mg NADH per kg bodyweight in oral form. In other words, a 10 kg heavy beagle dog received 1500 mg of the oral form of NADH or 300 tablets containing 5 mg NADH. The result of this study showed there were no deaths. Body weight and food consumption were considered to be unaffected by the treatment with NADH. The electrocardiography traces did not show any treatment-related changes. The haematology and the clinical chemistry parameters measured were not affected by the treatment, and there were no gross or microscopic findings suggestive of toxicity in the organs or tissues examined.

In a further study, rats received 1 tablet of 5 mg NADH per os every day for six months. This corresponds to 25 mg/kg bodyweight, an amount which is about 180 times higher than the therapeutic dose used in our patients.

All parameter examined, such as food uptake, body weight, and laboratory parameters, were not affected by the NADH treatment. There were no microscopic findings suggestive of organ or tissue toxicity.

The 17 patients evaluated in our study make up a rather low number, and no definitive conclusion may be drawn. This first trial can be regarded as a pilot study without placebo controls. Pharmacokinetic and other preclinical data are now being collected in order to fulfill the requirements for a double blind placebo controlled study in the United States.

References

1. Franssen, EH, Reisberg, B, Kluger, A, Sinaiko, E, Conrado, B. Cognition-independent neurological symptoms in normal aging and probable alzheimers's disease. Arch Neurol 1991;48:148-654.

2. Reisberg, B, Ferris, SH, Kluger, A, Franssen, E, De Leon, MJ, Mittelman, M, Borenstein, J, Rameschwar, K, Alba, R. Symptomatic changes in CNS aging and dementia of the Alzheimer type; cross-sectional, temporal and remediable concomitants. In: Bergener ?, Reisberg B. eds, Diagnosis and Treatment of Senile Dementia. Berlin, Springer-Verlag 1989;193-223.

3. McKhann, G, Drachman, D, Folstein, M, Katzman, R, Price, D, Stadlan, EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease, Neurology 1984;34:939-44.

4. Kopelman, MD. The cholinergic neurotransmitter system in human memory and dementia. Q J Exp Psychol 1986;38A:535-73.

5. Finch CE. Catecholamine metabolism in the brains of ageing male mice. Brain Res 1973;52:261-76.

6. Finch CE. The regulation of physiological changes during mammalian aging. Q Rev Biol 1976;51:49-83.

7. Algeri S, Calderini G, Lomuscio G, Toffano G, Ponzio F. Catecholamines and adaptive mechanisms in senescent rats. In: Corsini GU, Gessa, L, eds. Apomorpine and Other Dopaminomimetics. Vol. 2, Clinical Pharmacology, New York, Raven Press, 1981;2:225-34.

8. McGeer EG, McGeer PL, Wada SA. Distribution of tyrosine hydroxylase in human and animal brain. J Neurochem 1971;18:1647-51.

9. Nies A, Robinson DS, Davis JM, Ravaris CL. Changes in monoamine oxidase with ageing and depression in man. In: Eisdorfer C, Famm WE eds. Psychopharmacology and Aging: Advances in Behavioral Biology. New York: Plenum Press, 1973:41-52.

10. Carlsson A, Winblad B. Influence of age and time interval between death and autopsy of dopamine and 3-methosytyramine levels in human basla ganglia. J Neurol Transm 1976;38:271-301.

11. Gottfries CG, Gottfries L, Roos BE. Homovanillic acid and 5-hydroxyindoleacetic acid in the cerebrospinal fluid of patients with senile dementia, presenile dementia and Parkinsonism. J Neurochem 1969;16:1341-5.

12. Storga D, Vrecko K, Birkmayer JGD, Reibnegger G. Monoaminergic neurotransmitters in brains of morbus Alzheimer patients. Neurosci Lett (in print, 1996).

14. Reinkainen KJ, Soininen H, Riekkinen PJ. Neurotransmitter changes in Alzheimer's disease: implications to diagnostics and therapy. Neurosci Res 1990;27:576-86.

15. Allard P, Alafuzoff I, Carlsson A. Eriksson K, Ericson E, Gottfries CG, Marcusson JO. Loss of dopamine uptake sites labeled with (3H)GBR-12935 in Alzheimer's disease. European Neurol 1990;30:181-5.

16. Marcusson JO, Alafuzoff I, Bacstrom IT, Ericson E. Gottfries CG, Winblad B. 5-Hydroxytryptamine-sensitive 3 himipramine binding of protein nature in the human brain II, Effect of normal aging and dementia disorders. Brain Res 1987;425:137-45.

17. Pearce J. Mental changes in Parkinsonism. Brit. Med. J. Letter, 1974;1:445.

18. Gottfries CG, Adolfsson R, Aquilonius SM, Carlsson A. Oreland L, Svennerholm L, Winblad B. Parkinsonism and dementia disorders of Alzheimer type: similarities and differences. In: Rinne UK, Klinger M, Stamm G, eds. Parkinson's disease. Current Progress, Problems and management. Amsterdam, Elsevier/ North Holland Biomedical Press, 1980:197-211.

19. Birkmayer JGD, Birkmayer W. Stimulation of endogenous L-DOPA biosynthesis. A new principle for the therapy of Parkinson's disease. I. The clinical effect of nicotinamideadenindinucleotide (NADH) and nicotinamideadenindinucleotidephospate (NADPH). Acta Neurol Scand 1989;26:183-7.

20. Birkmayer W, Birkmayer JGD, Vrecko C, Paletta B, Reschenhofer E, Ott E. Nicotinamide Adenine Dinucleotide (NADH) as Medication for Parkinson's disease experience with 415 patients. New Trends Clin Neuropharmacol 1990;4:7-24.

21. Birkmayer JGD, Vrecko C, Volc D, Birkmayer W. Nicotinamide adenine dinucleotide (NADH). A new therapeutic approach to Parkinson's disease. Comparison of oral and parenteral application. Acta Neurol Scand 1993;87: Suppl. 146:32-5.

22. Corbisier P, Remacle J. Involvement of mitochondria in cell degeneration. Europ J Cell Biol 1990;51:173-82.

23. Birkmayer W. Birkmayer JGD. Nicotinamidadenindinucleotide (NADH): The new approach in the therapy of Parkinson's disease. Ann Clin Lab Sci 1989;19:38-43.

24. Birkmayer W, Birkmayer JDG, Vrecko C, Paletta B, Reschenhofer E, Ott E. Nicotinamide adenine dinucleotide (NADH) as medication for Parkinson's disease. Experience with 415 Patients. New Trends Clin Neuropharmacol 1990;4:7-24.

25. Birkmayer W, Birkmayer JGD, Vrecko K, Paletta B. The clinical benefit of NADH as stimulator of Endogenous L-dopa biosynthesis in Parkinsonian patients. In: Streifler MD, Korczyn AD, Melamed E, Youdim MBH, eds. Advances in Neurology. Parkinson's Disease: Anatomy, Pathology, and Therapy New York: Raven Press, 1990;53:545-9.

26. Vrecko K, Birkmayer JGD, Krainz J. Stimulation of dopamine biosynthesis in cultured PC 12 phaeochromocytoma cells by the coenzyme nicotinamide adeninedinucleotide (NADH). J Neural Transm 1993;12:189-98.

27. Folstein MF, Folstein SE, McHugh PR. Minimental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.

28. Reisberg B, Ferris SH, De Leon MJ, Crook T. The Global Deterioration Scale (GDS). Psychopharmacol Bull 1988;24:661-3.

29. Reisberg B, Ferris SH, Kluger A, Franssen E, De Leon MJ, Mittleman M, Borenstein J, Rameshwar K, ALBA ?. Symptomatic changes in CNS aging and dementia of the Alzheimer Type: cross-sectional, temporal, and remediable goncomitants. In: Bergener ?, Reisberg B, eds. Diagnosis and Treatment of Senile Dementia. Berlin, Springer-Verlag, 1989:193-223.

30. Reisberg B, Ferris SH, De Leon MJ. Senile dementia of the Alzheimer type: diagnostic and differential diagnostic features with special reference to functional assessment staging. In: Traber J, GISPEN WH, eds. Senile dementia of the Alzheimer type, vol. 2. Berlin, Springer-Verlag, 1985;2:18-37.

31. Samson JC. The biological basis of phosphatidylserine pharmacology. Clin Trials J 1987;24:1-8.