Acta Neuropathol (Berl) (1983) 61:101–108

Acta Neuropathologica


# Loss of Neurons in the Nucleus Basalis of Meynert in Alzheimer's Disease, Paralysis Agitans and Korsakoff's Disease

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**Summary.** The nucleus basalis of Meynert, the major source of cholinergic innervation of the cerebral cortex, was morphometrically investigated in 58 cases of neuropsychiatric disorders and compated to 14 controls. The results demonstrate a loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease (70%), paralysis agitans (77%), and Korsakoff's disease (47%) but no marked reduction of neurons in postencephalitic parkinsonism, Huntington's disease, chronic alcoholism without dementia, schizophrenia and infantile brain damage. Neurons of the three subdivisions of the nucleus basalis of Meynert (the nucleus septi medialis, the nucleus of the diagonal band of Broca and the nucleus basalis Meynert neurons in the substantia innominata) may be affected in a different manner in different patients within a single group homogeneous with respect to the usual clinical and neuropathological diagnostic criteria. Cell loss in the basal forebrain is restricted to the large neurons of the nucleus basalis, the immediately adjacent neurons of the globus pallidus externus not being affected. The selective degeneration of these neurons provides the morphological correlate of the cortical cholinergic deficiency in these neuropathological conditions. The degeneration of this discrete cholinergic neuronal population in several disorders of higher cortical function is probably directly related to the progressive deterioration of memory and cognitive processes in affected patients.

**Key words:** Nucleus basalis of Meynert – Neuronal loss – Dementia – Alzheimer's disease – Paralysis agitans – Korsakoff's disease

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## Introduction

Alzheimer's disease and senile dementia of the Alzheimer's type (SDAT) are the most common forms of dementia in old age (Tomlinson et al. 1970). Perhaps 10–15% of the population over 65 years of age suffer from mild to severe dementia (Wang 1977); 50–60% of these patients have SDAT (Terry and Davies 1980).

Several studies have shown deficits in specific neurotransmitters in Alzheimer's disease (for review see Terry and Davies 1980; Marchbanks 1982). The most prominent abnormality is the reduction of cholinergic parameters, e.g. the activity of choline acetyltransferase, the biosynthetic enzyme for acetylcholine (Bowen et al. 1976; Davies and Maloney 1976), acetylcholine (ACh) content (Richter et al. 1980); the activity of acetylcholinesterase, the degrading enzyme of ACh metabolism (Davies and Maloney 1976) and the high affinity uptake mechanism for choline (Bowen and Davison 1978) in the cerebral cortex.

Since quantitative cell counts in the neocortex of patients with Alzheimer's disease have not demonstrated major reductions in the number of neurons (Terry et al. 1977; Terry 1978; De Kosky and Bass 1980) and cholinergic neurons in the cerebral cortex are rare if present at all (Kimura et al. 1980, 1981), this loss can only reflect loss or dysfunction of ascending cholinergic projections (Terry and Davies 1980). As the main origin of this cholinergic input to the cerebral cortex the neurons of the nucleus basalis of Meynert (NbM) (Meynert 1872) have been demonstrated (Divac 1975; Mesulam and van Hoesen 1976; Lehman et al. 1980; Meyer et al. 1979; Wenk et al. 1980) which can be divided into at least three subpopulations: the nucleus septi medialis, the nucleus of the diagonal band of Broca and the NbM neurons in the substantia innominata (Brockhaus 1942; Jones et al. 1976; Wenk et al. 1981).

Selective degeneration of NbM neurons in the substantia innominata has been already described in

patients with Alzheimer's disease (Whitehouse et al. 1981, 1982). Recently it has been reported in one patient with Alzheimer's disease that there is a marked loss of the large neurons in the medial septal nucleus and the nucleus of the diagonal band in addition to neuronal loss in the substantia innominata (Nakano and Hirano 1982) but no quantitative data are given. Biochemical studies have indicated that deficiencies in the cholinergic system of the CNS occur also in Parkinson's disease (Ruberg et al. 1982), Huntington's disease (McGeer and McGeer 1976; Spokes 1982), alcoholic dementia (Antuono et al. 1980), schizophrenia (Bird et al. 1977) and Down's syndrome (Yates et al. 1980). Therefore, in this study, the involvement of cholinergic neurons of the three subdivisions of the NbM in Alzheimer's disease and other neuropsychiatric disorders with a similar deterioration of cognitive function was morphometrically investigated.

## Materials and Methods

Histological sections containing NbM neurons within the substantia innominata, the nucleus of the diagonal band of Broca and the nucleus septi medialis were obtained from the collection of the former Brain Research Institute, Karl Marx University, Leipzig. These sections had been formaldehyde-fixed, celloidin-embedded, cut (20 μm thick) and cresyl violet stained by standard techniques. The cases for this study were selected postmortem on the basis of their clinical history and neuropathological diagnosis. Atypical cases of each disease were deliberately excluded so that the material for the present study essentially consisted of unequivocal and typical examples (Table 1).

The total number of nucleolated NbM neurons was counted blind to diagnosis in the substantia innominata, in the nucleus of the diagonal band of Broca and in the nucleus septi medialis (Fig. 1) every 10th section throughout the entire length of the cell population. Neurons were regarded as part of the NbM on the basis of cell size (larger than 20 μm) and the presence of abundant Nissl substance. The maximum neuronal population density was determined by counting the number of neurons within a zone measuring 250 μm × 250 μm in the area of maximum cell density. Cell counts and population densities were compared in matching histological sections in 58 cases of neuropsychiatric disorders and 14 control brains and were expressed as percentages of control values. Controls were age- and sex-matched for the cases of Alzheimer's disease, but only age-matched for paralysis agitans, postencephalitic parkinsonism and Huntington's disease. Cell counts of the nucleus basalis in male and female controls revealed, however, no significant differences so that the same control could be used. For each case and control 65 sections on average were evaluated. The number of neurons and population density of the external segment of the globus pallidus were determined as internal controls within the same sections in a similar manner.

**Table 1.** Mean age, fresh brain weight and sex distribution of 14 controls and 58 cases of neuropsychiatric disorders

| Case | *n* | Sex | | Age (years) | Brain weight (g) |
|---|---|---|---|---|---|
| | | F | M | | |
| Control | 14 | 11 | 3 | 59.3 ± 2.6 | 1,290.0 ± 21.2 |
| Alzheimer's disease | 14 | 11 | 3 | 60.8 ± 1.3 | 1,004.5 ± 24.7 |
| Paralysis agitans | 5 | 3 | 2 | 58.5 ± 5,9 | 1,130.0 ± 20.5 |
| Postencephalitic parkinsonism | 7 | 4 | 3 | 59.0 ± 1.6 | 1,194.0 ± 32.3 |
| Huntington's disease | 9 | 4 | 5 | 60.7 ± 2.9 | 1,180.0 ± 19.6 |
| Korsakoff's disease | 3 | 1 | 2 | 43.3 ± 7.3 | 1,122.5 ± 20.9 |
| Chronic alcoholism without dementia | 5 | 3 | 2 | 58.6 ± 6.7 | 1,290.0 ± 22.4 |
| Schizophrenia (Katatonia) | 3 | 3 | 0 | 48.3 ± 5.6 | 1,286.6 ± 18.3 |
| Infantile brain damage | 12 | 9 | 3 | 22.1 ± 5.8 | 1,034.8 ± 21.6 |

## Results

### *Number of Neurons*

The number of neurons and maximum population density in the NbM and in the external segment of the globus pallidus in cases of Alzheimer's disease, paralysis agitans, postencephalitic parkinsonism, Huntington's disease, Korsakoff's disease, chronic alcoholism without dementia, schizophenia and infantile brain damage compared to controls are shown in Fig. 2. In the Alzheimer's disease group the number of neurons of the NbM is reduced by 70% (Fig. 3), in the paralysis agitans group by 77% and in cases of Korsakoff's disease by 47%. The latter changes might be slightly underestimated as the average age of the 3 Korsakoff cases available for this study is 16 years less than that of the control group (see Table 1) and preliminary results suggest that there seems to be a slight loss of large basalis neurons during normal aging. In cases of Huntington's disease, postencephalitic parkinsonism, chronic alcoholism without dementia, schizophrenia and infantile brain damage there was no marked loss of neurons in this nucleus. The number and density of neurons in the external segment of the globus pallidus are only affected in Huntington's disease, which demonstrates that the reduction of neurons in the NbM in patients with Alzheimer's disease, paralysis agitans and Korsakoff's disease is rather specific and not due to a diffuse cerebral atrophy. The involvement of basal ganglia in Huntington's disease is well documented.

The extent of neuronal loss in cases of Alzheimer's disease, paralysis agitans and Korsakoff's disease is markedly different in the three subpopulations of large nucleus basalis neurons, i.e. large neurons of the nucleus septi medialis, the nucleus of the diagonal band of Broca and the nucleus of the substantia innominata.

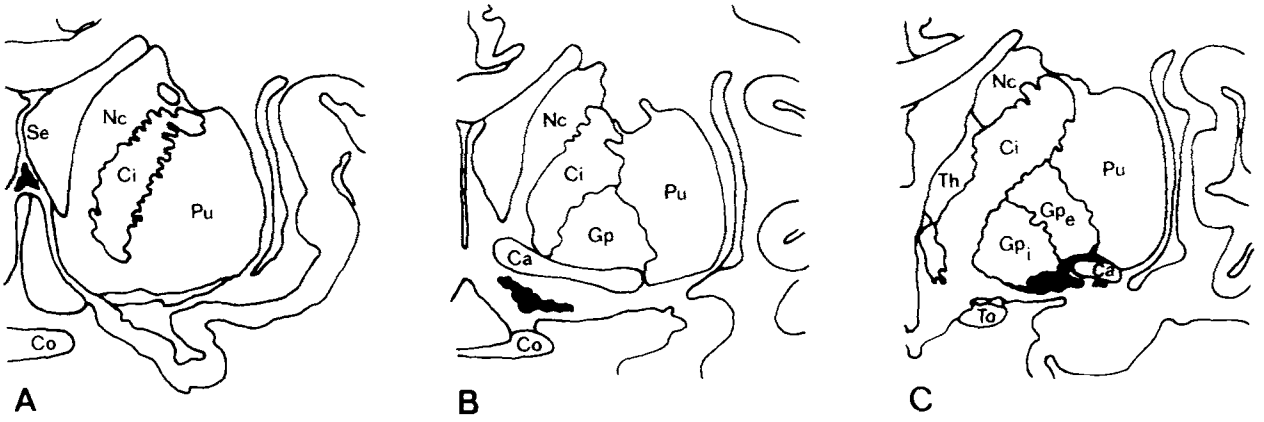


**Fig. 1A–C.** Schematic frontal sections through the human forebrain modified after Gorry (1963). The three subdivisions of the NbM are shown in black. (**A**) Section through junction of the caudate and lenticular nuclei containing the nucleus septi medialis, (**B**) section through the anterior commissure containing the nucleus of the diagonal band of Broca, (**C**) section through the cephalic limit of the thalamus containing the NbM neurons in the substantia innominata. *Abbreviations: Ca* Commissura anterior; *Ci* Capsula interna; *Co* Chiasma opticum; *Gp* Globus pallidus; $Gp_e$ Pallidum externum; $Gp_i$ Pallidum internum; *Nc* Nucleus caudatus; *Pu* Putamen; *Th* Thalamus; *To* Tractus opticus

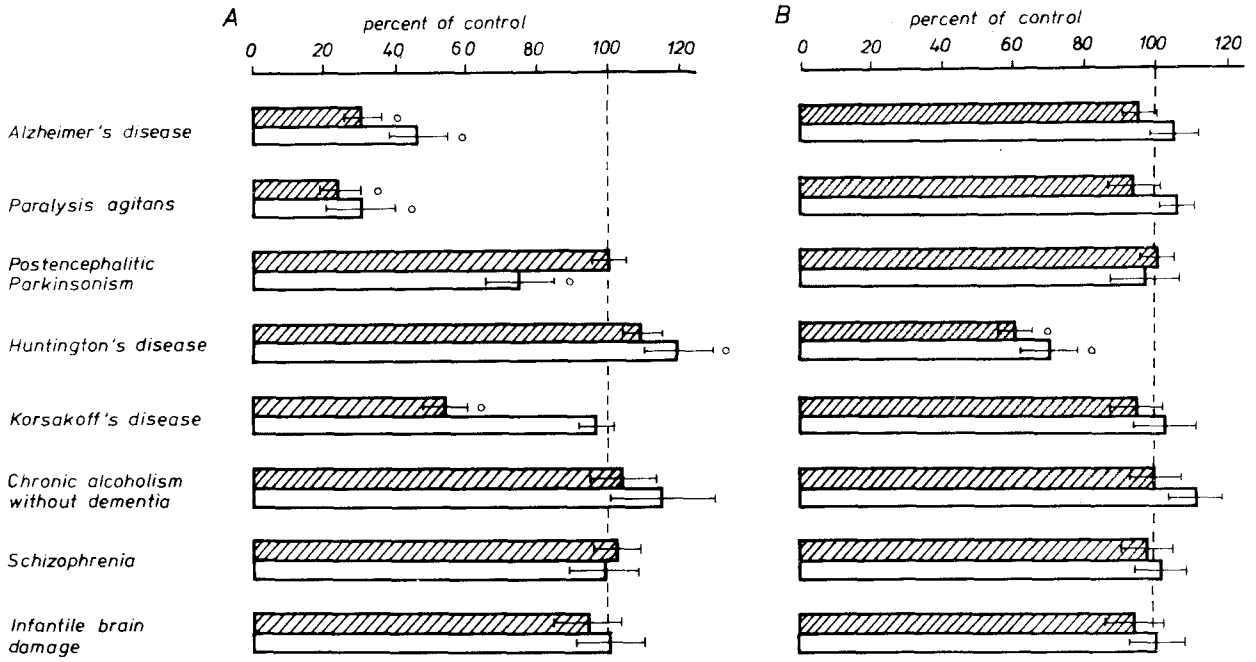


**Fig. 2.** Neuronal counts (*hatched bars*) and maximum population density (*white bars*) in the nucleus basalis of Meynert (**A**) and in the external segment of the globus pallidus (**B**) in patients with different neuropsychiatric disorders compared to controls. Bars with a circle indicate significant differences to the corresponding control patients (Mann-Whitney $U$ test, $P < 0{,}01$). For details see Materials and Methods

The individual cases show large variations of the overall neuronal loss of the nucleus basalis, but we did not observe any case in which the whole population was affected to the same degree (Table 2). In the majority of cases with Alzheimer's disease the neuronal loss was most pronounced in the substantia innominata (case 6–14, Table 2), in 4 cases in the nucleus of the diagonal band of Broca (case 2–5, Table 2) and only in one case (case 1, Table 2) the nucleus septi medialis was preferentially affected. In four cases of paralysis agitans (case 2–5, Table 2) the loss of large neurons in the substantia innominata was almost complete. One case (case 1, Table 2) was much less severely affected and neuronal loss was higher in the diagonal band nucleus than in the medial septal nucleus and in the substantia innominata. In Korsakoff's disease neuronal loss is also more pronounced in the nucleus of the diagonal band of Broca (case 1 and 2, Table 2) and in the substantia innominata (case 3, Table 2) than in the nucleus septi medialis.

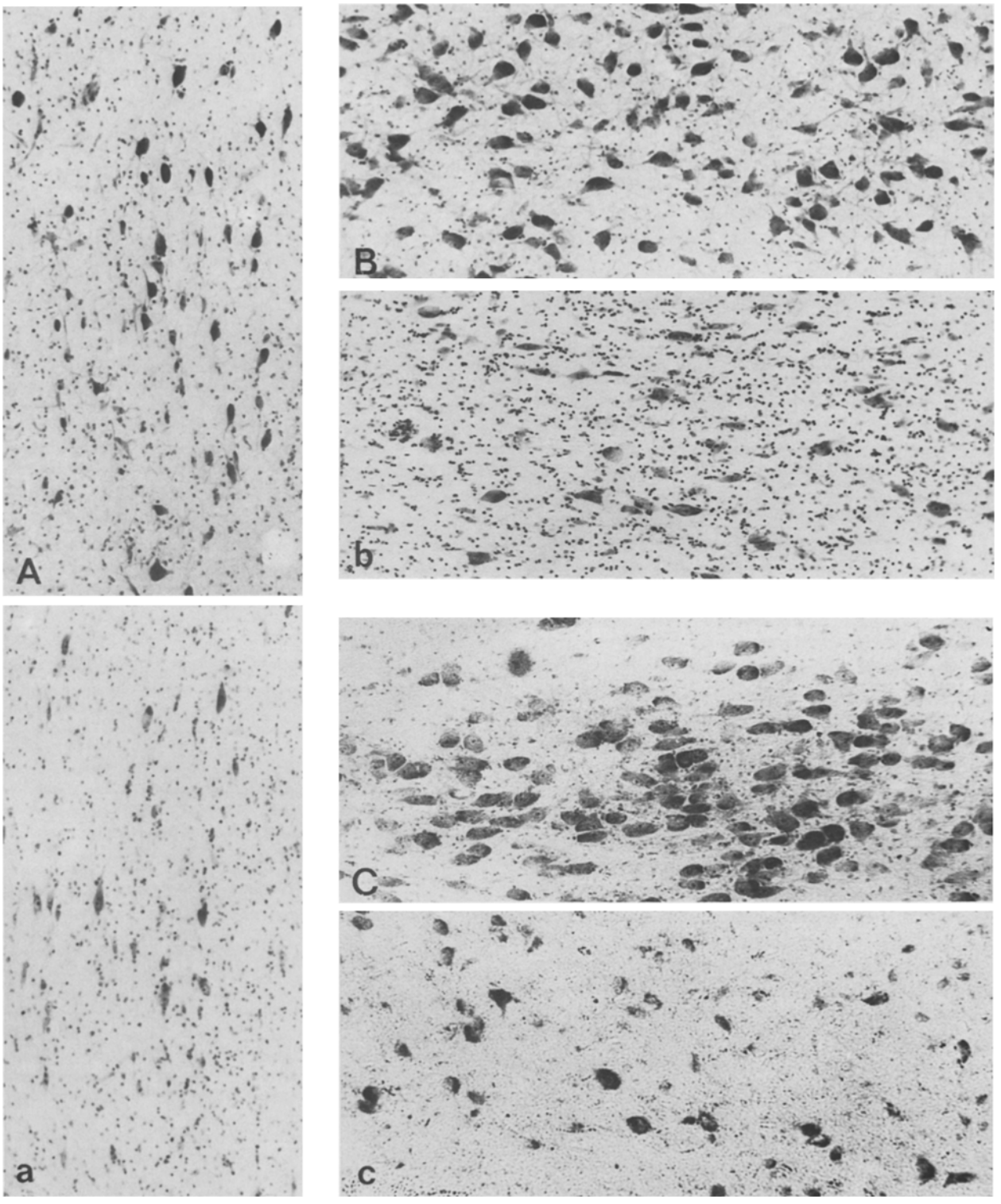


**Fig. 3.** The three subdivisions of the nucleus basalis of Meynert, the nucleus septi medialis **(A, a)**, the nucleus of the diagonal band of Broca **(B, b)** and the NbM neurons in the substantia innominata **(C, c)** of an age and sex-matched control **(A—C)** and three patients with Alzheimer's disease **(a—c)**. Note the reduction of large neurons in the nucleus basalis of Meynert in the brains of the patients with Alzheimer's disease (Nissl; × 110)

**Table 2.** Regional distribution of neuronal loss in different parts of the NbM in cases of Alzheimer's disease, paralysis agitans and Korsakoff's disease. Neuronal loss expressed as percentages of control values. Number of neurons was counted in the three subdivisions of the NbM in every 10th section (20 µm, Nissl) and compared to matching histological sections of the 14 control brains. For each case 65 sections on average were evaluated

| Case | Total neuronal loss | Nucleus septi medialis | Nucleus of the diagonal band of Broca | NbM neurons in the substantia innominata |
|---|---|---|---|---|
| Alzheimer's disease | | | | |
| 1 | 62 | 70 | 45 | 38 |
| 2 | 69 | 60 | 79 | 64 |
| 3 | 76 | 67 | 88 | 70 |
| 4 | 66 | 65 | 82 | 57 |
| 5 | 70 | 59 | 85 | 68 |
| 6 | 70 | 62 | 53 | 79 |
| 7 | 78 | 78 | 64 | 88 |
| 8 | 73 | 68 | 61 | 80 |
| 9 | 59 | 52 | 58 | 71 |
| 10 | 57 | 50 | 49 | 62 |
| 11 | 71 | 62 | 74 | 88 |
| 12 | 69 | 63 | 70 | 80 |
| 13 | 70 | 62 | 59 | 74 |
| 14 | 78 | 74 | 78 | 85 |
| Paralysis agitans | | | | |
| 1 | 65 | 53 | 79 | 60 |
| 2 | 81 | 79 | 77 | 96 |
| 3 | 84 | 80 | 81 | 95 |
| 4 | 76 | 67 | 72 | 93 |
| 5 | 79 | 70 | 74 | 91 |
| Korsakoff's disease | | | | |
| 1 | 60 | 52 | 71 | 60 |
| 2 | 48 | 39 | 70 | 33 |
| 3 | 33 | 30 | 29 | 49 |

*Maximum Neuronal Population Density*

As shown in Fig. 2 the maximum population density in the NbM was decreased in cases of Alzheimer's disease by 54 %, in cases of paralysis agitans by 70 % and in the postencephalitic parkinsonism group by 26 %, but not affected in cases of Korsakoff's disease, schizophrenia and infantile brain damage. The Huntington's disease group (119 %) and the cases of chronic alcoholism without dementia (116 %) showed an increase in maximum population density in the NbM. In the external segment of the globus pallidus the maximum population density was only affected in cases of Huntington's disease (71 %) and of chronic alcoholism without dementia (110 %).

*Histopathological Findings*

In the NbM we found several kinds of cell degeneration, e.g. swelling and disintegration. In all cases of Alzheimer's disease, paralysis agitans, Huntington's disease and Korsakoff's disease different extents of lipofuscinosis (Fig. 4) as well as massively enlarged neurons with vacuolated cytoplasm were seen. Only two cases of infantile brain damage (34 and 66 years old) showed lipofuscinosis. In one case of Alzheimer's disease Hirano bodies were noted.

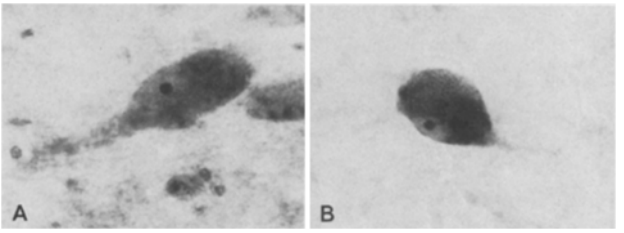


**Fig. 4A, B.** Two of the large NbM neurons in the substantia innominata. Compared to the age- and sex-matched control (**A**) the NbM neurons in the brains of the patients with Alzheimer's disease show swelling and a great amount of lipofuscin-like pigment in their cytoplasm (**B**) (Nissl; × 400)

## Discussion

Anatomical and biochemical studies have indicated that the whole cortex of the rat, cat and monkey telencephalon receives its cholinergic afferents from magnocellular neurons of the basal forebrain. In this projection there are three main cholinergic pathways to the palleocortical, archicortical and neocortical fields which originate in the cells of the nucleus septi medialis, in the nucleus of the diagonal band of Broca and in the NbM cells of the substantia innominata (Wenk et al. 1980, 1981). These neurons project directly to the cerebral cortex and while the cortical innervation by the terminals of the axons is widespread, a crude topographical relationship to the different sites of the NbM cells has been shown in the rat (Bigl et al. 1982) and monkey (Kitt et al. 1982). The basal forebrain structures are involved in a number of behavioural reactions such as sleep (McGinty and Sterman 1968; Siegel and Wang 1974), feeding behaviour (Robinson and Mishkin 1968; Rolls et al. 1979) and aggression (Fulton and Ingraham 1929) as well as attention, motivation and learning (DeLong 1972; Linseman 1974).

Exitotoxic lesions or electrocoagulation of the NbM neurons in the rat cause selective reduction in cholinergic presynaptic markers in the cortex (Johnston et al. 1979; Wenk et al. 1980). Reduction of total electrical activity (particularly at high frequencies) is also seen and is combined with alterations in learning and memory (Lo Conte et al. 1982) similar to those described in patients with Alzheimer's disease (Soininen et al. 1982; Obrist et al. 1962).

The results of the present study demonstrate that in Alzheimer's disease, paralysis agitans and Korsakoff's disease there is a selective loss of the cholinergic neurons of the NbM. Morphological abnormalities of the NbM have already been described in Alzheimer's disease (Buttlar-Brentano 1955; Averback 1981), Parkinson's disease (Lewy 1923; Hassler 1938; Buttlar-Brentano 1955), aging (Hassler 1965), schizophrenia (Buttlar-Brentano 1952, 1955; Averback 1981) and Huntington's disease (Averback 1981). Quantitative data on the loss of neurons in the NbM have been previously documented in Alzheimer's disease (Whitehouse et al. 1981, 1982), dementia pugilistica (Uhl et al. 1982), Parkinsonism-dementia-complex of Guam (Nakano and Hirano 1983) and a short abstract was published on paralysis agitans (Nakano and Hirano 1982). The number of cases in these studies was relatively small and only the population of NbM neurons in the substantia innominata had been taken into account. The reduction in the number of neurons in this area by 70% in our cases of Alzheimer's disease closely matches these findings as well as the report of a loss of cholineacetyltransferase activity in the substantia innominata in Alzheimer's disease (Rossor et al. 1982). However, as already discussed by Brockhaus (1942) the large neurons in adjacent structures of the basal forebrain have to be regarded as displaced NbM neurons (Jones et al. 1976) or as a subpopulation of this nucleus with different cortical projections (Wenk et al. 1980; Bigl et al. 1982; Kitt et al. 1982). Our finding that the subpopulations of the NbM are differently affected in the neuropathological conditions studied suggests that subgroups may exist within the broad spectrum of patients with Alzheimer's disease, paralysis agitans and Korsakoff's disease and that these may be characterised by a dysfunction of different ascending cholinergic projections and therefore by damage to different areas of the cerebral cortex. It has been postulated that damage to cholinergic circuits originating in the septum and basal areas may result in profound memory deficits in patients with Alzheimer's disease (Davis and Yesavage 1979; Smith and Swash 1978). In a similar fashion, loss of cholinergic projections from NbM to other parts of the neocortex may be reflected in some of the cognitive, emotional, and motivational abnormalities in other neuropsychiatric disorders.

The loss of neurons in the NbM in paralysis agitans and Korsakoff's disease is in agreement with the reduction of presynaptic cholinergic marker enzymes in the cerebral cortex in these disorders (Ruberg et al. 1982; Antuono et al. 1980). Taking into account the affection of the nucleus basalis in Alzheimer's disease and several other neuropsychiatric disorders associated with dementia, our demonstration of a severe reduction of neurons in the different parts of the nucleus basalis in cases of paralysis agitans gives strong support to the hypothesis that also in this disease the psychiatric symptoms are due to an affection of this neuron population (Hassler 1965).

Although there is some evidence of a deficit of choline acetyltransferase in the septohippocampal complex in Huntington's disease (Spokes 1982) and schizophrenia (Bird et al. 1977) we were unable to find a reduction in the number of cells in these conditions. The observed increase in cell population density in Huntington's disease may be related to shrinkage of the surrounding neuropil. Because of the different subclassifications of schizophrenia and infantile brain damage it is difficult to compare our findings with previous works on these disorders. The present study documents neuronal loss and histopathological abnormalities of the neurons in the NbM in cases of Alzheimer's disease, paralysis agitans and Korsakoff's disease which are neuropsychiatric disorders associated with progressive deterioration of memory and cognitive function (Slaby and Wyatt 1974; Bowen 1976; Fuld 1976; Meudell et al. 1978). The number of neurons in the external segment of the globus pallidus in these patients was unaffected, which demonstrates that the reduction of neurons in the NbM is specific and not due to a diffuse cerebral atrophy. This cell loss may represent a morphological correlate of the loss of cholinergic markers and may be responsible for the cognitive and behavioral disturbances in these degenerative disorders.

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Received February 17, 1983/Accepted May 27, 1983