Neurobiology of Aging, Vol. 8, pp. 552–554. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0197-4580/87 $3.00 + .00

Alzheimer's Disease as a Presumptive Threshold Phenomenon

THOMAS ARENDT AND VOLKER BIGL

Paul Flechsig Institute of Brain Research, Department of Neurochemistry
Karl Marx University, Leipzig, 7039, Karl-Marx-Städter Str. 50, GDR

With the example of the basal forebrain cholinergic system as a site of primary importance in AD, the existence of a critical neuron loss as a threshold between normal aging and AD is suggested. If the extent of degeneration exceeds this threshold the system decompensates and the clinical picture becomes apparent. The fully developed stage of AD might, therefore, represent a condition beyond the capacity of compensenation where plastic adaptive changes are still present but functionally insufficient.

THE known morphological correlates of normal brain aging and age-related pathological conditions such as Alzheimer's disease (AD) do not provide a basis for the understanding of the demarcation of changes which are functionally still compensated from those which reach clinical significance. Reviewing the results of quantitative studies of neuronal changes in brain aging and AD as it was done by Coleman and Flood [9] in a very comprehensive way might, therefore, help to provide a definite answer to the question whether AD represents an exaggeration of normal aging, or must be regarded as a disorder related to causes qualitatively different from those acting during normal aging.

In their paper, Coleman and Flood present not only a complete picture of the known facts but they also suggest some very interesting and provocative hypotheses which we believe require further discussion.

The suggestion AD might represent a partial failure to mount a successful compensatory dendritic response to changes in the neuronal microenvironment is one of the main conclusions drawn by Coleman and Flood ([9], p. 38).

Taking into consideration the statement of the authors that the static, post-mortem status of brain morphology may not adequately reflect the functional capabilities of the dynamic morphology of the living brain ([9], p. 39), the assumption of a partial loss in the dynamic dendritic response in AD could, however, easily by a methodological misapprehension.

One of the major methodological differences in studying the post-mortem brain in aging and AD lies in the fact that while looking at aging the subject of investigation differs from the cause of death whereas in AD the subject of investigation usually shows a causal relationship to the cause of death. This circumstance allows us to consider aging as a process with well defined functional stages, whereas in AD we usually see only the morphological equivalent of a terminal stage which is incompatible with living. Therefore, our morphological picture of the aging brain is naturally much more dynamic than that of AD.

The brain ages at different rates in different structures. Coleman and Flood suggest that the neurons susceptible to death in AD are largely part of the same population that are susceptible to death in normal aging in the human brain ([9], p. 35). Notwithstanding the fact that many brain structures are involved in degenerative alterations in AD, however, the excess loss of neurons found in AD is particularly pronounced in some brain regions. Therefore, one is tempted to regard these brain areas more likely as candidates for the neurobiological substrate of the behavioural impairment in AD than others.

One of the most extensive changes in AD which, furthermore, correlates best with the degree of dementia has been found in the cholinergic system [6, 8, 10, 18]. The cholinergic hypothesis of geriatric memory dysfunction [6] has gained support from many different fields in recent years. The assumption of the basal forebrain cholinergic system as a site of primary importance for the pathogenesis and clinical picture of AD is, among other facts, supported by the close relationship between the degree of neuronal degeneration in the cholinergic basal forebrain system and the density of plaques at the site of both the basal forebrain [4] and its target areas such as cerebral cortex and hippocampus [1].

Whereas the severe deficiency of this cholinergic system in AD and related dementing disorders is well documented [1,10] the question whether this system is particularly involved in aging is still a matter of controversy.

In agreement with biochemical studies on presynaptic cholinergic markers in the cerebral cortex during aging [8], we were not able to provide any evidence for a particular vulnerability of the cholinergic basal forebrain projection system in normal aging [2,7]. The discrepancy to two reports in the literature [16,17] describing a considerable loss of neurons in the basal forebrain cholinergic system might be due to some of the methodical confounding factors discussed in detail in the review by Coleman and Flood ([9], pp. 3–7).

Comparing neuron counts in the basal forebrain cholinergic system in relation to age with the extent of degeneration we found in cases of AD and related dementing disorders such as Parkinson's disease, postalcoholic Korsakoff's disease, and Creutzfeldt-Jakob's disease we were able to establish a threshold of about 140,000 neurons (one hemisphere) between the age and the dementia related changes [2]. McGeer *et al.* [16] reported a threshold of about 100,000 neurons, although their estimated counts in control cases were much higher than those found by us. The finding of a demarcation without any overlap is consistent with the behavioural differences between the fully developed clinical

picture of AD and an unimpaired normal old person. Contradictory to this situation in the basal forebrain cholinergic system, however, morphometric parameters in many other brain areas show an appreciable overlap between aging and AD ([9], p. 39).

Theoretically, a certain extent of neuron loss should be tolerated without concomitant functional loss because of redundant neuronal elements and plastic adaptive growth. Furthermore, one could assume that the capacity of the presumptive compensatory mechanisms is limited and that the function declines exponentially in a selfperpetuating process [1] when a certain critical number of remaining neurons is further reduced. This is what seems to happen clinically [15].

The threshold theory of causation of AD [19] is derived from observations on qualitative similarities and quantitative differences in the clinical picture and its neurobiological substrate in well preserved aged subjects and patients with AD. This threshold concept has important implications for diagnosis and for research into aetiology and treatment of AD (see [19]).

The concept of a critical neuronal loss in the basal forebrain cholinergic system as a threshold between functionally well compensated changes and those which reach clinical significance is supported by data from animal experiments.

Ibotenic acid lesions in the cholinergic basal forebrain system in rat brain result in an impairment of passive avoidance learning only when the lesion reaches a critical size (unpublished observation). Transplant related recovery in spatial memory in rat after impairment of the cholinergic basal forebrain system is almost complete if the impaired cholinergic function is restored above a certain critical value [5].

The demonstration of a critical neuron number in the cholinergic basal forebrain which demarcates age and dementia related changes supports the suggestion that mechanisms in AD which count for a compensation of neuron loss up to this threshold are comparable to those observed during normal aging.

Age-related changes in dendritic extent seem not to be monotonic ([9], pp. 23–25). Data from the aging human brain [12], from non-human primate [11,20] as well as from rodent brain [14] suggest that dendritic growth as a presumptive compensatory response is at least in some areas restricted to a certain period of aging and is followed by dendritic regression later on. This dendritic regression might be regarded as a collapse of the compensatory mechanisms ([9], p. 23). We would expect a similar picture with the predominance of regressive neuronal changes in AD when the clinical picture is fully developed. Data of the more recent literature, however, suggest that the brain in AD is also capable of a plastic response [3, 12, 13]. These presumptive compensatory changes might be restricted to certain brain areas, to certain types of neurons [3], and perhaps to certain stages of the disease. Since one might predict that morphological signs of compensatory mechanisms are more pronounced during the early course of a degenerative disorder the apparent duration of the disease is an important variable that should be defined in all quantitative morphological studies on AD (see [9], p. 6).

Interestingly, for the neurons of the basal forebrain cholinergic projection system, a system which seems to play a key role in the pathomechanism of AD, signs of axonal [13] and dendritic [3] sprouting were demonstrated occuring along with the degenerative events.

These findings indicate that the morphological equivalents of plastic adaptive changes are not restricted to the aging brain but also present in AD.

Therefore, it is suggested that AD represents a neuronal degeneration to an extent which lies beyond the functional compensatory capacity of the brain rather than a loss of the plastic capacity itself.

Compensatory growth during the course of degenerative disorders such as AD indicates that these conditions cannot simply be considered as functional terminal stages of monotonic neuronal regression. The understanding of the pathomechanism of degenrative disorders as a dynamic process of functional compensation which finally changes into decompensation might help to develop strategies to prevent or at least to ameliorate lost brain function under this condition.

REFERENCES

1. Arendt, T., V. Bigl, A. Tennstedt and A. Arendt. Neuronal loss in different parts of the nucleus basalis is related to neuritic plaque formation in cortical target areas in Alzheimer's disease. *Neuroscience* **14:** 1–14, 1985.
2. Arendt, T., S. Fischer, S. Fischer, V. Bigl and A. Arendt. Age related changes in human nucleus basalis of Meynert in comparison to dementing disorders. In: *Ontogenesis of the Brain*, Vol IV, Prague: Charles University Press, in press, 1987.
3. Arendt, T., H. G. Zvegintseva and T. A. Leontovich. Dendritic changes in the basal nucleus of Meynert and in the diagonal band nucleus in Alzheimer's disease—A quantitative Golgi investigation. *Neuroscience* **19:** 1265–1278, 1986.
4. Arendt, T., G. Taubert, V. Bigl and A. Arendt. Amyloid deposition in the nucleus basalis of Meynert complex: a topographic marker for degenerating cell clusters in Alzheimer's disease. *Acta Neuropathol*, in press.
5. Arendt, T., Y. Allen, J. Sinden, M. M. Schugens, R. Marchbanks and J. A. Gray. Cholinergic rich brain transplants reverse alcohol induced memory deficits. *Nature*, Submitted.
6. Bartus, R. T., R. L. D. B. Beer and A. S. Lippa. The cholinergic hypothesis of geriatric memory dysfunction. *Science* **217:** 408–417, 1982.
7. Bigl, V., T. Arendt, S. Fischer, S. Fischer, M. Werner and A. Arendt. The cholinergic system in aging. *Gerontology* **33:** 172–180, 1987.
8. Bowen, D. M. Cellular aging: selective vulnerability of cholinergic neurons in human brain. *Monogr Dev Biol* **17:** 42–59, 1984.
9. Coleman, P. D. and D. G. Flood. Neuron numbers and dendritic extent in normal aging and Alzheimer's disease. *Neurobiol Aging* **8:** 521–545.
10. Coyle, J. T., D. L. Price and M. R. DeLong. Alzheimer's disease: a disorder of cortical cholinergic innervation. *Science* **219:** 1184–1190, 1984.
11. Cup, C. J. and E. Uemura. Age-related changes in prefrontal cortex of Macaca mulatta: Quantitative analysis of dendritic branching patterns. *Exp Neurol* **69:** 143–163, 1980.
12. Flood, D. G., S. J. Buell, G. J. Horwitz and P. D. Coleman. Dendritic extent in human dentate gyrus granule cells in normal aging and senile dementia. *Brain Res* **402:** 205–216, 1987.
13. Geddes, J. W., D. T. Monaghan, C. W. Cotman, I. T. Lott, R. C. Kim and H. C. Chui. Plasticity of hippocampal circuitry in Alzheimer's disease. *Science* **230:** 1179–1181, 1985.

Neurobiology of Aging, Vol. 8, pp. 554–555. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0197-4580/87 $3.00 + .00

14. Hinds, J. W. and N. A. McNelly. Aging of the rat olfactory bulb: Growth and atrophy of constituent layers and changes in size and number of mitral cells. *J Comp Neurol* **171**: 345–368, 1977.
15. Jarvik, L. Genetic factors and chromosomal aberrations in Alzheimer's disease, senile dementia, and related disorders. In: *Alzheimer's Disease, Senile Dementia and Related Disorders. Aging* vol 7, edited by R. Katzman, R. D. Terry and K. L. Bick. New York: Raven Press, 1978, pp. 273–278.
16. McGeer, P. L., E. G. McGeer, J. Suzuki and C. E. Dolman. Aging, Alzheimer's disease and the cholinergic system of the basal forebrain. *Neurology* **34**: 741–745, 1984.
17. Mann, D. M. A., P. O. Yates and B. Marcyniuk. Changes in nerve cells of the nucleus basalis of Meynert in Alzheimer's disease and their relationship to aging and to the accumulation of lipofuscin pigment. *Mech Ageing Dev* **25**: 189–204, 1984.
18. Perry, E. K., B. E. Tomlinson, G. Blessed, K. Bergmann, P. H. Gibson and R. H. Perry. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Br J Med* **2**: 1457–1459, 1978.
19. Roth, M. The association of clinical and neurological findings and its bearing on the classification and aetiology of Alzheimer's disease. *Br Med Bull* **42**: 42–50, 1986.
20. Uemura, E. Age-related changes in the subiculum of Macaca mulatta: Dendritic branching pattern. *Exp Neurol* **87**: 412–427, 1985.

Differences Between Early and Late-Onset Alzheimer's Disease

L. L. IVERSEN

Neuroscience Research Centre, Merck Sharp and Dohme Research Laboratories
Terlings Park, Eastwick Road, Harlow, CM20 2QR, England

Alzheimer's disease of early onset versus that of late onset represent different syndromes, with distinct neuropathologies. Patients with early onset disease exhibit a more severe and more widespread loss of neurons from cortical and sub-cortical regions and the neurochemical changes involve not only the cholinergic system, but also neurons containing GABA, somatostatin and norepinephrine.

DRS. Coleman and Flood have written a comprehensive and valuable review of a confusing area. The study of neuropathological changes in normal aging and in Alzheimer's disease has been plagued by the lack of standard quantitative methods for assessing neuron loss, failure to recognise that the neuropathology may differ widely among brain regions, and the many other factors which Coleman and Flood describe so lucidly.

It is difficult to take exception to what they have written, which is both scholarly and accurate. The reader may, however, be left in a confused state of mind having read their review. The authors report many apparent contradictions in the findings reported by those who have studied the changes observed in Alzheimer's disease, but they do not make it clear how they believe such differences can be explained.

In my view, more emphasis could have been placed on the differences between Alzheimer's disease (AD) of early versus late onset. The marked differences in the neurochemical and neuropathological profiles of these sub-types may perhaps explain why different investigators, who have usually not taken this variable into account in their selection of AD material, can often come to very different conclusions from their analysis of post-mortem brain samples. A number of investigators, as reviewed by Coleman and Flood, have observed that the neuropathological changes in young AD patients (age at death<75–80 years) are more severe than in elderly patients (age at death>75–80 years). Indeed, as observed by Mountjoy *et al.* [6], Hubbard and Anderson [4] and others there may be no significant cortical neuron loss in many areas of cerebral cortex in these elderly patients, when allowance is made for the loss of cortical neurons in the normal aging process, which becomes prominent in the ninth decade [3]. Similar findings have been made in sub-cortical areas, notably in the noradrenergic brainstem locus coeruleus. Here the loss of pigmented neurons is often severe in younger patients, but normal numbers of cells may be present in elderly subjects [1,5]. In a recent detailed study of 46 AD patients and 44 age-matched controls, Bondareff *et al.* [2] used locus coeruleus cell counts to discriminate two subgroups of AD patients. The AD-1 group exhibited only modest reductions in noradrenergic cells, whereas the AD-2 group had a severe noradrenergic cell loss. The AD-1 and AD-2 sub-groups, although not differing significantly in age at death (80 vs. 78 years) showed marked differences in cortical neurochemical changes. The AD-2 sub-group had significantly greater reductions in CAT, norepinephrine, and somatostatin than the AD-1 group. In a previous study we had observed similar differences in neurochemical pathology between sub-groups dying<79 years or>79 years of age [7].

The more recent findings [2] suggest that it is not age at death that is the critical discriminant factor but the duration of illness—thus the AD-1 groups had a duration of illness of 60±10 months, versus 90±12 months for the more severely affected AD-2 group. It would seem, thus, that there is increasing evidence to support the hypothesis that AD of early onset may represent a different syndrome from AD of late onset [8]. It is perhaps worth recalling that the term "Alz-