CHANGES IN NERVE CELLS OF THE NUCLEUS BASALS OF MEYNERT IN ALZHEIMER'S DISEASE AND THEIR RELATIONSHIP TO AGEING AND TO THE ACCUMULATION OF LIPOFUSCIN PIGMENT

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SUMMARY

The number of nerve cells in the nucleus basalis of Meynert in normally aged persons is reduced by 30% by 90 years of age and cytoplasmic RNA content and nucleolar volume by about 20%. In Alzheimer's disease the changes are greatly exacerbated, with the cell number being depleted by a further 60% and cytoplasmic RNA content and nucleolar volume by an extra 35%. Moreover, younger patients with Alzheimer's disease show a much greater difference from controls of the same age than do older patients; indeed, by 90 years of age the levels of these changes are similar in Alzheimer's disease and in old age alone. Lipofuscin content is increased to a similar extent with age in both Alzheimer's disease and control patients and was associated with loss of cytoplasmic RNA content and nucleolar volume in both groups. It is suggested that mechanisms which result in the accumulation of this pigment during life also lower the capability of cells of the nucleus basalis of Meynert to withstand disease pathogens, leading to a certain degree of change in old age alone and one which in other persons may be compounded by secondary factors giving the extreme degeneration of Alzheimer's disease.

Key words: Nucleus basalis of Meynert; Alzheimer's disease; Ageing; Lipofuscin

INTRODUCTION

Only a small part of the total activity of the marker enzyme choline acetyltransferase (CAT) is thought to be present within cholinergic neurones intrinsic to the neocortex. The remainder resides within the terminals of ascending fibres [1] whose nerve cell
bodies are located within the nucleus basalis of Meynert (nbM), the septal nuclei and other rostral brainstem groups [2,3]. A loss of cerebral cortical CAT activity has been reported in old people and particularly so in those patients with Alzheimer's disease [4–12]. This may be due to a degeneration or at least a dysfunction of nerve cells within these other areas.

The intracellular accumulation of lipofuscin pigment with ageing has been associated in humans with a deterioration in function of nerve cells [13,14]. It is therefore possible that the large amounts of this material present in nerve cells of nbM [15] may reflect their viability in later life and in dementia. In this study, therefore, we have measured the amount of lipofuscin in nerve cells of nbM with age, and in Alzheimer’s disease, and related it to their functional capacity (i.e. the ability to form proteins) as assessed by measurement of nucleolar volume and cytoplasmic RNA content (see ref. 16 for review).

MATERIALS AND METHODS

Brains were obtained at post mortem from 10 moderately to severely demented patients over the age of 60 years, dying with histologically verified Alzheimer’s disease (Table I); care was taken to exclude from the study any patient in whom there was evidence of vascular disease and significant brain damage resulting from this. Average duration of illness, judged from clinical notes as lasting from first examination at hospital until time of death was 4.8 years (range 11 months to 9 years). Other brains were also obtained from an age- and sex-matched control group of 10 patients (Table I) and from a younger series of 10 patients of age range 10–60 years all dying without neurological or psychiatric illness. In these latter 20 patients there were no significant neuropathological changes, other than that in certain of the more elderly patients there were minimal amounts of cerebral softening or Alzheimer’s-type changes, or both. The immediate cause of death was similar in all patients, and there were no significant differences in brain weight or in post-mortem delay time between those with Alzheimer’s disease and the age-matched control group (Table I).

Following weighing, the fresh brains were suspended in 10% neutral formalin and from the fixed tissue standard blocks, including ones of the nbM, were cut. From these, paraffin sections cut at 5 μm were stained using conventional neuropathological techniques, including Gros-Bielchowsky (GB) silver staining for neurofibrils. Another 5 sections of that block containing the most extensive portion of the nbM (i.e. that part between the optic tract and the anterior commissure) were cut at 16 μm thickness and these were stained for RNA using Azure B [17]. In these the total number of nucleolated nerve cells within the nbM was counted and the average number per section, per patient, calculated. The lipofuscin content, cytoplasmic RNA content and nucleolar volume, in each of 60 nerve cells of nbM was measured for every patient [13] and from these individual patient and overall group mean values were determined. Measurements of frequency of senile plaques and nerve cells containing neurofibrillary tangles were made on the GB-stained sections in a standard area of middle temporal gyrus using the
**TABLE I**

SELECTIVE CLINICAL AND PATHOLOGICAL DETAILS OF 10 PATIENTS WITH ALZHEIMER'S DISEASE AND 10 AGE- AND SEX-MATCHED CONTROL PATIENTS

<table>
<thead>
<tr>
<th>Patient and sex</th>
<th>Alzheimer's disease</th>
<th>Age (years)</th>
<th>Brain weight (g)</th>
<th>Post-mortem delay (h)</th>
<th>Neocortex Senile plaques (n/mm²)</th>
<th>Neurofibrillary tangles (n/mm²)</th>
<th>Age-matched controls</th>
<th>Patient and sex</th>
<th>Age (years)</th>
<th>Brain weight (g)</th>
<th>Post-mortem delay (h)</th>
<th>Neocortex Senile plaques (n/mm²)</th>
<th>Neurofibrillary (n/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F 63</td>
<td>1130</td>
<td>40</td>
<td>45.4</td>
<td>42.3</td>
<td>1 F 63</td>
<td>1325</td>
<td>46</td>
<td>0.3</td>
<td>0.1</td>
<td></td>
<td></td>
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<tr>
<td>2 F 68</td>
<td>970</td>
<td>28</td>
<td>50.4</td>
<td>43.8</td>
<td>2 F 66</td>
<td>1305</td>
<td>14</td>
<td>2.4</td>
<td>1.6</td>
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<tr>
<td>3 M 71</td>
<td>1450</td>
<td>14</td>
<td>66.2</td>
<td>67.6</td>
<td>3 M 70</td>
<td>1355</td>
<td>10</td>
<td>0.6</td>
<td>0.8</td>
<td></td>
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<tr>
<td>4 F 73</td>
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<td>35</td>
<td>24.4</td>
<td>58.0</td>
<td>4 F 73</td>
<td>1280</td>
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<td>3.6</td>
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<td>5 F 75</td>
<td>1170</td>
<td>17</td>
<td>10.7</td>
<td>23.2</td>
<td>5 F 76</td>
<td>1205</td>
<td>56</td>
<td>1.4</td>
<td>1.9</td>
<td></td>
<td></td>
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<tr>
<td>6 M 75</td>
<td>1350</td>
<td>12</td>
<td>25.8</td>
<td>31.4</td>
<td>6 M 73</td>
<td>1240</td>
<td>20</td>
<td>1.2</td>
<td>1.0</td>
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<td>7 M 76</td>
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<td>79</td>
<td>18.6</td>
<td>24.1</td>
<td>7 M 79</td>
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<td>8 F 78</td>
<td>1100</td>
<td>47</td>
<td>19.2</td>
<td>22.6</td>
<td>8 F 77</td>
<td>1255</td>
<td>34</td>
<td>2.5</td>
<td>4.3</td>
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<td></td>
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<td>9 F 82</td>
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<td>35.4</td>
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<td>9 F 82</td>
<td>1150</td>
<td>15</td>
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<td>10 F 89</td>
<td>1020</td>
<td>33</td>
<td>16.3</td>
<td>20.4</td>
<td>10 F 88</td>
<td>1100</td>
<td>26</td>
<td>8.2</td>
<td>7.0</td>
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</table>

Mean ± S.E. 75.0 ± 2.3 1169 ± 54 31.3 ± 6.7 31.2*** ± 5.9 36.0*** ± 5.5 Mean ± S.E. 74.7 ± 2.3 1259 ± 28 31.6 ± 5.6 3.0 ± 0.8 3.1 ± 0.9

***Significantly different from control mean value, p < 0.001.
method of Aherne and Diggle [18]; details of this technique have been given by us elsewhere [19].

Histological changes

Controls. The nbM contains clusters of large neurones which contain abundant cytoplasmic RNA (Nissl substance) within their cell bodies and a large open nucleus with finely granular chromatin in which the nucleolus is prominent and strongly basophilic (Fig. 1). These features make the neurones of nbM clearly distinguishable from other neurones in the substantia innominata and in adjacent structures. The density of nerve cells in nbM appeared less in some controls though this may reflect slight variations in level of sectioning, as much as any actual difference in population.

However, at all ages, there were some neurones which showed an enlarged, vacuolated, cell body and in which the nucleus was peripherally displaced and the Nissl substance indistinct (Figs. 1 and 2). In the older patients most neurones of nbM contained large amounts of lipofuscin pigment and in some of these elderly patients nerve cells with neurofibrillary tangles were occasionally seen. There was no overall glial cell reaction, though occasional glial clusters around degenerating neurones were present. No changes in blood vessels in, or in close proximity to, the nbM were noted.

Alzheimer's disease. In all 10 patients there was a loss of neurones from nbM (Fig. 3), and many of those still present showed a shrinkage of the cell body, a loss of cytoplasmic

Fig. 1. The nucleus basalis of Meynert in a control patient of 63 years showing nerve cells in large clusters. Most contain abundant Nissl substance within their perikarya and the large open nucleus shows finely dispersed chromatin and contains a prominently basophilic nucleolus. An enlarged vacuolated nerve cell is arrowed. Weigert's haematoxylin-eosin, ×250.
Fig. 2. Nerve cell (arrowed in Fig. 1) shown at higher magnification. Weigert’s haematoxylin–eosin, \( \times 400 \).

Fig. 3. The nucleus basalis of Meynert in a 63-year-old man with Alzheimer’s disease. Loss of nerve cells is apparent and those remaining are atrophied. Weigert’s haematoxylin–eosin, \( \times 250 \).
RNA and a small nucleolus within a shrunken nucleus. Vacuolated neurones and others containing much lipofuscin were again present and the proportion of neurones showing neurofibrillary degeneration (Fig. 4) was greatly increased. No significant changes in glial cells or blood vessels in or around nbM were observed.

RESULTS

Mean values of the number of nucleolated nerve cells in nbM per 16 µm section, together with those of their mean nucleolar volume, cytoplasmic RNA and lipofuscin content, for all 20 control patients are plotted against patient age and shown in Fig. 5A—D.

The mean number of nerve cells in nbM is significantly reduced with age (Fig. 5A, Table II) such that by the age of 90 years about 30% of the cell complement has been lost. Moreover, the cytoplasmic RNA content and nucleolar volume of the remaining cells are also both significantly decreased with age (Fig. 5C,D; Table II) with reductions of 18% and 21%, respectively, being achieved by 90 years of age. Conversely, the mean lipofuscin content of these nerve cells increases throughout life (Fig. 5B; Table II). Moreover, in these 20 patients, number of nerve cells, nucleolar volume and cytoplasmic RNA content all correlated inversely ($p < 0.05$ in each instance) (Table II) with lipofuscin content. These findings are consistent with those previously reported by ourselves in other nerve cell types [13,14]. Although reductions in RNA content with age matched

![Fig. 4. The nucleus basalis of Meynert in a 63-year-old man with Alzheimer's disease showing neurofibrillary degeneration of nerve cells. Palmgren's silver stain, X400.](image)
Fig. 5. Graph showing the mean number of nerve cells in the nucleus basalis of Meynert (A), their mean lipofuscin content (B), mean cytoplasmic RNA content (C) and mean nucleolar volume (D) in 20 control patients plotted against patient age.

those in nucleolar volume (Table II), neither of these two features correlated with the extent of nerve cell loss.

Since none of the 10 control patients aged under 60 years showed senile plaques or cells bearing neurofibrillary tangles within their neocortex, no correlations linking these two features to the other histological changes were performed. The frequencies of plaques and tangles did, however, increase with age ($p < 0.001$) in the 10 controls aged over 60 years ($r = 0.843$ and $r = 0.861$, respectively).

Values of frequency of senile plaques, neurofibrillary tangles in neocortex, mean number of cells in nbM and those of nucleolar volume, cytoplasmic RNA and lipofuscin content are shown for each patient with Alzheimer's disease and each age-matched control in Table I and III respectively. These individual values are pooled and overall means for each group of patients derived (Tables I and III). When compared with average values from the age-matched control group, the frequency of senile plaques and neurofi-
TABLE II

PRODUCT MOMENT CORRELATIONS (r) BETWEEN AGE, NUMBER OF NERVE CELLS IN nbM AND THEIR NUCLEOLAR VOLUME, CYTOPLASMIC RNA AND LIPOFUSCIN CONTENT FOR ALL 20 CONTROL PATIENTS

<table>
<thead>
<tr>
<th>Patient age (years)</th>
<th>Nerve cell number</th>
<th>RNA content (AU)</th>
<th>Nucleolar volume (μm³)</th>
<th>Lipofuscin content (FU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve cell number</td>
<td>-0.613**</td>
<td>-0.463*</td>
<td>-0.549*</td>
<td>0.950***</td>
</tr>
<tr>
<td>RNA content (AU)</td>
<td>-0.463*</td>
<td>0.289</td>
<td>0.126</td>
<td>-0.510*</td>
</tr>
<tr>
<td>Nucleolar volume (μm³)</td>
<td>-0.549*</td>
<td>0.126</td>
<td>0.691***</td>
<td>-0.453*</td>
</tr>
<tr>
<td>Lipofuscin content (FU)</td>
<td>0.950***</td>
<td>-0.510*</td>
<td>-0.453*</td>
<td>-0.609**</td>
</tr>
</tbody>
</table>

aAU = arbitrary units of light absorption.
bFU = arbitrary units of light fluorescence.
*,**,***, Significant at levels p < 0.05, <0.01, <0.001, respectively.

brillary tangles in neocortex is significantly greater (p < 0.001 for both) in the Alzheimer's disease patients (Table I). However, the frequency of neurofibrillary tangles in neocortex correlated significantly with frequency of senile plaques in both Alzheimer (r = 0.759; p < 0.01) and the age control (r = 0.904; p < 0.001) group. Such a relationship has been demonstrated previously in Alzheimer's disease in temporal cortex [19,20] and also in the hippocampus [21]. The number of nerve cells in nbM is reduced (p < 0.001) in Alzheimer's disease by about 60% and nucleolar volume and RNA content of those remaining cells are both decreased by 34% (p < 0.001 in both instances).

The effect of age, in Alzheimer's disease, on these histological and cytological changes was investigated. The percentage losses of nerve cells from nbM and reductions in RNA content and nucleolar volume of those remaining were calculated for each patient with Alzheimer's disease, by comparing actual patient values of these features with those expected for patient age alone, as derived from the linear regressions shown in Fig. 5. The frequency of senile plaques and neurofibrillary tangles in neocortex both correlated inversely with patient age [r = -0.572 plaques, r = -0.597 tangles, p < 0.05 for both (Fig. 6)]. Percentage loss of nerve cells in Alzheimer's disease similarly correlated inversely with patient age (r = -0.613, p < 0.05), as did percentage reductions in RNA content (r = -0.831, p < 0.01) and nucleolar volume (r = -0.792, p < 0.01) (as shown in Fig. 7). In other words, younger patients with Alzheimer's disease show a much greater difference from controls of the same age than do older patients. Indeed, after about 90 years of age all five features show similar levels of change in both Alzheimer's disease and in old age alone. Percentage loss of nerve cells from nbM and percentage reductions in RNA content and nucleolar volume of remaining cells were correlated with frequency of senile plaques and neurofibrillary tangles within neocortex (Table IV). Percentage loss of nerve cells from nbM correlated only weakly with plaque and tangle frequency, though these correlations with percentage reductions in nucleolar volume and RNA content in remaining cells were highly significant (Table IV).
TABLE III
NUMBER OF NERVE CELLS IN nbM AND THEIR MEAN NUCLEOLAR VOLUME, CYTOPLASMIC RNA AND LIPOFUSCIN CONTENT IN 10 PATIENTS WITH ALZHEIMER'S DISEASE AND 10 AGE- AND SEX-MATCHED CONTROL PATIENTS. OVERALL GROUP MEAN VALUES ARE ALSO SHOWN.

<table>
<thead>
<tr>
<th>Alzheimer's disease</th>
<th>Age-matched controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Nerve cell number</td>
</tr>
<tr>
<td>1</td>
<td>102</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>118</td>
</tr>
<tr>
<td>4</td>
<td>102</td>
</tr>
<tr>
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<td>164</td>
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<td>6</td>
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<td>131</td>
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<td>8</td>
<td>190</td>
</tr>
<tr>
<td>9</td>
<td>160</td>
</tr>
<tr>
<td>10</td>
<td>121</td>
</tr>
</tbody>
</table>

Mean ± S.E. 130.8*** ± 10.6 20.5*** ± 1.6 21.8*** ± 1.4 62.4 ± 2.7 Mean ± S.E. 317.8 ± 13.2 30.6 ± 1.1 30.8 ± 0.5 65.7 ± 2.6

²AU = arbitrary units of light absorption.
³FU = arbitrary units of light fluorescence.

***Significantly different from control group mean value, p < 0.001.
Although the average amount of lipofuscin pigment within remaining cells of nbM increases with age, within the group of patients with Alzheimer's disease ($r = 0.920$, $p < 0.001$; Fig. 7B) this is at the same rate as in the control patients (Fig. 5B). These findings are similar to those we have reported elsewhere for other nerve cell types [22]; i.e., the average amount of this waste pigment within nerve cells of nbM in Alzheimer's disease is no different, at any age, from that present within control patients (Table III).

The relationship in individual patients between the amount of lipofuscin within individual nerve cells of nbM and the volume of their nucleolus and their RNA content, was also investigated by regression analysis for one of the younger control patients, an older patient with Alzheimer's disease (Alzheimer patient 7) and an age-matched older control (control patient 7). These three were chosen to be representative of their respective group as their ages and values for nerve cell number, nucleolar volume, RNA and lipofuscin contents, all most closely matched their respective mean group values.

In both the younger and the older control the amount of lipofuscin within neurones of nbM correlated inversely ($p < 0.001$ in each instance) with both cytoplasmic RNA content ($r = -0.899$ young, $r = -0.922$ older) and nucleolar volume ($r = -0.884$ young, $r = -0.864$ older). Moreover, covariant analysis showed that the regression lines for the relationships between lipofuscin and cytoplasmic RNA content, and between lipofuscin content and nucleolar volume, were similar in both:

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**Fig. 6.** Graph of frequency of senile plaques (A) and neurofibrillary tangles (B) in neocortex in 10 patients with Alzheimer's disease plotted against patient age. Also shown as dotted line is the regression line for these changes in the 10 age-matched control patients derived from data in Table I.
(Young) RNA (Y) X lipofuscin (X): $Y = 46.3 - 0.25X$
(Older) RNA (Y) X lipofuscin (X): $Y = 45.8 - 0.23X$
(Young) Nucleolar volume (Y) X lipofuscin (X): $Y = 46.0 - 0.27X$
(Older) Nucleolar volume (Y) X lipofuscin (X): $Y = 46.6 - 0.25X$

In the patient with Alzheimer's disease lipofuscin content (X) again correlated inversely ($p < 0.001$) with both cytoplasmic RNA content ($Y = 39.2 - 0.27X; r = -0.801$) and nucleolar volume ($Y = 36.2 - 0.23X; r = -0.707$). Although both nucleolar volume and RNA content were decreased overall in the Alzheimer's disease patient (when compared with the age-matched control) by 35%, it is notable that both these features were reduced by over 45% in nerve cells with high (>80 units) levels of lipofuscin, but only by 20% in cells with low (<20) levels.
TABLE IV

PRODUCT MOMENT CORRELATIONS (r) BETWEEN PERCENTAGE LOSS IN NUMBER OF NERVE CELLS IN nbM AND PERCENTAGE REDUCTIONS IN NUCLEOLAR VOLUME AND CYTOPLASMIC RNA CONTENT WITH FREQUENCIES OF SENILE PLAQUES AND NEUROFIBRILLARY TANGLES IN NEOCORTEX, FOR THE 10 PATIENTS WITH ALZHEIMER'S DISEASE

<table>
<thead>
<tr>
<th>Neocortex</th>
<th>Senile plaques (n/mm²)</th>
<th>Neurofibrillary tangles (n/mm²)</th>
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</thead>
<tbody>
<tr>
<td>Nucleus basalis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve cell number</td>
<td>0.543*</td>
<td>0.662*</td>
</tr>
<tr>
<td>RNA content (AU)ᵃ</td>
<td>0.687*</td>
<td>0.831**</td>
</tr>
<tr>
<td>Nucleolar volume (μm³)</td>
<td>0.813**</td>
<td>0.872***</td>
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</table>

ᵃAU = arbitrary units of light absorption.
* , ** , *** Significant at levels p < 0.05, <0.01, <0.001, respectively.

DISCUSSION

In this study we have shown that both the number and the function of nerve cells of the nbM are progressively decreased with ageing such that by the 10th decade about 30% of the original complement is lost and the capacity to form proteins for physiological action is also reduced in those nerve cells that are still present. This pattern of damage is, however, greatly exacerbated in Alzheimer's disease where nerve cell numbers are on average depleted by a further 60% (making an overall cell loss of 70% when compared with young adults); the capacity for protein production is decreased by an extra 35% (making 40% difference overall). Other degenerative features of old age such as neurofibrillary tangle formation are more common in Alzheimer's disease. These findings confirm and enlarge those of Whitehouse et al. [23,24], Perry et al. [25] and Candy et al. [26], who reported a loss of nerve cells from nbM in patients with "sporadic" Alzheimer's disease [23,25,26] and also in a single patient with the familial form of this illness [24]. The correlations between the cell loss and reductions in indices of perikaryal function within the nbM and the frequency of senile plaques within neocortex suggest that at least some of the degenerating neurites within evolving plaques may be branches of axons from nbM. Indeed the demonstration of acetylcholinesterase activity in such neurites [27,28] would substantiate this. Correlations between changes in nbM and neurofibrillary tangle frequency may simply reflect parallel degeneration within cortex and subcortex and need not necessarily imply any close causal relationship.

The reductions in markers of cholinergic activity in the cerebral cortex in old age and in Alzheimer's disease [4–12] are probably due to the loss of nerve cells from nbM combined with the decrease in protein synthesis capacity in those that survive; the failure to produce CAT and synthesize acetylcholine may be only one aspect of this metabolic change. Damage to cholinergic neurones in the septal nuclei [29] is, in a
similar way, probably responsible for loss of CAT activity within the hippocampus [5,7,8].

Furthermore, our finding of a lessening in the severity of changes in nbM in Alzheimer’s disease, with advancing age, in conjunction with the fact that the changes we have shown become more severe with ageing alone reconciles other studies [23–26] in which, when compared with age-matched controls, younger patients with Alzheimer’s disease lose over 75% of nerve cells from nbM [23], yet in older patients the loss is only 33% [25,26]. Such findings also explain why losses of CAT activity are usually much more pronounced in younger persons with Alzheimer’s disease [8,9,11,12] and also why either only slight or no significant losses of CAT activity can occur in some of the very old people with Alzheimer’s disease when compared to age-matched controls, at least as far as areas of frontal cortex are concerned [11,12]. Since no correlation was found between duration of illness and patient age it may be that the more pronounced changes in the younger person with Alzheimer’s disease actually reflect a more severe process of disease. Unfortunately we were unable to confirm that the younger patients were more mentally impaired by relating the severity of the pathological changes to the degree of dementia because, even though most patients had been formally assessed (usually on several occasions) during the course of their illness, there was no common point in time before death at which such ratings could be reliably compared.

Damage to neurotransmitter systems in Alzheimer’s disease is not, however, restricted to that based on acetylcholine. Degeneration and loss of the melanin-containing nerve cells of the locus coeruleus, which forms the main part of the brain’s noradrenergic system, have also been well established [30–33]. Other reports [34,35] indicate involvement of serotonin pathways based on the raphe nuclei of the brain stem and mid brain. As is seen with the cholinergic system, damage to the noradrenergic and serotonin systems is also more pronounced in the younger person with Alzheimer’s disease, in old people with dementia the difference from the changes already observed without dementia is again much less marked [35a]. Moreover, the extent of degeneration of the noradrenergic and serotonin systems with a group of patients with Alzheimer’s disease broadly parallels that of the cholinergic system [35a].

These three nerve cell types give rise to ascending pathways which, although projecting to different regions of the cerebral cortex, all form part of a larger group that has been collectively termed “the isodendritic core” [36] and which extends from the basal forebrain to the spinal cord and subsumes what corresponds to the reticular formation.

A feature of nerve cells of this area is the particularly large quantities of lipoprotein pigments that they accumulate by middle age and beyond: lipofuscin in cells of nbM and raphe nuclei, neuromelanin in those of the locus coeruleus. An increasing amount of pigment within these cell types has been shown both here and elsewhere [13,14,37] to be associated with reductions in the quantity of cytoplasmic RNA and the volume of the nucleolus. Such findings imply a progressive lowering of protein synthetic capacity as pigment is accumulated. Thus these heavily pigmented nerve cells of the isodendritic core would, as time passes, not only be less able to respond quickly in terms of activity
or stress, but would also be less capable of withstanding the effects of chance exposure to pathogens which might easily lead to their metabolic collapse and the progressive fall off in number that occurs in later life (see here and ref. 38). By this argument, the changes seen in these cell types in Alzheimer's disease would represent a worsening of this ageing process, precipitated by a pathogenic insult of sufficient severity as to result in the rapid loss of cells within the isodendritic core. Since these nerve cell types are "fitter" in younger persons (Figs. 5 and 3C), so a "higher level" of exposure to pathogen would be required to precipitate Alzheimer's syndrome in such patients and consequently greater degrees of pathological damage and neurological disturbance would be expected. With ageing, these nerve cell types become weaker, so progressively lower levels of exposure to pathogen would be able to precipitate the illness and, in turn, the extent of the pathological changes and that of the dementia would become less severe. The changes we have reported here and the observation that the incidence of Alzheimer's disease rises with age [39], would all be consistent with such a mechanism of disease.

We suggest, therefore, that the subcortical changes of Alzheimer's disease stems from an aggravation by secondary factors of basic alterations associated with pigment accumulation within neurones of nbM, locus coeruleus, raphe nuclei (and perhaps also other groups of the isodendritic core) which occur as part of their "normal process of ageing". Any one of a wide spectrum of compounding factors (and not necessarily the same one in every instance) such as the action of viruses (i.e. Herpes simplex [40–43]) or toxins such as aluminium [44–46] or perhaps deficiencies in the blood–brain barrier [47,48] which allow these agents to gain access to the central nervous system, might therefore be the change that tips the balance between acquisition and non-acquisition of disease. This could explain why attempts to relate a single specific factor to the incidence of the disorder have so far been unsuccessful.

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REFERENCES
