GRANULOVACUOLAR DEGENERATION IN THE AGEING BRAIN
AND IN DEMENTIA

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ABSTRACT

Quantitative morphometry with a sampling stage light microscope was performed to determine the severity of granulovacuolar degeneration of hippocampal neurones in serially sectioned temporal lobe from mentally normal subjects of different ages and from demented patients.

The degree of granulovacuolar change in control brains increased slightly with increasing age; the "granulovacuolar index" of cases with Alzheimer's disease exceeded by many times that of age-matched controls. This significant difference was demonstrable whether the granulovacuolar severity was expressed as number of affected cells per volume of cortex analysed, or as the percentage involvement of total neurones counted in the hippocampus. The posterior half of each dement's hippocampus was found to be more susceptible to this augmented granulovacuolar degeneration than the anterior half, a selectivity already observed for neurofibrillary tangle formation in the same material.

INTRODUCTION

The specific histological change in the cytoplasm of hippocampal pyramidal neurones known as granulovacuolar degeneration was first described by Simchowicz (9) in cases of senile dementia of the Alzheimer disease type. This alteration consists of one or more unstained, spherical vacuoles, 3 to 5μ in diameter, in the centre of each of which is an argyrophilic, hematoxylinophilic granule, 0.5 to 1.5μ wide (Figure 1). Some reduction of the stainable Nissl material may be seen near the granulovacuole(s) if only a few are present in the perikaryon, but when many (up to 20) vacuoles are present in a single paraffin section, the neurone may appear swollen and bulging.

Ultrastructural examination of granulovacuoles (4, 5, 10) has not appreciably elucidated the nature of this degeneration. With the electron-microscope the vacuoles located in the cytoplasm have a limiting membrane, an electronlucent or "empty" core and a central, irregular, very electron-dense granular body. Histochemical analysis has been similarly unrewarding (6, 7); the granules are negative to staining with periodic acid-Schiff, Alcian blue and Congo red, show a slight affinity for Luxol fast blue, and are much less intensely argyrophilic than the neurofibrillary tangles of Alzheimer or senile

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plasques which commonly accompany the granulovacuolar change (7).

More helpful have been the studies of the occurrence and distribution of granulovacuolar degeneration in normal brains of various ages and in demented patients (11, 12, 13, 15). In a report of 28 non-demented old people, aged 65 to 92 (mean 75) years, Tomlinson et al. (11), using a single histological section of each hippocampus, found in 25 subjects that the change was absent in 11, present to a mild extent (1 to 4 pyramidal neurones out of 1000 or more in the section) in 8, and considerable in 6 cases, most commonly in Rose's H₁ field (Sommer's sector), next the H₂ field, and rarely the end-plate. In the most severely affected brain, one of four cells in some parts of Sommer's sector showed the change; but no case had more than 7% of involved neurones when all cells from Rose's H₁ and H₂ fields were counted. Since 8 of 11 cases older than 75 years had some granulovacuolar degeneration, whereas only 6 of 14 below that age showed the change, the results suggested that the incidence of granulovacuolar degeneration increases with normal ageing.

From a similar aged series of 50 definitely demented patients, varying from 56 to 92 years (mean 76 years), these authors (12) found that of 49 brains there was no granulovacuolar degeneration in 9, it was occasionally present in 8, and was present in moderate numbers in 8 others. However, in 24 other demented greater numbers of pyramidal neurones were so affected than in any non-demented control, with some fields in Sommer's sector showing 50% of all cells involved. In the entire Sommer sector 13 of these 24 had over ½ of the
H-1 neurones affected, also an observation never noted in the control group. Both the incidence and the degree of granulovacuolar degeneration were thus judged to be significantly greater in dEMENTS, especially in those brains diagnosed as senile dementia of the Alzheimer disease type.

In 200 unselected autopsies from patients with all forms of mental disease, Woodard (15) examined one section of each hippocampus, using hematoxylin-eosin and Bielschowsky stains. In all cases where granulovacuolar change was found, he counted all neurones in the ventrolateral quadrant (partly Rose's H, field, plus some adjacent prosobiculum) of the hippocampus on one paraffin section; the change again was most prevalent there. The percentage of neurones so affected was thus determined. In 62 cases (31%), granulovacuolar degeneration involved between 9 and 66% of the (counted) hippocampal neurones. All but two of these met all the clinical and neuropathological criteria for a diagnosis of Alzheimer's (presenile or senile) disease; two were cases of Pick's lobar atrophy. An involvement of 9% or more of the cells was never found in any case lacking a clinical history consistent with Alzheimer's disease. Woodard's remaining 138 cases showed no correlation between the occasional instance of granulovacuoles and any diagnostic category of mental disease. Contrary to Tomlinson's results, Woodard found no real predilection of the mild degree of degeneration for the older age-groups. He claimed that granulovacuolar change does not tend to become a function of age in the "senile" period; and that occurrence of 9% or more involvement among hippocampal cells retains its specificity for Alzheimer's disease even in the very aged patients.

From a much larger series of consecutive necropsies on people dying in an acute-treatment general hospital, Tomlinson and Kitchener (13) quantitated granulovacuolar degeneration in the brains of 219 patients aged 14 to 98 years. Clinical information as to presence or absence of dementia was not sought. One 5μ paraffin section, stained with hematoxylin and eosin was available from each hippocampus. Only 2 of 71 cases younger than 50 years showed any affected neurones; only 2 of 35 cases were affected in the 50-59 year age-group; but thereafter the incidence rose sharply, reaching 74% (of 39 cases) in the 80-89 year old group, and 75% (of 8 cases) in the tenth decade. The authors also counted all neurones present in Rose's five H fields (again H-1 and H-2 were most often and most severely involved). The percentage of cells affected by granulovacuolar change in any area was 1 to 2% below age 60 years, and increased with increasing age in the seventh, eighth and ninth decades — none in the 60's showed 9% or more involvement, 4 of 36 brains (11%) showed this degree of involvement in the 70's (with the worst case having 20% affected), and 7 of 39 brains (18%) showed at least 9% involvement in the 80's (with 3 of these between 22 and 50%). Thus both the incidence and to a lesser extent the severity of granulovacuolar degeneration were increased with age.

By contrast, their study included the brains of 30 old people clinically shown by psychiatric testing not to have dementia, and 25 cases proven to be demented from Alzheimer's disease. In the 30 non-demented cases, 21 (79%)
had either no affected cells (8) or less than 1% affected (13). Six cases (20%) had from 1 to 5% involvement; and only 3 had 9% or greater affliction. In the 25 Alzheimer brains, however, none was free of granulovacuolar degeneration; only 3 had less than 9% involvement; and 22 (88%) had 9% or more neurones affected, with 15 cases as high as 14 to 42%. Tomlinson and Kitche-
er concluded that old non-dements' hippocampi rarely exceed 9% affection, while the great majority of hippocampi from Alzheimer's disease do exceed 9% involvement of H1 and H2 neurones. A scattergram using the "9%-limit", however, showed that 1 of 30 non-demented and 5 of 25 Alzheimer's disease cases did not conform to this separation.

Since quantitative morphometry with a semi-automated scanning stage microscope has enabled our laboratory to distinguish clearly the severity of neurofibrillary tangle formation in hippocampal neurones of aging control brains from that in Alzheimer's disease (1), a similar approach has been applied to measure granulovacuolar degeneration in the same material. The results indicate a quantitative significance for this histologic change in the pathogenesis of dementia.

MATERIALS AND METHODS

Twenty-six cases were studied in this report.1 Eighteen control brains were examined from patients aged 47 to 89 years (mean 68.7), considered neurologically normal and mentally sound from detailed clinical information. The patients had been on the wards of a large general hospital and a veterans' hospital. Pertinent clinical data are given in Table 1. Also available were the brains of eight patients dying with dementia of the Alzheimer's disease type, from a provincial psychiatric institute and the veterans' hospital.

The neuropathological features of the 8 demented cases included abundant senile plaques and neurofibrillary tangles in the cortex (2); reduced brain weight; generalized cortical atrophy; and the absence of any arteriolosclerosis or significant infarction from appreciable cerebrovascular disease. If the clinical course began before 65 years of age, the designation "Alzheimer's disease" was assigned in Table 1; if the history began after that age, it was termed "senile dementia, Alzheimer disease type". This arbitrary distinction will not be employed hereafter.

All brains were suspended in 10% formalin for two weeks. After removal of brainstem and cerebellum, each entire hippocampus (from 2 cm. posterior to the rostral tip of each temporal lobe, to the coronal plane of the callosal splenium) was excised, cut sequentially in the coronal plane, and all the tissue blocks (totalling 40 to 50 mm. of fixed tissue anteroposteriorly) were processed for paraffin and serially sectioned at 6μ thickness.

The middle section of each tissue block from the left hippocampus was stained with hematoxylin-eosin-Luxol fast blue. The area to be screened, outlined on each coverlip with ink, included all five of Rose's H fields, the ventrolateral quadrant of Woodard (15), and the prosubiculum as far laterally as the point where the large pyramidal neurones of the stratum pyramidale disappear in the four-layered subicular allocortex (usually at the same sagittal plane as the lateral end of the hippocampal fissure; Figure 2). Since Tomlinson and Kitchener had noted granulovacuoles in neurones of the prosubiculum and subiculum in a prolonged search of a few of their more severely affected cases (13), we felt it important to include this region. Those sections from blocks anterior to a well-formed "capital C" configuration of the fascia dentata were not screened for granulovacuoles. An average of 6 sample sections was thus surveyed per case; a total of 33,811 microscopic fields was screened in the 154 sections studied.

The entire area within each inked border was scanned in serial fashion with the Wild M501

1 One of the 27 cases reported in the neurofibrillary tangle study (1) was unsuitable for granulovacuolar analysis due to technical artefact.
microscope employing a semi-automated (scanning) mechanical stage, at a magnification of 200 times, with a square ocular (Weibel) graticule. All neurones in the pyramidal layer of the hippocampal cortex and whose nuclei were visible were counted, as well as all nucleolated neurones showing one or more granulovacuoles (Figure 3). Photographic enlargements of each slide enabled us to measure the area of cortex thus screened, using a digitizer linked to a Hewlett-Packard calculator. Since the real thickness of each section was known (5.85 μ), the number of nerve cells showing granulovacuolar degeneration per cubic millimeter of cortex could also be calculated.

The number of cells with granulovacuolar degeneration was also calculated per cu. mm. of cortex for the anterior half of each (left) hippocampus, and for the posterior half (Table 3). (When a hippocampus had provided an odd number of tissue-blocks, the Adjusted Granulovacuolar Index of the middle block was included in the calculation of the mean both of the anterior portion and of the posterior half.)

### TABLE 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Immediate cause of death</th>
<th>Neuropathological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>47</td>
<td>Cirrhosis &amp; hepatic failure</td>
<td>(Alcoholic) cerebellar atrophy</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>52</td>
<td>Myocardial infarct</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>53</td>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>56</td>
<td>Breast carcinoma</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>59</td>
<td>Metastatic carcinoma from colon</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>60</td>
<td>Aortic stenosis &amp; mitral insufficiency (rheumatic)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>63</td>
<td>Bronchogenic carcinoma</td>
<td>Pineal metastasis</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>67</td>
<td>Aortic stenosis (rheumatic valve disease)</td>
<td>Microscopic arteriovenous malformation, lt. occipital lobe</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>69</td>
<td>Prostatic abscess causing septicaemia</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>70</td>
<td>Chronic obstructive lung disease</td>
<td></td>
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<td>11</td>
<td>M</td>
<td>76</td>
<td>Infarctions of bowel</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>76</td>
<td>Myocardial infarct</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>76</td>
<td>Prostatic carcinoma</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>77</td>
<td>Ruptured aortic aneurysm</td>
<td></td>
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<td>15</td>
<td>F</td>
<td>81</td>
<td>Vesico-colonic fistula</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>82</td>
<td>Myocardial infarct</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>83</td>
<td>Mesenteric thrombosis</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>89</td>
<td>Bronchopneumonia</td>
<td>Small old infarct, right parietal lobe</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>56</td>
<td>Bilateral bronchopneumonia</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>67</td>
<td>Bilateral bronchopneumonia</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>71</td>
<td>Aspiration pneumonitis</td>
<td>Alzheimer's disease; history of controlled epilepsy</td>
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<tr>
<td>22</td>
<td>M</td>
<td>77</td>
<td>Aspiration pneumonia</td>
<td>Alzheimer's disease; old infarcts; congophilic angiopathy</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>77</td>
<td>Pulmonary embolism</td>
<td>Senile dementia, Alzheimer type</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>78</td>
<td>Myocardial infarction</td>
<td>Senile dementia, Alzheimer type; 2 small old infarcts, basal ganglia</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>80</td>
<td>Bilateral bronchopneumonia</td>
<td>Alzheimer's disease; leptomeningeal fibrosis; blast injury 30 years before death</td>
</tr>
<tr>
<td>26</td>
<td>F</td>
<td>91</td>
<td>Coronary artery disease</td>
<td>Senile dementia, Alzheimer type</td>
</tr>
</tbody>
</table>
The number of affected neurones per cubic millimeter of cortex was also determined in one section from the right hippocampus of each case, but since comparison with the matched sections from the left side showed no significant differences, either for controls (t = 0.78; p > 0.1) or for dement (t = 0.22; p > 0.1), we have assumed, as Tomlinson suggested (13), that there is no lateralizing tendency for granulovacuolar change; and our results are discussed with reference to left hippocampal data only.

It is likely that this lack of lateralizing tendency would have been shown even if all slides from both hippocampi were compared, since in a severely involved case (#22) the values for the seven left-sided samples did not differ from those of the six right-sided sections (t = 0.58; p > 0.1).

RESULTS

The number of hippocampal neurones showing granulovacuolar degeneration in all the slides screened for each case provided a "Raw Granulovacuolar Index" for each brain (Table 2). This number was then corrected by dividing by the total number of cubic millimetres of hippocampal grey matter analysed per case, to provide an "Adjusted Granulovacuolar Index" (the density of granulovacuolar changes standardized for cortical volume), Table 2.

The age of the 18 control patients is comparable to that of the eight demented patients (two-tailed t = 1.2, p > 0.1). When the age of the controls is plotted against their Adjusted Granulovacuolar Index (Figure 4), the best
linear regression line shows a significant correlation coefficient ($r = 0.59$, $p < 0.01$). If the eight demented indices are included, however, such a correlation can no longer be shown. Thus the severity of granulovacuolar degeneration definitely increases, although very gradually, with normal ageing; but patients with Alzheimer's dementia, while showing no age-correlation, have a severity of involvement markedly in excess of that for controls of similar age (from 2 to 100 times greater). The mean Adjusted Index for the demented cases, 353 affected cells per cu. mm., is much greater than for the controls, 17 cells per cu. mm. ($t = 5.7$, $p < 0.001$).

Since two similarly distinct populations had been discerned in a previous study of the severity of neurofibrillary tangle formation in the hippocampus (1), we plotted the already determined "Adjusted Tangle Index" (number of tangle-bearing neurones/cu. mm. hippocampal cortex) of the same 26 cases reported here against their Adjusted Granulovacuolar Index (Figure 5). The best linear regression line showed a striking positive correlation ($r = 0.91$, $p < 0.001$) between these two histological alterations in controls' and dement's brains.

Using total neurone counts of the area outlined earlier, we next calculated the percentage of the total number counted which had been affected by granulovacuolar degeneration (Table 4). The actual nerve cell numbers will be presented in a future paper, but a scattergram of the percentage involved by granulovacuolar change (Figure 6) illustrates the fact that the affection
attributable to normal ageing is quantitatively different from that occurring in Alzheimer's dementia, irrespective of the age of the demented patient (two-tailed \( t = 8.16, p < 0.001 \)). None of the control brains exceeds 1% involvement, whereas all the demented cases do. The mean for normals is 0.27%, that for Alzheimer's disease is 9.16%.

Comparison of the Adjusted Granulovacuolar Index by sex (Table 2) showed no statistically significant difference between men and women (two-tailed \( t = 1.83, p > 0.05 \)).

Finally, the Adjusted Granulovacuolar Index for those samples of the anterior half of the hippocampus (Table 3) was compared with that for the sections in the posterior half (Table 3). There was no statistically significant difference within the control group between the Anterior and the Posterior indices (\( t = 0.28, p > 0.1 \)); nor was there any difference between densities in front and back halves within the demented group, either (\( t = 1.29, p > 0.1 \)). The mean anterior index of the controls (Column 3) is 18.63; that of the dement is significantly different at 232.99 (\( t = 5.06, p < 0.001 \)). This indicates that the granulovacuolar density anteriorly has increased by a factor of 12 in dementia. The mean posterior index of the controls (Column 4) is 17.32; that of the dement is significantly different at 380.43 (\( t = 5.89, p < 0.001 \)). The mean granulovacuolar affection posteriorly has therefore increased by a
factor of 22 in dementia, i.e., nearly twice as large an increment as in the anterior half of the hippocampus. These two factors can furthermore be shown to be different to a statistically significant degree by calculating a "Posterior/Anterior Ratio" in each case (Column 5 of Table 3) and then comparing the mean Ratio for all controls (Column 5), which is 1.05 (S.D. ± 0.51), with the mean Ratio for all cases of Alzheimer's disease, which at 1.63 (S.D. ± 0.72) is significantly greater (two-tailed t = 2.36, p < 0.05).

DISCUSSION

Our data indicate that the degree of granulovascular degeneration in hippocampal neurones of mentally normal subjects shows a positive correlation with age (Figure 4), during the sixth to ninth decades of life. The magnitude of this increase in the number of affected cells per cubic millimetre of temporal cortex is, however, slight. Our sampling method is considerably more detailed and representative than Woodard's (15); his statement that granulovascular degeneration is not a function of age in the "senile" period appears incorrect in the light of our results. In brains from dementia of the Alzheimer disease type, we have found a markedly accentuated tendency for granulovascular change, in which the density of affected cells may be of the order of from 2 to 100 times that of age-matched controls.
FIG. 4. Number of hippocampal neurones with granulovacuolar degeneration per mm$^3$ cortex, at different ages. Best linear regression for controls (white circles) shows significant correlation (coefficient $r = 0.59$, $p < 0.01$). Adjusted Granulovacuolar Index of brains with Alzheimer's disease (black circles) exceeds that of controls at any age.

FIG. 5. Comparison of number of hippocampal neurones showing granulovacuolar change with number having neurofibrillary tangle formation per mm$^3$ cortex, for each brain. A striking positive linear correlation exists ($r = 0.91$, $p < 0.001$).
A good separation of the degree of affliction by Simchowicz's change can also be demonstrated in another manner, by calculating the numbers of affected neurones as a percentile of all pyramidal nerve cells in a designated area (Figure 6). None of the mentally normal subjects, but all of the demented in our study, have greater than 1% of neurones involved by the process. Our actual percentage figures are smaller in all instances than those of Tomlinson and Kitchener (13), whose "dividing-line" was at about 9%; however, they restricted the neurone-counting to the most severely affected areas (Rose's \( H_1 \) and \( H_2 \)), whereas we deemed it more representative to include all five fields, the ventrolateral quadrant of Woodard and part of the prosubiculum as well. Our percentile "scattergram" may show a "cleaner" separation of the two populations simply because the sampling was considerably more extensive than theirs.

As with neurofibrillary tangles (1), we found no predilection for granulovacuolar degeneration attributable to the patients' sex.

A highly significant positive correlation could be demonstrated in the entire series between the severity of neurofibrillary tangle formation in the same brains (1) and the severity of granulovacuolar change (Figure 5). This observation disagrees with that of Tomlinson et al. (11); in 25 non-demented old subjects, they could show no relationship between the two parameters'
intensity. We did note, however, that the correlation for our demented only ($r_{d0} = 0.81$, $p < 0.02$) was much better than that for the normal population only ($r_{dn0} = 0.45$, $p < 0.1$). (The much smaller actual values at the lower end of each axis (Figure 5) may, of course, account for the less impressive degree of correlation in the control cases.)

Finally, an important phenomenon of "posterior selectivity" has been found when the severity of granulovacuolar change is examined in both the front and in the back halves of each hippocampus. If the effect of normal ageing alone is considered, a comparison (from Table 3) of the mean granulovacuolar index for the anterior half of the younger controls, cases #1 to 9 (average age 58.4 years) with the mean for the anterior half of the older controls, cases #10 to 18 (average age 78.9 years) shows that there is in fact some difference between the severity anteriorly in those under age 70 (mean 12.35, S.D. ± 12.31) and in those age 70 or older (mean 24.91, S.D. ± 11.70); t = 2.29; 0.02 < p < 0.05. However, there is no significant difference between the index for the
posterior half of the younger controls (mean 11.44, S.D. ± 10.55) and the older controls (mean 23.20, S.D. ± 15.51); t = 1.88, 0.1 > p > 0.05. Alzheimer's disease, on the other hand, results in a roughly 12-fold worsening of the granulovacuolar density anteriorly, and an even more marked 22-fold worsening posteriorly. In other words, normal ageing is accompanied by a slightly greater granulovacuolar change in the anterior hippocampus, but no appreciable change in its posterior portion. In dementia, by contrast, while the severity of change is markedly increased throughout, many more of the additionally affected neurones in the "Alzheimerization" process make their appearance in the posterior half of the hippocampus than in the anterior half. This anatomicity localizing phenomenon of "posterior selectivity" in dementia was hinted at by Tomlinson and Kitchener (13), who re-examined four brains and concluded that when the overall affection is mild, involved cells may not be found in sections taken anterior to the level of the lateral geniculate body; and when severe, involved cells may be fewer in number in more anterior sections and more plentiful in posteriorly located pyramidal cells. They did not state whether dementia was diagnosed or excluded in the four cases studied.

A previous quantitative analysis of neurofibrillary tangle formation by Ball (1) has already indicated an identical predilection may be operating in the posterior hippocampus for the augmented tangle formation seen in Alzheimer's disease. The current study further supports this "predisposition", particularly since we have selected the same mid-point of the antero-posterior length for both analyses. Penfield and Mathieson (8), in suggesting that the hippocampus is essential in the recollection of experience for the automatic mechanism of perception and interpretation, have speculated that the "lines of permanently facilitated connection" between the hippocampal "keys of access" and the diencephalic memory "tape recorder" may be laid down early in life at the posterior end of the hippocampus and more anteriorly later in life. Penfield estimates the posterior portion is 22 mm. long. The average length of our hippocampi is 45 mm., so that our "posterior half" is probably the same segment to which he refers. The granulovacuolar change may well represent some type of autophagic abnormality (3, 10, 14). The predilection of this degenerative alteration in mild degree for the anterior hippocampus in older control brains, but in very severe degree for the posterior hippocampus in dementia (like that for neurofibrillary degeneration (1)) may thus help to explain the lost ability for recall of all experience which sets apart the devastating incapacity of Alzheimer's disease from the annoying forgetfulness for recent events seen in normal old age.

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