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Original Investigations

Topographic Distribution of Neurofibrillary Tangles and Granulovacuolar Degeneration in Hippocampal Cortex of Aging and Demented Patients. A Quantitative Study

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Summary. Topographic analysis was performed of the distribution of Alzheimer's neurofibrillary tangles and the granulovacuolar degeneration of Simchowicz in the hippocampal cortex of patients with Alzheimer's dementia and mentally normal aged controls. A semiautomated scanning stage microscope was linked potentiometrically to an XY pen recorder in order to plot cytoarchitectonic "scattergrams" from the sequentially screened hippocampal formations. The density of both lesions per cubic mm of pyramidal cortex was quantified by measuring the area of each of six "zones", using a digitizer and programmable calculator.

In elderly normal brains as well as those of Alzheimer's disease, the statistically most representative ranking order of predilection for *neurofibrillary tangles* (in decreasing severity) was: entorhinal cortex > subiculum > H_1 > end-plate > presubiculum > H_2. For *granulovacuolar degeneration* the best rank order was: subiculum > H_1 > H_2 > end-plate > entorhinal cortex > presubiculum. The notable similarities of both such orders of predilection to the well-recognized "selective vulnerability" of certain hippocampal neurones in clinical conditions of hypoxia, ischemia and epilepsy suggest some common, focally accentuated cytotoxic mechanism may underlie all these regional predispositions.

Key words: Aging – Dementia – Neurofibrillary tangles – Granulovacuolar degeneration – Hippocampus – Topography.

Although several studies have measured the degree of neurofibrillary tangle formation or of granulovacuolar degeneration of Simchowicz in both mentally normal aging populations and the brains of demented people (Woodard, 1962; Tomlinson et al., 1968, 1970; Corsellis, 1970; Dayan, 1970; McLardy, 1970; Tomlinson and Kitchener, 1972; Hooper and Vogel, 1976; Ball, 1976; Ball and Lo, 1977), the pertinent literature contains almost no observations about the precise topographic distribution of such histological changes within areas of known involvement. A notable exception is the report by Hirano and Zimmerman (1962) on the cytoarchitectonic localization of neurofibrillary tangles, based on examination of five most severely afflicted regions: Ammon's horn with the hippocampal gyrus, hypothalamus, midbrain, pontine tegmentum and medulla. In silver preparations of mesial temporal lobe both from 28 mentally normal patients over 70 years of age and from 97 neurologically ill patients (including cases of Alzheimer's disease; Parkinsonism-dementia complex and amyotrophic lateral sclerosis from Guam; postencephalitic Parkinson's disease; and sporadic ALS from New York), these authors observed that the pyramidal neurones in two regions – the glomerular formation of the hippocampal gyrus, and the Sommer sector (Rose's H_1 field) of Ammon's horn – were more noticeably affected by tangles than virtually any other foci. Despite schematic diagrams to illustrate this predilection, Hirano and Zimmerman offered no quantitative data to substantiate this impression. Goodman (1953) had previously made a similar observation in 23 cases of Alzheimer's disease, commenting that neurofibrillary tangle formation was most severe in the glomeruli substantiae reticulatae Arnoldi, and next most severe in the cornu Ammonis of the hippocampus. Using silver carbonate, he quantified the incidence of tangle formation in some cases by counting 100 nerve cells in all cortical layers, expressing the result as a percentage. This averaged 80% in the glomerular cortex of the presubiculum (6 cases), and 38% in Sommer's sector (7 cases studied), but ranged as high as 100% in the glomerular substance of some and 87% in the Sommer sector of some.

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A morphometric approach to granulovacuolar degeneration in Alzheimer's disease was attempted by Woodard (1962), who analyzed each hippocampus from a series of 200 consecutive, unselected autopsies on patients in a large state mental hospital. The percentage of neurones showing this change was calculated for an area Woodard called the "ventrolateral quadrant" of the hippocampus, which includes part of Rose's H_1 field and part of the adjacent prosubiculum. This zone was selected because Woodard noted the change was "usually more prevalent" there than in the rest of the hippocampus and parahippocampal cortex present in his single 7-μ coronal section through the mid-portion of the hippocampal formation. The author claimed that granulovacuolar degeneration was never focal among the hippocampal neurones except for this prevalence in the ventrolateral quadrant.

From the brains of 219 patients aged 14–98 years consecutively autopsied in a general hospital, Tomlinson and Kitchener (1972) also measured granulovacuolar change in one section of each hippocampus. Although the actual percentage of pyramidal neurones affected was reported only for those in Rose's H_1 and H_2 fields, the topographic distribution within the hippocampus was felt to be the same as that found in the brains of 30 old people shown by psychiatric testing not to have dementia and in 25 cases proven to be demented from Alzheimer's disease – areas H_1 and H_2 were most involved, whatever the severity of the change; while the other fields (H_3, H_4 and H_5) were affected if counts in H_1 or H_2 reached or exceeded 10% (as in only 12 of the 219 routine necropsies). "Small numbers" of cells in the subiculum were "occasionally" affected by granulovacuoles, usually when the change was severe in hippocampal neurones.

Jamada and Mehraein (1968) quantified the distribution of Alzheimer's neurofibrillary tangles in two von Braunmühl-stained sections from the limbic system of 48 demented patients. In their 22 cases of "Alzheimer's presenile" dementia, the rank order of severity of tangles (corrected to an area of 1 sq. mm) was H_1 > presubiculum > subiculum > H_3 and H_2. For their 28 cases of "senile dementia" the rank order was H_1 > presubiculum, subiculum and H_3 > H_2.

In the limbic system of 8 cases of Alzheimer's disease, Hooper and Vogel (1976) graded the tangle formation from 0 to 4+ and the granulovacuolar degeneration from 0 to 3+, in only five microscopic fields from each hippocampus. Neurofibrillary change was "generally severe" in the hippocampus proper; and in the entorhinal, parasubicular and presubicular cortex, the subiculum was "better preserved" between the "confluently involved" prosubiculum and the altered presubiculum. Granulovacuolar degeneration in the hippocampus was "most commonly found" in Sommer's sector (Rose's H_1 field). Corsellis (1970) had already made a similar observation on the predilection of tangles and granulovacuoles for H_1 and the adjacent medial subiculum, with much less involvement of H_2 and the end-plate or of the lateral subiculum.

From the brains of 85 patients with Alzheimer's disease, McLardy (1970) claimed that in the subiculum the "vast majority" showed "no neurofibrillary pathology of significance", whereas in the lateral entorhinal portion tangle formation was "usually at least as widespread and advanced" as in H_1. The medial entorhinal cortex was "as strikingly spared" as H_2 and the end-plate in the majority of cases. The details of that study remain unpublished.

During quantitative analyses in our laboratory of neurofibrillary tangle formation (Ball, 1976) and granulovacuolar degeneration (Ball and Lo, 1977) in serially sectioned hippocampi of mentally normal patients' brains and of some cases of Alzheimer's dementia, a tendency to regional predilection was also apparent. The present study was undertaken to quantify this impressive topographic phenomenon.

Materials and Methods

Four control brains were examined from patients aged 63–83 years (mean 72.8), from a large general hospital and a veterans' hospital, and judged neurologically normal and mentally intact from detailed clinical information (Table 1). Pertinent clinical and neuropathological data have already been reported (Ball, 1976; Ball and Lo, 1977; Cases Nos. 7, 10, 12 and 18 of earlier series). Also examined were the brains of eight patients dying with dementia of the Alzheimer disease type, aged 56–91 years (mean 74.6), in a provincial psychiatric institute and the veterans' hospital (Table 1). The neuropathological features of these latter included abundant senile plaques and neurofibrillary tangles in the cortex (Corsellis, 1976); decreased brain weight; generalized cortical atrophy; and the lack of arteriolosclerosis or significant infarction from appreciable cerebrovascular disease.

After the brainstem and cerebellum were removed from the formalin-fixed brains, each entire hippocampus (from a coronal level

Table 1

Case	Sex	Age (years)
Controls		
1	M	63
2	M	69
3	M	76
4	F	83
Alzheimer's disease		
5	F	56
6	F	67
7	F	71
8	M	77
9	F	77
10	M	78
11	M	80
12	F	91

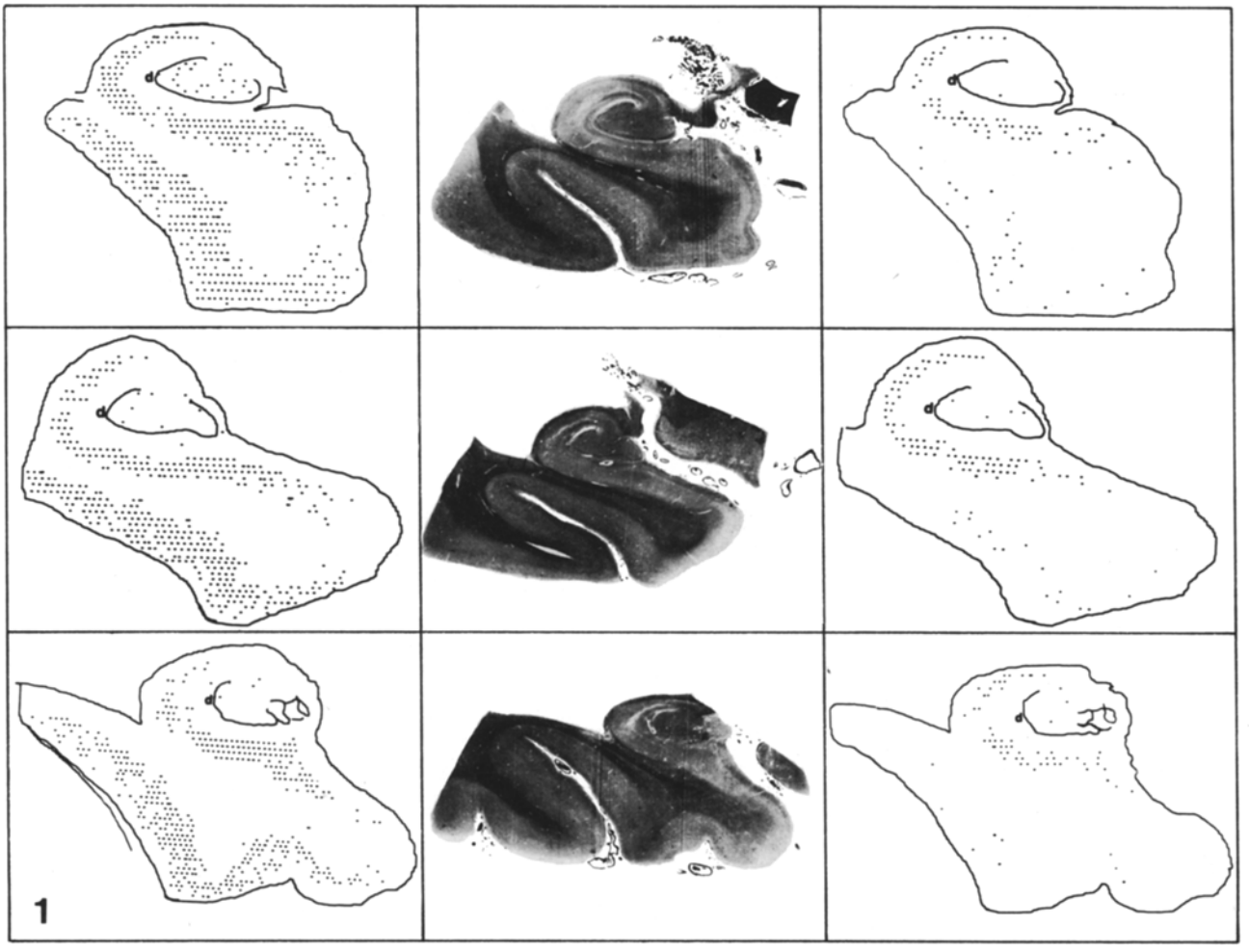

Fig. 1. Coronal microscopic sections of left hippocampus. H.- E./Luxol fast blue, × 1 (middle frames). Topographic "scattergrams" showing distribution of fields containing neurofibrillary tangles (left frames) and granulovacuolar degeneration (right frames); original mag. × 64. Upper rows, more anterior sections; middle rows, middle sections; lower rows, more posterior sections. Small "d", fascia dentata. (These examples from Case 9)

2 cm posterior to the rostral tip of each temporal lobe, to the plane of the callosal splenium) was excised, cut sequentially in coronal planes, and all the tissue blocks were serially sectioned in paraffin at 6 μ.

The middle section of each tissue block (Ball, 1976) was stained with hematoxylin-eosin-Luxol fast blue, and the very next serial section with Congo red-gallocyanin to permit easy visualization of neurofibrillary tangles under polarized light (Stokes and Trickey, 1973). The area to be screened included the hippocampal formation (Ammon's horn), the prosubiculum, the subiculum and presubiculum of the hippocampal gyrus, and the parahippocampal gyrus as far laterally as the collateral sulcus.

The complete area within the inked border outlined on each coverslip was then scanned sequentially with a Wild M 501 microscope employing a semi-automated mechanical stage, at 400 times magnification, with a square ocular (Weibel) graticule. Neurones with granulovacuoles were easily visualized in H and E-LFB stained sections; and with the addition of a second order red interference filter, neurofibrillary tangles in the Congo red stained sections exhibited brilliant congophilic birefringence and an anomalous yellow-green dichroism against the faint blue-orange background.

With the gears of the mechanical stage potentiometrically coupled to an X-Y Pen Recorder (Rikadenki BW-200), the recording pen produced a dot at the location of each visual field containing *one or more neurones* with a tangle or a granulovacuole (Fig. 1). Such fields were marked as "positive" irrespective of whether or not the affected cells' nucleus or nucleolus could be visualized. A total of 156,985 microscopic fields was examined, each representing 0.051 mm^2 in a section 5.85 μ in true thickness.

The outer borders of the hippocampus and the configuration of the fascia dentata were also drawn onto the "scattergrams" with the pen recorder by tracking these with the microscope (Fig. 1). These anatomical demarcations permitted easy comparison with the histological sections from which each "scattergram" had been made (Fig. 1, centre row).

In 12 cases, six coronal sections of the left hippocampus were thus surveyed – one from more anteriorly, one close to the middle, and one from a more posterior portion of the hippocampus for tangle formation (Fig. 1, left-hand row), and the three next serial sections respectively for granulovacuolar degeneration (Fig. 1, right-hand row). Four coronal sections from right hippocampi had been

analyzed in identical fashion, but as no differences were apparent in those additional 7,671 microscopic fields examined, the results of the left hippocampi only will be presented.

The total area of hippocampal cortex scanned was subdivided into six "zones" – the end-plate (Rose's fields H_3, H_4 and H_5); H_2; the lateral portion of H_1 (the Sommer sector), corresponding to CA_1 of Lorente de Nó's cornu Ammonis; the medial portion of H_1 (prosubiculum) and the contiguous subiculum; the presubiculum; and the entorhinal area, including the parasubiculum and the parahippocampal gyrus (Fig. 2). Boundaries between these 6 "zones" were drawn onto the "scattergrams", and the cortical area within each zone's borders was measured (in square mm) with a digitizer linked to a Hewlett-Packard calculator. Since the magnification from the actual glass slides was known (X64), as was the true thickness of the paraffin sections, it was possible to calculate the *number of positive fields per cubic mm of* (paraffin embedded) *tissue* ... i.e., an "*Adjusted Field Index*" ... for each "zone" (Tables 2 and 3). The Adjusted Field Indices of the three slides in each case were averaged to derive a *Mean* Adjusted Field Index for each "zone" (Tables 2 and 3).

The relative density of positive *fields* had been deemed a very reasonable reflection of the relative density of the actual neuronal changes, since (although positive fields contained anywhere from one to fourteen tangle-bearing neurones) the *mean* number of tangle-bearing neurones in any one field showed little variation, ranging in the ten cases reviewed for this purpose only from 1.15 to 2.81 tangled neurones per field (Table 4); and in the eight Alzheimer cases varying from only 1.10 to 1.69 neurones with granulovacuolar degeneration per field (Table 5). Hence a rank order number could be assigned to each Mean Adjusted Field Index (see numbers in parentheses, Tables 2 and 3), with "1" representing the largest Field Index of each case and "6" the smallest.

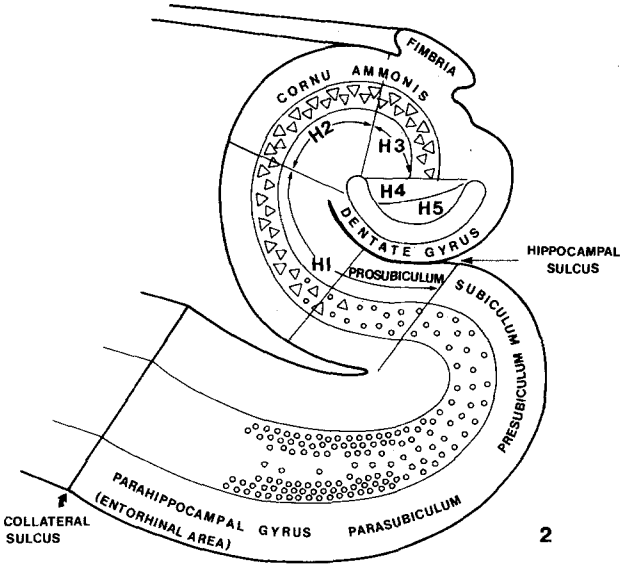

Fig. 2. Micro-anatomy of hippocampal cortex, showing the six "zones" surveyed: end-plate (Rose's H_3, H_4 and H_5 fields); H_2; lateral part of H_1 (Sommer sector); medial H_1 and subiculum; presubiculum; entorhinal area

Results

The *actual* ranking orders of the Mean Adjusted Field Indices for neurofibrillary tangles (Table 2, numbers in parentheses) were compared using Spearman's rank correlation test against each possible order of permutation for each of the six "zones". The overall rank order having the best statistically significant correlation was "Entorhin. > Subic. > H_1 > End-plate > Presubic. > H_2" (in descending order of density of tangle fields). For this permutation the mean of the six coefficients of correlation r_s was 0.910; and in all six instances $P < 0.01$. (This order might also have been predicted from the rank order of magnitude of the six *means* of all twelve rank numbers in each "zone".) In other words, in each "zone" the likelihood that all twelve actual ranking numbers would have so closely approximated the best rank number of each "zone" merely by chance is less than 1 in 100.

For granulovacuolar degeneration, the rank order of Mean Field Indices with the best statistically significant correlation was somewhat different-"Subic. > H_1

Table 2. Mean adjusted field index, neurofibrillary tangles (numbers in parentheses indicate rank order within each case)

Case	Zone					
	End-plate	H_2	H_1	Subic.	Presubic.	Entorhin.
1	26.88 (2)	4.11 (6)	14.99 (5)	20.53 (4)	21.15 (3)	199.23 (1)
2	8.08 (5)	0 (6)	12.69 (4)	14.08 (3)	61.60 (2)	70.40 (1)
3	15.71 (4)	11.12 (5)	57.60 (1)	28.35 (3)	9.68 (6)	28.56 (2)
4	8.88 (6)	10.27 (5)	36.77 (2)	33.71 (3)	27.25 (4)	58.05 (1)
5	73.68 (6)	83.52 (5)	259.95 (3)	635.57 (1)	163.23 (4)	305.84 (2)
6	192.59 (4)	58.59 (6)	277.47 (3)	393.39 (2)	99.00 (5)	458.19 (1)
7	353.92 (2)	115.41 (4)	63.23 (6)	98.29 (5)	331.25 (3)	434.37 (1)
8	639.79 (3)	472.91 (5)	873.65 (2)	1001.57 (1)	290.45 (6)	630.24 (4)
9	410.16 (4)	192.77 (6)	926.16 (3)	1420.48 (2)	346.99 (5)	1493.76 (1)
10	59.52 (6)	63.17 (5)	100.00 (4)	292.29 (1)	143.04 (3)	163.95 (2)
11	249.71 (5)	472.21 (3)	820.67 (2)	878.72 (1)	108.48 (6)	430.51 (4)
12	265.96 (5)	620.91 (3)	1177.01 (1)	939.31 (2)	189.73 (6)	442.08 (4)

Table 3. Mean adjusted field index, granulovacuolar degeneration (numbers in parentheses indicate rank order within each case)

Case	Zone					
	End-plate	H_2	H_1	Subic.	Presubic.	Entorhin.
1	19.68 (3)	7.01 (5)	24.99 (2)	8.88 (4)	0 (6)	26.59 (1)
2	14.03 (3)	8.88 (4)	20.43 (2)	22.69 (1)	0 (6)	5.20 (5)
3	0 (6)	30.48 (2)	25.97 (3)	38.21 (1)	2.77 (5)	14.45 (4)
4	39.49 (4)	7.63 (6)	78.80 (1)	51.41 (3)	14.61 (5)	58.59 (2)
5	143.81 (4)	333.25 (3)	627.81 (2)	637.81 (1)	53.87 (6)	93.31 (5)
6	103.31 (4)	175.76 (3)	352.40 (2)	364.48 (1)	0 (6)	96.37 (5)
7	77.15 (3)	58.61 (4)	105.97 (1)	81.41 (2)	24.56 (6)	57.49 (5)
8	314.93 (3)	177.76 (4)	625.25 (1)	608.93 (2)	9.57 (6)	40.13 (5)
9	78.11 (5)	255.36 (3)	576.51 (1)	462.32 (2)	17.15 (6)	103.28 (4)
10	3.87 (5)	4.37 (4)	0 (6)	56.77 (1)	7.84 (3)	18.13 (2)
11	102.61 (4)	326.67 (1)	176.53 (2)	130.13 (3)	42.96 (5)	35.95 (6)
12	103.08 (4)	147.52 (3)	387.65 (1)	340.96 (2)	6.83 (6)	12.08 (5)

Table 4

Case	Number of positive fields	Number of tangled neurones	Mean number of tangled neurones per field
			(± 1 S.D.)
3	27	31	1.15 (± 0.36)
4	119	170	1.43 (± 0.88)
5	311	657	2.11 (± 1.83)
6.	597	1180	1.98 (± 1.47)
7	175	276	1.58 (± 0.99)
8	634	1315	2.07 (± 1.57)
9	974	2740	2.81 (± 2.16)
10	165	320	1.94 (± 1.26)
11	144	279	1.94 (± 1.45)
12	315	716	2.27 (± 1.53)

Table 5

Case	Number of positive fields	Number of neurones with granulovacuoles	Mean number of neurones with granulovacuoles per field
			(± 1 S.D.)
5	73	120	1.64 (± 0.95)
6	48	60	1.25 (± 0.48)
7	10	11	1.10 (± 0.32)
8	95	131	1.38 (± 0.64)
9	32	54	1.69 (± 0.93)
10	10	11	1.10 (± 0.32)
11	13	15	1.15 (± 0.38)
12	41	57	1.39 (± 0.80)

> H_2 > End-plate > Entorhin. > Presubic.". For this permutation the mean of the six correlation coefficients r_s was even higher, 0.929; and again in all six "zones" $P < 0.01$.

Comparison of these two best ranking orders shows that while the entorhinal area most often exhibits the heaviest density of fields positive for neurofibrillary tangles, the same region is much less preferentially involved by granulovacuolar degeneration. This difference is in accord with the comment by Hirano and Zimmermann (1962) and with Goodman's finding (1953) that tangle formation is worst within the glomerular formations of Arnold, since many of these clusters of neurones are located in the entorhinal cortex of the parahippocampal gyrus; and with Woodard's claim (1962) that granulovacuolar change is considerably less prevalent in the parahippocampal cortex.

Our ranking orders also indicate that the neurones of both H_1 and of the adjacent subiculum are virtually always heavily affected both by tangles, as Hirano and Zimmerman (1962), Hooper and Vogel (1976) and Goodman (1953) remarked, and by granulovacuoles, as indicated by Tomlinson and Kitchener (1972) and Corsellis (1970). In contrast, nerve cells both in H_2 and in the end-plate (H_3, H_4 and H_5) are less frequently affected by these same two processes again in agreement with the suggestions of earlier investigators (Hirano and Zimmerman, 1962; Corsellis, 1970; McLardy, 1970; Tomlinson and Kitchener, 1972; Hooper and Vogel, 1976). Morel and Wildi (1955) had claimed that both the Sommer sector (H_1) and equally the "resistant zone" of H_2 were the most vulnerable areas affected by Alzheimer tangles. However, their only *quantitative* data actually pertained to the numbers of microscopic foci of ischaemic glial scars, wherein of 233 lesions in 128 brains both of older control patients and of psychiatric cases (including dements), the subiculum with H_1 was most heavily involved (102 lesions), less so the H_2 zone (95 lesions), still less the end-plate (18), and rarely the presubiculum (6).

McLardy's observation (1970) of a strikingly spared "medial entorhinal cortex" and the "most resistance"

Table 6. Mean value of the mean adjusted field indices

	Neurofibrillary tangles					
	End-plate	H_2	H_1	Subic.	Presubic.	Entorhin.
Controls	14.89	6.38	27.34	24.17	29.92	89.06
Alzheimer's	280.66	259.94	562.27	707.45	209.02	544.87
increment	×18.8	×40.7	×20.6	×29.3	×7.0	×6.0
	Granulovacuolar degeneration					
Controls	18.30	13.50	37.55	30.30	4.35	26.21
Alzheimer's	115.86	184.91	356.51	335.35	20.35	57.09
increment	×6.3	×13.7	×9.5	×11.1	×4.7	×2.2

to neurofibrillary tangles seen in area HD of Morel and Wildi (1955) may also be in accord with our ranking numbers for the presubiculum (probably the same area), which has comparatively little involvement by either process.

While these best ranking orders hold true for tangle and granulovacuole formation both in control brains and in cases of Alzheimer's disease, the *magnitude* of such involvement, as the "scattergrams" themselves indicated, is obviously different. Table 6 shows the *mean* of the Mean Adjusted Field Indices (from Tables 2 and 3) for the four controls and the eight Alzheimer patients, in each of the six "zones", for neurofibrillary tangles and granulovacuolar degeneration. Although the values are of course always higher in the brains with Alzheimer's disease than in the age-matched control brains, the increment attributable to Alzheimer's disease varies for tangles from a 6-fold increase in the entorhinal area to a more than 40-fold increase in H_2; and for granulovacuoles from a 2-fold increase in the entorhinal area to a nearly 14-fold increase in H_2. Interestingly, *for both parameters*, the entorhinal indices increase by the smallest incremental factor, those of the presubiculum by the next largest, the end-plate by the next, H_1 the next, the subiculum by the next (the second largest), and H_2 by the largest incremental factor (Table 6).

These data suggest that while each of the six hippocampal "zones" has a different, individual susceptibility to the histological changes in Alzheimer's disease not attributable merely to the patients' age, the "zones" maintain a similar *relative* susceptibility to the *degree* of augmented affliction by these two lesions.

Discussion

The reason for such striking topographic predilections in tangle-formation and granulovacuolar degeneration in the hippocampal cortex of aged or demented people's brains is not clear. However, the notable similarities in topography between these two very different neuronal alterations – the preferential affliction of Rose's H_1 field both in the Sommer sector of its lateral extent and in its medial portion with contiguous subiculum; the marked sparing of the presubicular zone; or the relative sparing of H_2 and of the end-plate – make it possible that a common "localizing" pathogenetic mechanism is at work in both lesions.

An obvious analogy is with the phenomenon of "selective vulnerability" of hippocampal neurons to the effects of hypoxia (Brierley, 1976) or epilepsy (Corsellis and Meldrum, 1976). In this phenomenon, H_2, the so-called 'resistant zone', is less vulnerable, whereas H_1 and the end-folium (H_3, H_4 and H_5) are the most vulnerable. The entorhinal cortex is frequently affected when H_1 is involved. The fascia dentata (dentate gyrus) is the least vulnerable component of all.

Certainly our best ranking orders suggest that H_2 is likewise less predisposed to both tangles and granulovacuoles; that H_1 is very vulnerable (along with the adjacent subiculum); that the entorhinal cortex is often involved, at least by neurofibrillary tangles; and that the dentate fascia is the least vulnerable, as neither tangles nor granulovacuoles have ever been noted in its neurones.

While a similar topographic pattern appears to hold for control brains as well, comparison of the *quantitative* densities of positive fields (Table 6) indicates that H_2, the 'resistant zone', undergoes the largest degree of increment of any region when the process of Alzheimer's dementia is added to that of aging alone – augmenting its affliction by a factor of 40.7 for tangles and 13.7 for granulovacuoles. These latter data have not, of course, been corrected for possible differences in neuronal packing densities within the six "zones"; the same reservation must be noted regarding our ranking order tests. However, a "zone" with far fewer nerve cells per unit volume than its neighbours might *not* show far fewer tangles or granulovacuoles per unit volume in any case. In fact, in an earlier study (Ball, 1977) we found (at least in the posterior hippocampus) that these lesions in Alzheimer's disease are proportio-

nately more severe compared to controls than would have been predicted from the relative differences in nerve cell populations in the same slides.

Two major hypotheses have been popularized to explain the topographic selectivity of hypoxic cortical lesions (Brierley, 1976): the anatomical 'vascular theory' originally advanced by Spielmeyer (1925), and the local physicochemical concept of 'pathoclisis' invoked by the Vogts (C. and O. Vogt, 1937). Neither hypothesis can account completely for the phenomenon. Certain facets of the 'vascular theory' might be relevant to the very similar selective topography of tangles and granulovacuoles we have shown in the hippocampi of patients with Alzheimer's disease. The terminal hippocampal arterioles, rather than branching dichotomously as most other parts of the cerebral arteriolar tree do, divide instead into a system of arcades arranged in a *rake*-like pattern. Scharrer (1940) has suggested that any drop in blood-pressure exerts a far more profound hydrodynamic effect upon the terminal vascular bed of this rake-like configuration, than occurs in dichotomously branching vessels where the fall in intravascular pressure is distributed equally. If Coceani and Gloor (1966) are correct in stating that the hippocampus definitely lies on the watershed between the carotid and the vertebro-basilar territories, even transient episodes of cerebrovascular hypotension might jeopardize the effective perfusion-pressure in these arteriolar arcades. Furthermore, Nilges' injection studies (Nilges, 1944) in the rhesus monkey have shown that along the course of the septal hippocampal branches of the posterior cerebral artery, these anastomotic arcades are confined to the region nearest the medial end of the hippocampal sulcus – i.e., closest to the end-plate, to H_1 and to the subiculum; whereas none is found among the septal arteries in their more peripheral extent – i.e., closest to H_2. Finally, these rake-like arcades are much more prominent in the lower, posterior end of the cornu Ammonis, whereas its upper or anterior tip is supplied by independent vessels coming directly off the posterior cerebral's larger hippocampal branch. If applicable to man, this last observation would support our own finding (Ball, 1977) that the posterior half of the hippocampal formation in Alzheimer's disease is more prone to develop increased numbers of both neurofibrillary tangles and granulovacuoles than its anterior half.

It is not known why focal cortical regions of underperfusion would lead to neurofibrillary or to granulovacuolar degeneration. No good experimental models for inducing granulovacuoles in the central nervous system are available. Neuronal hypoxia per se is not a widely favoured experimental mechanism for inducing neurofibrillary tangles, although in tissue culture anoxic motor neurons from chick embryo spinal cord have apparently developed neurofibrillary tangles (Kim, 1971). If focal oligemia disturbed the permeability of the blood-brain barrier, any metalloprotein carrying an appropriately neurotoxic trace metal might preferentially enter the affected region. Acute tetraethyl lead intoxication in rabbits has produced classical neurofibrillary tangles predominantly in the hippocampus and especially in the Sommer sector (Niklowitz, 1975). Liss et al. (1976) have argued from human cases of carbon monoxide poisoning, ischemic infarction and post-irradiation damage that lowering of the blood-brain barrier's threshold to aluminium predisposes to tangle formation. The notion of a tangle-inducing factor entering from the vascular compartment has also been entertained by Scheibel et al. (1976), who note in a study of nine aged patients' hippocampi that 'spindle bodies' on adjacent apical shafts of entorhinal pyramidal neurones – possibly the counterpart by the Golgi impregnation method of neurofibrillary tangles – appear with intriguing regularity at approximately the same intracortical (subpial) depth. These authors propose this may be related to the course of individual vessels in the cortical microcirculation. Such indirect evidence tempts us to ask whether some angioarchitectonic peculiarity can account for the "specific vulnerability" for tangles and perhaps also granulovacuoles which the hippocampus both in aging and demented patients has demonstrated.

Alternatively, a chemical specificity of particular "chains" of neurones linked by a common neurotransmitter might underlie these regional hippocampal variations. Selective experimental destruction of cell groups by adrenergic antagonists (Gallagher et al., 1977) and glutamate agonists (Herndon and Coyle, 1977) has recently been postulated. If the memory functions of the limbic system prove to be dependent upon cholinergic synapses (Drachman, 1977), and if a cortical deficiency of choline acetyltransferase in Alzheimer's disease (Bowen et al., 1976; Davies and Maloney, 1976; Perry et al., 1977) reflects a special weakness of one neurochemical system, the sparing of certain perikarya in the hippocampus from tangles and granulovacuoles might mean that the neurotransmitter for that afferent pathway is resistant, whereas a different neurotransmitter utilized by another set of afferent fibres (perhaps choline-dependent) is especially at risk.

Whether vascular in nature, neurochemical or both, some focally accentuated cytotoxic mechanism apparently affects certain hippocampal cells in Alzheimer's disease far more than their immediate neuronal neighbours.

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