they were orientation specific (Fig. 1D). Thus, the maximum threshold elevation occurred when the test and background stimuli were at the same orientation; when the test and background gratings were 45° apart, no masking was evident. Similar interactions occurred when the visual display was limited to restricted retinal regions, including the suppression scotoma. The binocular interactions were also contrast specific. In normal observers, when the test and background were similar in spatial frequency and orientation, a background contrast below threshold lowered the threshold for discrimination of the test grating. Subthreshold summation for dichoptically presented gratings has been described in normal observers by Blake and Levinson (*11*). When the contrast of the background exceeds threshold, however, it acts as a mask, elevating threshold for discrimination of the test grating (Fig. 1E). The increase in threshold has a slope of approximately −1 when plotted against the background contrast (on log-log coordinates). While the masking effects of the background above threshold were similar for these two observers, the observers with abnormal binocular vision failed to show subthreshold summation. The experiment was repeated for a wide range of test and background spatial frequencies from 0.12 to 8 cycle/deg without our finding any evidence for subthreshold summation in the subjects with abnormal visual experience. Thus, although these observers with abnormal visual experience showed inhibitory binocular interactions similar to those seen in normal vision, they failed to show either binocular summation at threshold or subthreshold summation.

The finding of spatially tuned binocular interactions in observers with abnormal binocular vision is surprising even though evidence for binocular interactions in the cortical evoked potentials of humans with strabismic amblyopia that depend on the spatial frequency and contrast of the stimulus has recently been reported (*12*). These findings suggest that in humans deprived of normal visual experience early in life, some binocular neurons escape the profound effects reported in physiological studies of animals reared with induced strabismus, anisometropia, or occlusion. In light of single-unit studies in animals deprived of normal binocular vision, however, the robustness and specificity of the binocular interactions found for humans with strabismus and anisometropia was unexpected. Whereas the failure of binocular summation at threshold and subthreshold summation suggests that it is the excitatory connections which are disrupted, the suprathreshold masking data suggest that the interactions may be inhibitory in nature (interactions not easily seen in single unit recordings) or that binocular interactions in humans deprived of normal visual experience have an elevated threshold and are seen only when the stimuli presented to at least one eye have sufficient suprathreshold contrast (*13*).

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8. Conventional electronic techniques [F. Campbell and D. Green, *J. Physiol. (London)* **181**, 576 (1965)] were used to produce the sinusoidal grating patterns. Each screen was surrounded by a mask similar in brightness and color to the screen, and these provided a fusion lock. High-contrast vernier lines on the two masks ensured that peripheral suppression did not occur during the experiments and that the stimuli were presented to corresponding points in the two eyes. Cover testing was also used to obtain accurate binocular alignment. The experimental paradigm is a modification of the forced-choice temporal discrimination procedure of D. Tolhurst and L. Barfield [*Vision Res.* **18**, 951 (1978)]. The contrast of the test grating was adjusted with a logarithmic attenuator in successively smaller steps from above or below threshold until a .05 log unit change in stimulus contrast resulted in a reversal of the observers' forced-choice response. Each threshold is the mean of at least five such reversals.
9. We tested three observers with normal binocular vision and three with abnormal binocular vision. All of the abnormal observers were stereoblind. Stereopsis was assessed with the random dot E, the American Optical Vectograph, and the Titmus Stereofly. Although the relationship between interocular transfer of the threshold elevation aftereffect and stereopsis is not clear [R. Hess, *Perception* **7**, 201 (1978)], all observers failed to exhibit any significant interocular transfer of the threshold elevation aftereffect and showed an absence of binocular summation at threshold. For the abnormal observers, the following relevant visual characteristics are provided: T.T. is an anisometropic amblyope (amblyopia due to unequal refractive error) with 20/15 vision in the right eye and 20/80 in the left. M.M. is both strabismic (left eye esotropic) and anisometropic with 20/15 vision in the right eye and 20/200 in the left. For both of these observers, the visual anomaly was noted early in life, but was untreated. R.L. was a congenital esotrope. Surgery was performed at age 18 months. He now demonstrates a 4^{Δ} alternating esotropia and has equal vision in each eye (20/15). All three observers have central fixation in each eye, and only R.L. demonstrates anomalous correspondence. All observers were optically corrected during these experiments.
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14. Supported by grant R01 EY 01728, R01 EY 01139, and K 07 EY 000052 from the National Eye Institute.

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Dendritic Growth in the Aged Human Brain and Failure of Growth in Senile Dementia

Abstract. *Golgi-stained dendrites of single randomly chosen layer-II pyramidal neurons in the human parahippocampal gyrus were quantified with a computer-microscope system. In nondemented aged cases (average age, 79.6 years), dendritic trees were more extensive than in adult cases (average age, 51.2), with most of the difference resulting from increases in the number and average length of terminal segments of the dendritic tree. These results provide morphological evidence for plasticity in the mature and aged human brain. In senile dementia (average age, 76.0), dendritic trees were less extensive than in adult brains, largely because their terminal segments were fewer and shorter. Cells with shrunken dendritic trees were found in all brains. These data suggest a model of aging in the central nervous system in which one population of neurons dies and regresses and the other survives and grows. The latter appears to be the dominant population in aging without dementia.*

Aging and senile dementia (SD) (*1*) in the central nervous system have been characterized as processes of deterioration, with both death of neurons in most regions (*2*) and regression of dendrites of the cells that have not yet died (*3*). In cerebral cortex of human aged and senile dementia patients, this regression reportedly progresses in some cells until only stubs of dentrites remain (*4*). We present evidence that, although this regression of dendrites can be seen in some cells,

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the dendrites of other cells are growing. Growth of dendrites is the dominant observation in the cell type we examined.

We collected at autopsy samples of parahippocampal gyrus from 15 human brains. Postmortem time, which ranged from 2.25 to 21.50 hours, was not significantly related to total dendritic length (linear regression analysis, $P > .30$). Cases represented three groups (*5*, *6*). Five were neurologically normal adults (mean age, 51.2 years; range 44 to 55 years), five were normal aged adults (mean age, 79.6 years; range 68 to 92 years), and five were SD cases (mean age, 76.0 years; range 70 to 81 years). Tissue was processed according to the Golgi-Cox method of van der Loos (*7*). Sections were cut at 200 μm. Slides were coded so that during data gathering it was not known which slides came from the same block of tissue or which slides came from which brain. Dendritic trees of single layer-II pyramidal neurons were quantified in three dimensions through the use of a semiautomatic computer-microscope dendrite tracking and analysis system (*8*). Apical and basal portions of the dendritic plexus were examined separately. Cells to be tracked were chosen randomly from the population of impregnated neurons whose somata lay near the center of the thickness of the section and whose processes were not obscured by other elements in the section (*9*). Fifteen cells were tracked from each brain for a total of 225 cells. All tracking was done with an oil immersion lens (×100) with a long working distance.

Our analysis was a three-dimensional analog of Sholl's (*10*) concentric circles analysis. The computer constructed concentric spheres at 10-μm intervals centered on the cell body. The computer then counted dendritic intersections with each sphere, which provided a measure of dendritic density as a function of distance from the cell body. Since the basal and apical trees were treated separately, the spheres became essentially hemispheres. Both figures show the data from the apical portion of the dendritic plexus. Neurons from the aged brain had more extensive apical dendritic trees than those found in either adult or SD brains. The comparisons between pairs of these curves were significant according to the sign test (aged versus adult and versus SD, $P < .001$; adult versus SD, $P < .025$). The differences in the midrange of distances from the cell body ranged as high as 98 percent (aged > SD).

Comparing the three groups on the basis of length of the average dendritic segment (total dendritic length divided by number of segments) revealed significant differences (Kruskal-Wallis one-way analysis of variance, $P < .02$). The aged group had longer dendrites than either the adult or the SD group (Mann-Whitney U test, $P < .01$). The adult and SD groups were not significantly different.

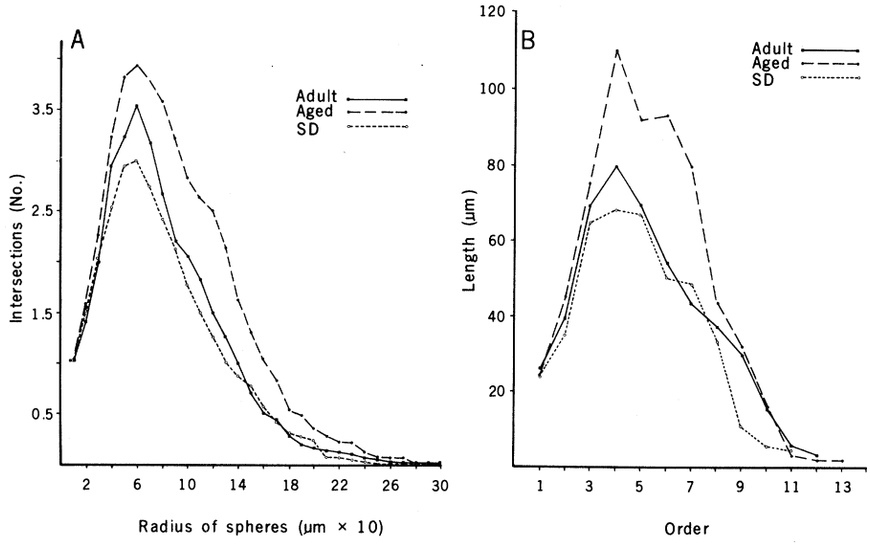

Fig. 1. (A) Number of dendritic (apical) intersections per cell with concentric spheres centered around the cell body and spaced 10 μm apart. Points represent averages of the 75 cells in each group. (B) Dendritic length per apical tree as a function of centrifugal orders. Points are means of 75 cells in each group.

Figure 1B represents the dendritic length for the average cell of each group expressed as a function of centrifugal orders (the first order begins at the cell body and branches to give rise to second order, which branches to give rise to third order, and so forth). The profile for the aged group is significantly higher than that of the adult and SD groups (sign test, $P < .03$ and $P < .01$, respectively) with differences in the fourth through seventh orders between 25 percent (aged-adult fifth order) and 46 percent (aged-SD sixth order). The curve for SD lies somewhat below that of the adult (sign test, $P < .01$).

In a centripetal ordering the dendritic segments that ended without giving rise to further segments were classified as terminal segments, and those that gave rise to these terminal segments were classified as next-to-terminal segments. All remaining segments were grouped together. Figure 2 shows that the increase in dendritic length in aged brains and the decrease in dendritic length in SD brains demonstrated by centrifugal ordering (Fig. 1B) are largely attributable to increases or decreases in the total dendritic length of the terminal segments of the dendritic trees (*11*). Next-to-terminal segments contributed less to these differences. The remaining segments, which constituted a very small proportion of the dendritic tree, contributed still less to the differences among groups (Fig. 2). The increases in length of terminal segments seen in apical dendritic trees of aged brains and the decreases seen in SD brains seem to be results of differences in both the number of dendritic segments and lengths of individual segments (Kruskal-Wallis one-way analysis of variance, $P < .05$). In aging, therefore, the terminal apical dendrites both branch and elongate. This process does not appear to take place in SD. Both qualitative observation and the similarity of patterns of quantitative data from all three groups suggest that the growing and branching in aged brains represent a continuation of normal growth rather than an abnormal pattern of dendritic growth as reported elsewhere (*12*).

Changes in the basilar dendritic trees of these same cells were far less pronounced than those seen in apical trees. Differences between groups generally failed to reach significance ($\alpha = .05$). This differential between apical and basal dendritic trees suggests that local factors relating to portions of the dendritic tree play an important role in dendritic responses to aging.

Linear regression analysis of the data from the adult and normal aged brains (*13*) indicates that the net length of individual terminal segments of the average apical tree will increase by 0.21 μm per year over the span we studied (44 to 92 years of age) ($P < .05$). Since there are

an average of 9.49 terminal segments per cell in the ten cases in these two groups, this amounts to a net increase in total length of terminal segments of 1.99 μm per cell per year (*14*). Since no directly comparable quantitative data exist for the net rate of dendritic growth during early development, the relationship of the net rates of growth in normal aging to the rates to be expected during the first few years of life (*15*) is not clear. Qualitative judgment suggests that dendritic growth is more rapid during early than during later development.

These data show that in normal human aging, the dendritic tree continues to grow. Senile dementia represents an apparent failure of this growth and perhaps even a regression of the dendritic tree. This demonstration of continued growth of dendrites in normal aged human brain is at variance with earlier descriptions (*4*) of regressed dendritic trees. It is consistent with a small number of quantitative reports showing dendritic growth in the central nervous system of adult and aged rodents (*16*) and is (to our knowledge) the first morphological report of plasticity in the mature and aged human brain. The differences between our results and earlier human data are probably a consequence of differences in technique and interpretation of data (*17*). Although we saw the grossly atrophic dendritic trees described by Scheibel *et al.* (*4*) in all our samples (as a rule within a field of cells with normal appearance), we were not able to distinguish adult, aged, and SD cases on this qualitative basis. Even though such grossly atrophied cells can easily catch an observer's attention and undoubtedly represent a real phenomenon, they apparently do not adequately represent the population of neurons under consideration. When quantitative methods are applied to neurons sampled blindly and randomly (*18*), the conclusion is inescapable that growth of dendrites prevails over regressive dendritic changes in at least one region of the aging human brain.

Thus, currently available data suggest a model in which there are two populations of neurons in normal aging cortex, one a group of dying neurons with shrinking dendritic trees, the other a group of surviving neurons with expanding dendritic trees. In normal aging, the latter population prevails. With the passage of time there must be a shift of individual neurons from the surviving population to the dying population. The rate at which this shift takes place is probably a function of genetic and nongenetic or extrinsic (toxicological, behavioral, infectious) factors. We do not yet know either the age at which this process starts [if not during early development (*19*)] or the age at which the surviving, growing neurons no longer predominate. Nor is it known whether there is in normal aging a limit to the potential for the growth of healthy neurons.

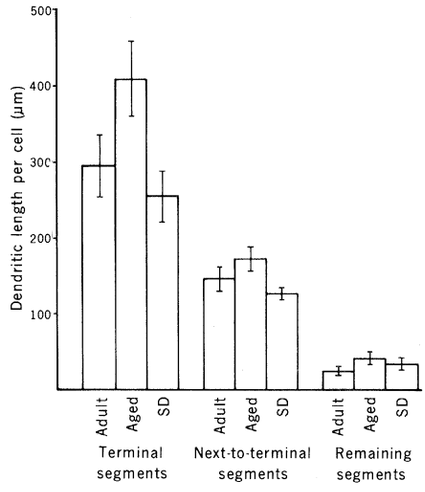

Fig. 2. Centripetal ordering. Dendritic length at the terminal, next-to-terminal, and remaining segments. Error bars represent standard errors of the means based on five brains in each group.

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References and Notes

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5. Assignment of specimens to these groups was on the basis of age, clinical information obtained from consultations with physicians and nurses, and hospital charts. Neuropathological confirmation was based on the relative abundance of senile plaques and neurons affected by neurofibrillary degeneration. Sexes were approximately evenly represented in the three groups.
6. Causes of death were cardiovascular-pulmonary (11 cases) or neoplastic diseases without cerebral involvement (4 cases). There appeared to be no relationship between final cause of death, duration of the agonal period, and dendritic measures. Mean times (in hours) from death to fixation of tissue were: adult, 14.9; aged, 10.5; and SD, 12.6.
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9. Dendrite ends cut by sectioning were not a criterion in the choice of cells since this could bias the sample toward small dendritic trees. Cut terminal dendrites, which were included in the sample, constituted 6 percent of all terminal dendrites.
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11. These results imply that a large proportion of the (centrifugal) fourth- through seventh-order dendrites were terminal dendrites and that higher-order terminal segments did not show group differences, because of either small sample size or a real biological phenomenon.
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13. These two groups were chosen since they represent the normal continuum of aging.
14. This may be an underestimate of the rate of growth of cells with expanding dendritic trees, since cells with regressing dendrites are also part of the sample on which this analysis was based. These two groups of cells were not distinguished in this analysis because the absence of a clear breakpoint in distribution of dendritic variables made it impossible to place specific cells into one or the other group.
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17. It is necessary to consider the possibility that our data resulted from a differential loss of smaller layer-II pyramidal neurons of the parahippocampal gyrus with aging rather than from an actual growth of dendrites with age. Evidence consistent with the hypothesis that the data were not a function of differential loss of small cells was obtained from blind measurement of cell-body sizes in the Golgi-stained tissue used for dendrite quantification. These measurements showed no difference in mean cell body size between the aged (182 μm^2) and the adult (204 μm^2) groups (Mann-Whitney U test, $P > .05$). Cell body sizes were measured with an image quantification system (Zeiss MOP III). Measurements were taken from Golgi-stained material rather than from Nissl-stained sections to eliminate any possibility of an interaction between differential Golgi staining and cell sizes or age.
18. To ensure a representative sample of dendritic extent, it is important that sections be thick enough to contain almost all of the dendritic tree of larger cells or that cut dendrites be followed from section to section. Otherwise, if there are both regressive and progressive changes, the regressive ones would be overestimated and the progressive ones underestimated. This may account for the differences between our results and those of previous quantitative studies of aging in rodent cortex (*3*). In those studies, 125-μm-thick sections were used and the criteria for selection of cells for analysis included whether dendritic ends were cut in sectioning. In contrast, we examined sections that were 60 percent thicker with a special oil-immersion objective, and we examined cut dendritic segments during data analysis rather than during sample selection. Fewer than 6 percent of the terminal segments in our sample were cut in sectioning, and the number and length of cut segments did not differ among the three study groups (Kruskal-Wallis one-way analysis of variance, $P > .3$).
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20. We thank J. Romano for his assistance with clinical aspects of the study, L. Lapham for helping with the pathological observations, and M. Moore for writing the computer programs used to analyze the data. A preliminary report of these data was presented at the 1979 meetings of the American Association of Anatomists. Supported by grant AG1121 from the National Institute on Aging.

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