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COMMENTARY

PREVALENCE, INCIDENCE AND DURATION OF BRAAK'S STAGES IN THE GENERAL POPULATION: CAN WE KNOW?

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THE article by Heiko and Eva Braak raises a number of fascinating questions. It provides a large amount of data in a concise form; the authors wisely chose to present facts rather than interpretation. Having the facts at our disposal, and with the indulgence of the authors and readers, we have chosen to propose some interpretations.

The authors studied 2,661 postmortem individuals, who were grouped by classes of age. The prevalence of neurofibrillary and amyloid changes was determined in each class. The prevalence of neurofibrillary pathology in the young age group was found to be higher than usually thought. Amyloid pathology was present in a smaller proportion of cases and in older patients. Incidentally, the term "amyloid" should be understood as Aβ pathology because the lesions so described are not detected by stains such as Congo red and thioflavin S, which reveal proteins only in the β-pleated configuration. The silver method used here probably shows not only the amyloid plaques but also a large proportion of A-β deposits.

While examining this exceptional set of data, the reader may rapidly point out their imperfections, which may be summarized in a few lines: the aim of this study is at least partly epidemiological. It intends to uncover the incidence and prevalence of Alzheimer lesions at different ages. However, the study, because it is post-mortem, deals with a highly biased population: healthy people do not die. Moreover, clinical information is lacking. Finally, the validity of such "post-mortem epidemiology" heavily depends on the way the brains have been collected. Recruitment from Neuropsychiatry Ward or Gerontology Department would, for example, artificially increase the prevalence of Alzheimer lesions.

HYPOTHESES

These difficulties of the study may, however, not keep the reader's attention as long as other questions that could all come under the title: "If all these data were fully valid, what would they mean?" Could we take the values, which are presented here, and treat them as if they were standard epidemiological data? In so

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doing, we would implicitly accept a set of hypotheses that we will try to state here explicitly to facilitate further discussion.

Hypothesis 1: Random Death

The data are to be taken as if they had come from a large population, in which death had occurred randomly at all ages. If this condition were fulfilled, prevalences of lesions would be representative of the living population.

Hypothesis 2: Irreversibility of the Lesions and Hierarchical Involvement

Heiko and Eva Braak have devised two staging schemes, from I to VI for the neurofibrillary pathology and from A to C for the amyloid lesions (5). This hypothesis states that in one given case, the lesions progresses from I to VI and from A to C without ever going back to a previous stage (stage 0 included), jumping over intermediate stages (for example from stage I to VI) or starting at "late" stage (for example starting at stage V–VI).

Hypothesis 3: Disease Homogeneity

The post-mortem sampling was by necessity cross-sectional. The autopsies were, indeed, performed within a short period of time and were made on individuals of various ages. The data, grouped by age classes, may be interpreted as the longitudinal follow-up throughout their entire life of a small group of individuals who would, so to speak, have been regularly autopsied.

The artificial nature of this interpretation need not be underlined. If for example 50% of the population is at a stage 1 in a given age group, and then 50% at stage 1 and 25% at stage 2 in another older group, the data will be taken as indicating that 25% of a hypothetical population had left stage 1 for stage 2, and 25%, in the spared part of the population, had gone from stage 0 to 1. It could well mean, if this hypothesis were wrong, that 25% of the populations had developed a severe disease at an old age which had rapidly reached stage 2, although 50% of the population had remained stable at stage 1. If this working hypothesis were not verified, what we call stages 1 and 2 could be two different diseases, with their own courses, artificially mixed in one unique disorder.

Hypothesis 4: Absence of Cohort Effect

This hypothesis states that young patients will behave in the future as the patients who are presently old.

Accepting these four hypotheses makes it possible to combine the static pictures obtained from different samples at different ages into a dynamic process, taking place in one single imaginary population of aging people.

INTERACTION OF THE LESIONS: THEIR GENERAL INCIDENCE AND PREVALENCE IN THE STUDY

The cases have been considered by groups of 5 years. The prevalence of cases with lesions (i.e., the number of cases with at least one lesion, all stages together, compared to the total number) is 78% for the neurofibrillary tangles and 43% for the amyloid lesions. The interaction between the two lesions is obvious: if they were independent, only 43% of the individuals with tangles should have had amyloid lesions; they were 54%. Only 78% of the cases with amyloid should have had tangles; they were 97%. These values also underline the assymetry of the relationship: almost all the cases with amyloid deposits have tangles. A significant proportion of cases with tangles have no amyloid deposits.

Because the lesions are supposed to accumulate (hypothesis 2), we may consider that current observation actually covers a long period of time equal to the number of brains × their ages. The number of "brain-years" reaches, over the whole cohort, the astronomic value of 179,298. The incidence rate of the neurofibrillary pathology is then 0.0115 brain-year and the incidence rate of the amyloid pathology 0.0064 brain-year. However, these values are global and give no information on the distribution of the lesions in the various age groups, information that might be gained by studying the prevalence of neurofibrillary and amyloid pathologies in each age class.

TABLE 1

CHARACTERISTICS OF THE ESTIMATION OF THE PREVALENCE CURVES

Lesions	r	% of Var ($r^2 \times 100$)	Age of Mid-Prevalence (Years)
Tangles (all stages)	0.97	95	47.4
Tangles III–IV + V–VI	0.98	95	85.7
Tangles V–VI	0.96	92	104.9
Amyloid (all stages)	0.99	98	73.9
Amyloid B + C	0.99	98	84.0
Amyloid C	0.98	95	98.8

r: coefficient r of Pearson of the linear regression after logit transformation of the prevalence values P (= LN(P/(1-P)). All values significant at $p < 0.0001$. % of the variance of the prevalence explained by the equation. Age of mid-prevalence: age for which the estimated prevalence is 0.5.

A MODEL OF THE PROGRESSION OF THE LESIONS

Prevalence varies from zero to one and, confirming hypothesis 2 of lesion irreversibility, increases with age. This increase suggests the use of a regression analysis to describe the relationship between time and pathology. Because prevalence values are ratios varying from 0 to 1, direct linear approximation is unsatisfactory and a logistic transformation has to be performed before the calculation of the linear regression; the results may be converted from logit of prevalence to prevalence values after the linear regression has been calculated on the transformed data. The approximations appeared to be excellent (Table 1) and to fit the data with a very good accuracy (Fig. 1 and Table 1). They allowed us to extrapolate the curves, a procedure that may obviously lead to serious errors of interpretation but has the advantage of visualizing the trends.

DELAY BETWEEN NEUROFIBRILLARY AND AMYLOID STAGES

To evaluate the time delay between the occurrence of neurofibrillary changes and amyloid deposits, we compared the age at which the same prevalence was found for both types of lesions. The point of prevalence 0.5 was chosen because it is easily identified on the curve, often corresponds to its linear portion and is easily calculated with the logistic equation. This value will be referred to later as the age of mid-prevalence. If we were studying longitudinally one cohort of people, the age of mid-prevalence would be the time at which half the population would have been affected. It was found to be 47.4 years for the neurofibrillary pathology and 73.9 for the amyloid pathology, 26.5 years intervening between the two values.

DURATION OF THE STAGES

Estimating the chronology of individual stages is more difficult. The number of cases included in each stage except in the last

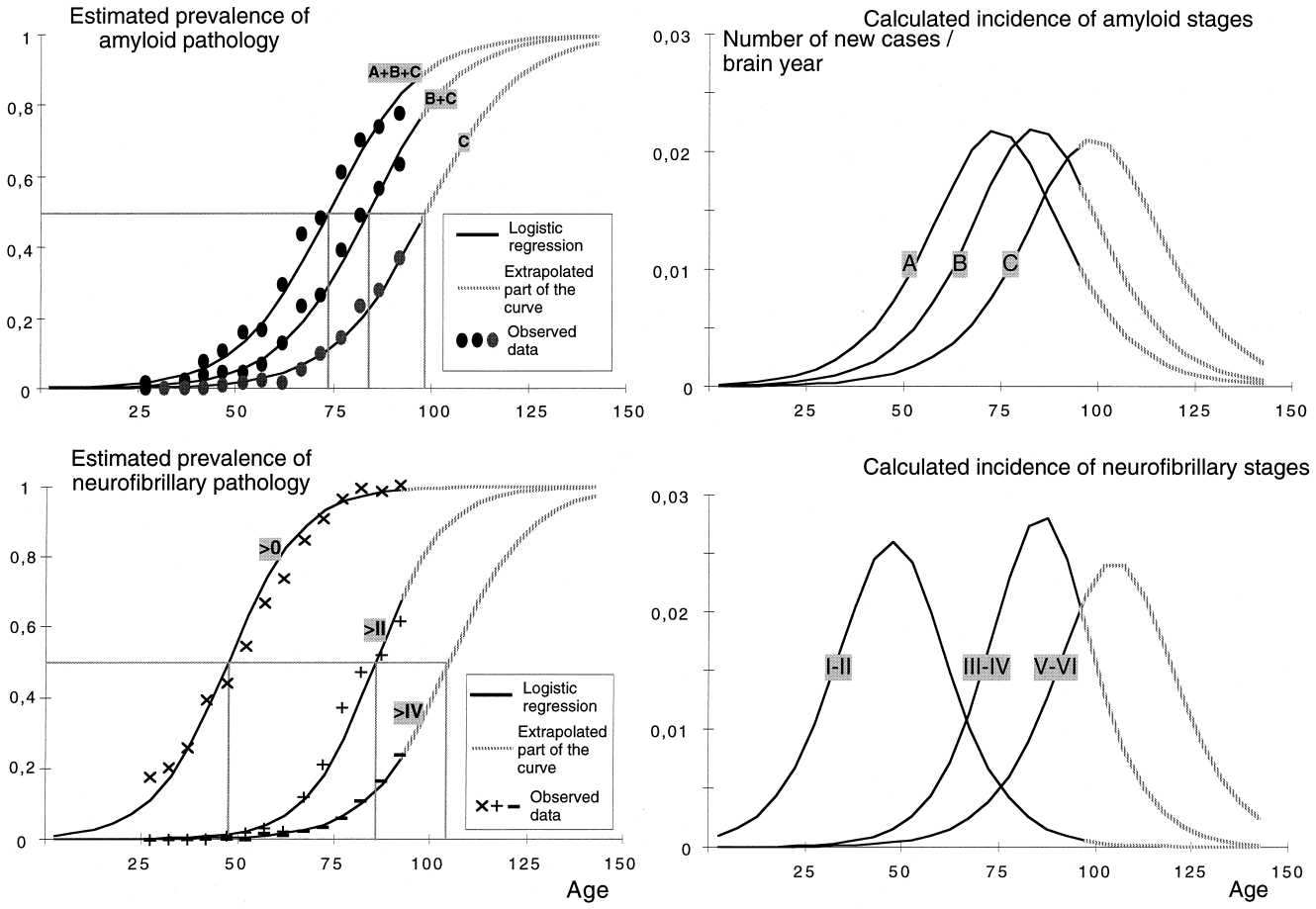

FIG. 1. Estimated prevalence and calculated incidence of the amyloid (top) and neurofibrillary (bottom) stages. Prevalences (left), X-axis: age in years. Y axis: prevalence. The curves have been obtained by a logistic regresion [Ln (P/1-P) = a × age + b where P is the prevalence Ln = natural logarithm; a and b coefficients of the equation]. Observational data provided by H. Braak and E. Braak are shown. The gray part of the curve is extrapolated. The horizontal and vertical lines indicate the ages of mid-prevalence. Incidences (right), Incidences have been calculated by differentiating the logistic equation (shown in the left half) giving the prevalence as a function of age. Incidence is expressed as a number of new cases per brain year. The gray part of the curve corresponds to the extrapolated part of the prevalence function.

ones (VI and C) is indeed the balance between two flows: the occurrence of new cases (increasing the prevalence) and the passage to more severe stages (decreasing the prevalence). The dynamic equilibrium is impossible to reconstruct if each stage is studied separately. In the last stages, C and V–VI, on the contrary, there is no outflow in the hypothesis of lesion irreversibility. The prevalence of these stages may only increase. One may thus group the stages in such a manner that these groups always include the last stages, thereby making the flow unidirectional (only inflow; no outflow). The prevalence of the grouped stages will then be ever increasing with age, making the approximation of the data by a linear (first degree) logistic regression possible. This is why the following prevalence curves were compared: A + B + C, B + C, C for the amyloid pathology; I–II + III–IV + V–VI, III–IV + V–VI, V–VI for the neurofibrillary changes (Fig. 1). For each curve, an age of mid-prevalence could be calculated and the differences between them were considered an estimate of the duration of each stage (Table 2). The amyloid stages were found to be of shorter duration than the neurofibrillary stages. The estimated duration of stage I–II was particularly long (38.3 years).

INCIDENCE OF THE STAGES

The first derivative of the prevalence curve as a function of age is an estimate of the number of new cases per brain-year, i.e., of the incidence. (The derivative of the logistic regression equation is: $(a.e^{-at + b})/(1 + e^{-at + b})^2$ where a and b are coefficients of the equation; t = age.) The incidence curves had the shape of a Gaussian function (Fig. 1, right). All the peaks of incidence (Table 2) were of the same order of magnitude (from 2.1 to 2.8% according to the stages). The curves had a broad base, suggesting an important dispersion of the age of onset. The curve of stage I–II was distinctly shifted to the left, toward the younger ages, its peak being separated by 40 years from the peak of incidence of stage III–IV. The peaks of incidence of the amyloid stages were closer to each other than the peaks of the neurofibrillary stages.

PREVALENCE OF THE STAGES

The difference between the first curve (all stages) and the second curve (all stages minus the first) gives the prevalence curve, in relation to age, of the first stage (I–II for the neurofibrillary pathology or A for the amyloid changes) and the difference

TABLE 2

CHARACTERISTICS OF THE INCIDENCE AND PREVALENCE CURVES OF THE NEUROFIBRILLARY AND AMYLOID CHANGES

Stages	Age of Max Incidence	Age of Max Prevalence	Peak of Incidence	Peak of Prevalence	Duration
I + II	47.5	67.5	0.026	0.78	38.3
III + IV	87.5	97.5	0.028	0.46	19.2
V + VI	102.5		0.024		
A	72.5	82.5	0.022	0.22	9.9
B	82.5	92.5	0.022	0.31	15.1
C	97.5		0.021		

Age of max incidence = age of maximum incidence: the age (calculated with a step of 5 years) at which the curve reaches a maximum. The incidence was estimated by calculating the first derivative of the logistic regression of the prevalence on age for the stages C, B + C, A + B + C and V–VI, V–VI + III–IV + I–II (see Fig. 1, left). Peak of incidence in number of new cases per brain year. Age of max prevalence = age of maximum prevalence: the age (calculated with a step of 5 years) at which the curve of prevalence reaches a maximum. The prevalences of each stage was calculated by subtracting the curves of Fig. 1, left. Duration: duration of each case estimated by computing the difference of the ages for which the prevalence is 0.5 in each stage. Indicated by vertical and horizontal lines in grey on the curves of the left portion of Fig. 1.

between the third and second curves estimates the prevalence of the second stages (III–IV and B) (Fig. 2). Those curves, also shaped as Gaussian functions, reached a maximum value 10 years after the peak of incidence, except for stage I–II for which 20 years separate the peaks of incidence and of prevalence. This is due to the fact that stage III–IV, the "exit" of stage I–II, occurs after a delay of 35–40 years. The prevalence of stage I–II may thus keep increasing for a long period of time, up to values of almost 0.8, before the progression of some cases to stages III–IV "empties" the stage I–II compartment.

RELATION WITH DEMENTIA

The clinical data of the autopsied cases were not available. However, the pathological data provided by Heiko and Eva Braak may be compared with the prevalence curves of dementia that have been published. We used the data proposed by Katzman and Kawas (25), and relied on the logistic regression to facilitate the comparison with the pathological data (Fig. 3). The prevalence of dementia in the younger age groups coincide fairly well with the prevalence values of stage V–VI and was clearly below that of stages >II (i.e., III–IV + V–VI). However, in the older age groups, prevalence of dementia was much greater than the prevalence of stage V–VI and approached that of stages >II.

HYPOTHETICAL PROGRESSION OF THE STAGES

We may now summarize the main conclusions of the analysis and suggest a sequence of events by taking into account the peaks of prevalence and the mean duration of the stages: around the age of 40, the first neurofibrillary changes appear in the entorhinal region; their incidence increases, reaching a maximum at age 47—by that age, half the population is affected. Then, around the age of 62, amyloid precipitates in the basal neocortex; the maximal incidence of stage A is observed at age 72. By the age of 74, half the population exhibits amyloid deposits. They diffuse to larger areas of the brain around the age of 70 and by the age of 84 half the population has reached stage B. Tangles appear in the limbic cortex by the age of 82; at the age of 86 half the population has reached stage V–VI. The amyloid deposits involve the neocortex by the age of 97. Were we to wait long enough, half the population would have reached stage V–VI by the age of 105. This is obviously an "average" and, for values >95 years, an extrapolated

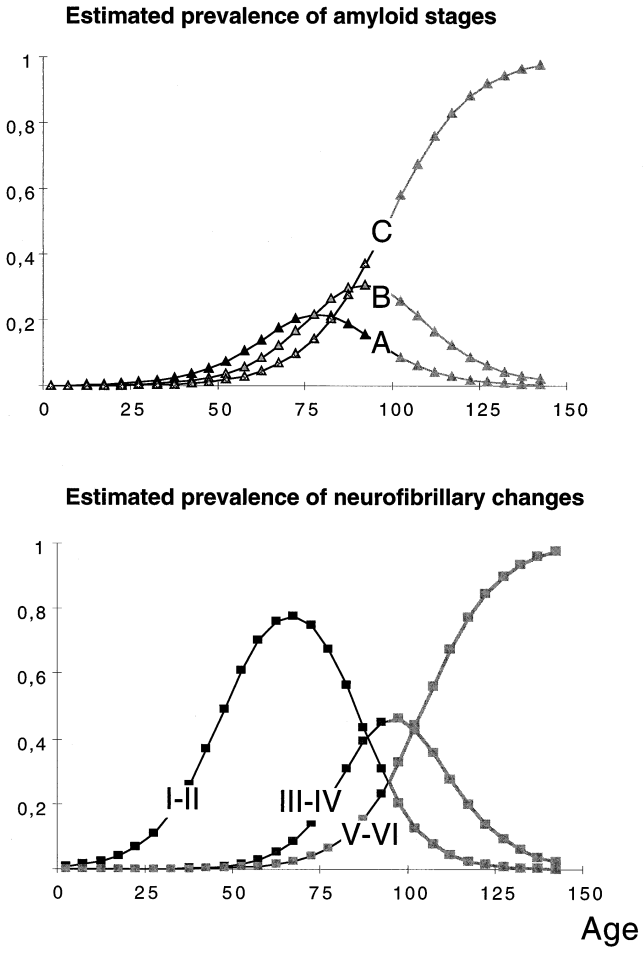

FIG. 2. Prevalence of the stages. The curves of stages C (top) and V–VI (bottom) are the logistic regression curves as in Fig. 1. The curves for stages A, B, I–II, III–IV have been obtained by subtracting the curves of Fig. 1 (A + B + C) − (B + C) for stage A; (B + C) − C for B; (> 0) − (> II) for stages I–II and (> II) − (> IV) for stages III–IV. The extrapolated parts of the curves are in gray.

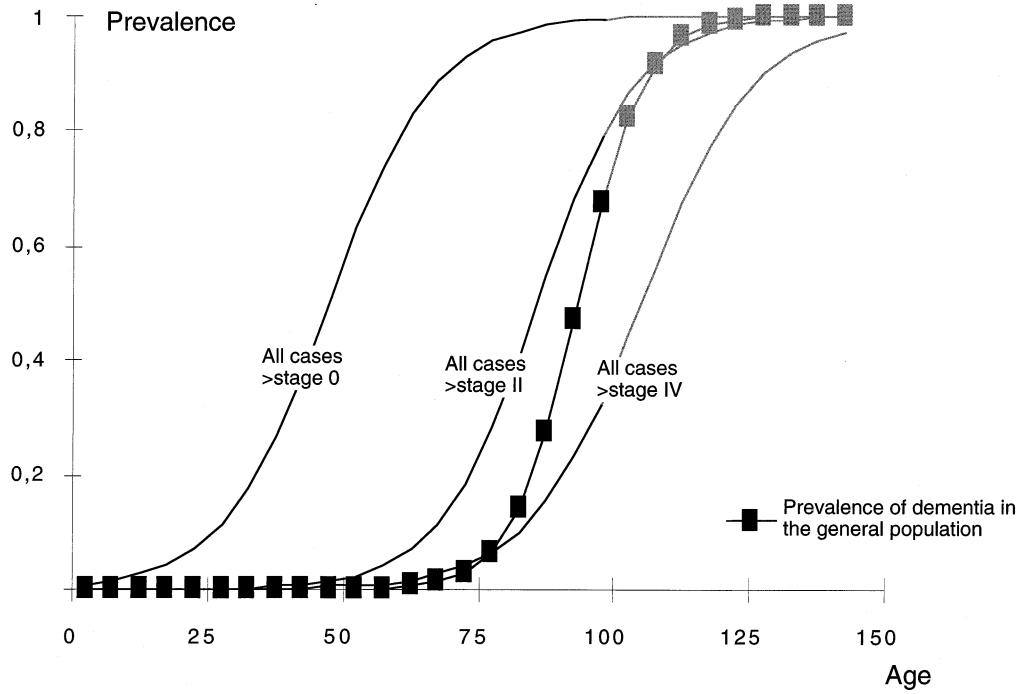

FIG. 3. Comparison of the prevalences of the neurofibrillary stages and of dementia. The prevalence curve of dementia is a logistic approximation from data obtained in Ref. 25. The prevalence curves of the neurofibrillary stages are the same as in Fig. 1. The prevalence of dementia is close to the prevalence of stages V–VI in the sixth and seventh decade but is much higher later in life. It then approaches the prevalence of stage III–IV or more. This might be due to the occurrence of other causes of dementia in the eldest old, to a higher sensitivity to lesions in aged people, or to bias of recruitment (see text).

course, taken from mean values calculated in an imaginary population, after having accepted a set of hypotheses that are difficult to prove. If we choose to interpret the data in this simple and straightforward way, this explicit model appears to be coherent and does not give rise to statements that would be incompatible with present knowledge. But are the initial hypotheses acceptable?

HOW VALID WERE THE INITIAL HYPOTHESES?

The "random death" hypothesis cannot be easily accepted. It is, indeed, probable that the mortality rate is higher for cases with lesions than for those who are spared. It is also probable than intellectually deficient patients are more often dying in hospitals, where autopsies can be performed, than at home. This bias, which seems at least plausible, leads to an overestimation of the lesion prevalence rate. It underlines the necessity of undertaking longitudinal study, including postmortem examination, in the community (29). The irreversibility of the neurofibrillary tangles would certainly be easily endorsed by most neuropathologists. It might, however, be an erroneous belief; one can also imagine that in the whole pool of neurons, the balance of phosphorylation and deposphorylation leaves an ever-changing percentage of cells with tangles. However, this possibility is poorly compatible with the known insolubility of the neurofibrillary tangles and with the presence of "ghosts." It might also be that tangles are finally eliminated by phagocytosis, a possibility that would induce an underestimation of tangle pathology in the severe cases but also in quiescent, long standing lesions. The data, obtained by Heiko and Eva Braak, and the calculated estimates of the time course of the disease, however, emphasize the exceptional duration of the neurofibrillary lesions. If stage I–II lasts more than 30 years and still leaves some neurons unaffected or at least alive, the survival of a tangle-bearing neuron seems to be protracted. Gomez-Hysla et al. (20) have estimated that the neuronal loss taking place in layer II of the entorhinal cortex, even in the mildest cases, reaches 60%. Accepting that this loss is due to tangles and has taken 30 years to occur would mean that roughly $60/30 = 2\%$ of the neurons are to be affected per year if the lifetime of a tangle reaches 12 full months. If, however, 60% of the neurons at an early stage bear tangles, then one is led to accept a life duration close to 30 years for the tangle-bearing neurons, an astonishingly long time and certainly a counterintuitive notion.

The irreversibility of the Aβ deposits, at least in their preamyloid stage, is more disputable than the irreversibility of the neurofibrillary pathology. Diffuse deposits sometimes seen in such a high density in old individuals (14) have to disappear, at least for some of them, without forming plaques. The dynamic character of the Aβ deposits might be a factor that makes the link between known alterations of Aβ metabolism and tangle formation so difficult to understand.

The involvement of the cortical areas seems indeed hierarchical in most cases. However, the occurrence of (clinically) focal Alzheimer diseases (24) leaves the possibility of atypical courses that would not follow the hierarchical scheme. These cases have not been observed by Heiko and Eva Braak. They should be systematically sought in the future.

The third hypothesis, "disease homogeneity," is probably the most difficult to endorse. It has been suggested that the course of the lesions is not progressive: they could accumulate in a short

period of time (26) and progress by fits and starts. Moreover, many genetic causes of Alzheimer disease have been elucidated. The courses of some of these identified disorders differ from those of so-called sporadic cases, occurring in the aged. Alzheimer disease—or rather "syndrome"—is probably a mosaic of disorders, and the average course that we have imagined here is to be taken cautiously because it might well be the mean of extreme values: malignant diseases with a fulminating course and slowly progressive alterations, hard to distinguish from aging. The 2661 autopsied cases of Heiko and Eva Braak could tell us many more stories than the unique, averaged course that we have imagined. Finally, the absence of cohort effect in Alzheimer disease may probably be accepted without much controversy, the neuropathology of cases collected decades from now appearing quite similar to what is seen today, although this point has not been systematically studied as far as we know.

DISCUSSION OF THE CONSEQUENCES OF THE MODEL

This discussion has perhaps convinced the reader of the limits of the model. It may also have led the reader to believe that some consequences of these hardly questionable observations will remain valid even if the hypotheses are not fully verified, most noticeably the relation between lesions and aging, the long duration and early onset of the tangle pathology, the dissociation and time-lag between neurofibrillary and amyloid changes. We would like to discuss in more detail several of these questions.

AGING AND DISEASE

The disease, as described in this model, appears so systematically and closely associated with age than one may reasonably ask if the two processes can be distinguished. The extrapolations of the curves over 100 years (an age that obviously has to be taken as the vanishing point in a perspective) converge to a disease prevalence of 1, because the slopes of the estimated prevalence curves of the lesions are positive and steep when the usual life span stops their lines. There is, to our knowledge, no operational way, theoretical or practical, of distinguishing aging from a disease that reaches, with age, a prevalence of 1. In this respect, Heiko and Eva Braak may well be right when they state that the disease is age-related but different from aging; in our opinion, the definitive proof is still lacking, in this situation where all the individuals of a population, when old, exhibit lesions (12). The problem of distinguishing aging from disease, however, is theoretical; the real question is to avoid dementia in old age by some preventive measures, as already pinpointed (18).

RELATION BETWEEN AMYLOID AND TANGLES

The relationship between neurofibrillary changes and amyloid appears asymmetrical in this model. Tangles are more frequent and precocious than most neuropathologists would have probably thought. Moreover they anticipate the amyloid pathology for 27 years. More than half (54%) of the cases with tangles are devoid of Aβ lesions. This is not what was expected in the light of the recent findings concerning APP (8) and presenilin mutation (32), trisomy 21 (31) and the ApoE4 genotype (3,33) all inducing an increase in Aβ secretion. At least in these disorders, Aβ is thought to be the initial cause of the cascade of lesions leading to the disease (22), although this cascade hypothesis has been challenged (35). Accumulation of Aβ should then logically precede the formation of tangles as in trisomy 21 (27). This is clearly not the case in this study nor in others (2,5). But this relation has to be qualified: the tangle-only cases are for most part at stage I–II. Amyloid invades the neocortex (B) in many cases where the tangles are still confined to the limbic system (4). The peaks of incidence of stage A and B are intercalated between those of stage I–II and III–IV. These data might suggest that in the isocortical areas, Aβ deposits precede neuritic pathology (17). Different hypotheses may be formulated to explain the occurrence of entorhinal tangles before Aβ accumulation in the isocortex; it might simply be a lack of sensitivity in the detection of the deposits, and in this respect much remains to be done to explore these tangle-only cases or limbic form of AD (2); new antibodies directed to special parts of the Aβ molecule might be more efficient in showing light accumulation, as we recently experienced. It may also be that the relation between increase of Aβ metabolism and tangle formation is closer than previously thought. Because tangles appear in cases with known APP mutation and because tangles seem, in this study, to precede cortical Aβ deposits, one may imagine that the resorption of Aβ is possible in the young patient but, in the aged, leads to tangles that kill the neuron and prevent the correct handling of the oversecretion. It might finally be that AD is a "two-variable disease," one that is the "normal" aging of the brains characterized by tangle formation in the entorhinal cortex, the other that is Aβ increased synthesis, noxious only in the presence of tangles that would permit its accumulation. This would explain why AD develop relatively late in life, even in genetically determined cases, and why Aβ deposits have been found so well correlated with dementia in some studies (9).

WHEN DOES AD START? WHAT IS THE SIGNIFICANCE OF STAGE I–II?

The high prevalence of stage I–II, even in the young, and its extraordinary long duration had certainly not been fully appreciated until now, although the presence of lesions in young people has already been reported in the literature (34). Because stage I–II is so common, how can it be so serious? It could be normal aging, and remain stable. This possibility is supported by the long interval between stages I–II and III–IV (around 40 years). The main argument presented by Heiko and Eva Braak against the mildness of stage I–II is the presence of both ghost and intracellular tangles, i.e., evidence of past toxicity (killing of neurons) and of present progression (alive tangle-bearing neurons). We wonder, however, if various disorders could have been mixed together in the mean values that were previously proposed. The rapid course of some severe presenile cases of Alzheimer disease has been known since the initial description. In those cases, the succession of the stages has to be more rapid than described herein. We examined, for example, samples from a patient with a presenilin mutation, who died at the age of 38 (7). The passage from stage I–II to stage V–VI obviously had to be shorter than 40 years in this particular case. If some of those patients with an early onset and a rapid course have been included in the group of 2,661 autopsies, then the peak values of the stage prevalence have been deviated to the younger ages. The "real," i.e., common, age of onset of the limbic and isocortical lesions would then be particularly old, superior to most life spans. If this were true, then the once common view that Alzheimer disease is accelerated aging would be plausible: we would all be doomed to develop Alzheimer disease, . . . but when older than 100 years. In a few people, said to be affected by the disease, the lesions would appear earlier and progress more rapidly. We, as many, are reluctant to accept this simplistic view, but we should also recognize that nothing in the presented data contradicts this "accelerated aging" hypothesis and we wonder how Heiko and Eva Braak consider this question.

RELATIONSHIP OF THE LESIONS WITH DEMENTIA

Finally, we would like to examine the differences between dementia prevalence and the prevalence of the lesions, although

many confounding variables may obscure the relation between the lesions and the clinical symptoms, most noticeably the presence of Lewy bodies (21) and vascular lesions (30). It is usually admitted that the cognitive decline is more significantly correlated with the neurofibrillary tangles than with the Aβ deposits (1,6,10,11, 13,15,16,28). The lesions are thought to be clinically silent at stage I–II. "Mild" or "very mild" intellectual alterations may be detected in some cases with abundant tangles in the limbic system (19,20). The prevalence curves of dementia and of stages III–IV could then coincide. This is clearly not the case. Dementia prevalence coincides with stage V–VI in the seventh decade and then approaches, in the older age groups, prevalence of stages III–IV + V–VI. This could be explained by a bias in the recruitment of the histological specimens. Too many autopsied cases with stage III–IV would overestimate its prevalence and obscure its relation with dementia. It might also be that dementia in the middle-aged population is fully recognized at a late stage, whereas its clinical threshold is lowered in the aged (19). It could finally be that many other causes of dementia (especially vascular diseases) interfere in the very old, the proportion of degenerative dementias decreasing in this age group (23).

CONCLUSIONS

The length of this article should at least convince the reader of the deep interest these findings have raised. Whatever criticisms, doubts or discussion that arouse, the large amount of data brought by Heiko and Eva Braak will have to be assimilated by the scientific community. They cannot be simply dismissed. We believe that they add highly significant information to our understanding of brain aging and Alzheimer disease.

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COMMENTARY

NEUROPATHOLOGICAL STAGING OF ALZHEIMER-RELATED LESIONS: THE CHALLENGE OF ESTABLISHING RELATIONS TO AGE

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THE possibility of histopathological staging of Alzheimer disease (AD) and related lesions, analogous to staging of gliomas, has intrigued neuropathologists since Blessed et al. (1968) reported a correlation between the number of senile plaques (SP) and dementia scores (6), and Brun and Englund (10) proposed five progressive stages of degeneration in AD based on the regional pattern of spongiosis and nerve cell loss with little emphasis to SP and neurofibrillary tangles (NFT). Defining the criteria for the histopathological diagnosis of AD, currently based on age-adjusted (semi)quantitative assessment of SP or neuritic plaques (NP) and NFT (23,27,35) has proven difficult because of the genetic and phenotypic heterogeneity of the disease, the absence of specific disease markers, and an overlap of AD neuropathology with that observed in a number of non-demented aged subjects (1,5,11,12,15,19,21,28,31,38). For these and other reasons, a reevaluation of the current diagnostic criteria of AD has been suggested at a recent consensus meeting at NIA, Bethesda, MD (37). Independently of the numeric assessment of morphological AD markers (SP, NP, NFT, etc.), a staging of neuritic AD pathology, particularly NFT demonstrated by sensitive silver techniques, based on its hierarchical spreading from the inferotemporal allocortex via the hippocampus to areas of the association isocortex (7), is now widely used. This spreading of neuritic AD lesions is independent of the pattern and quantity of amyloid deposits for the progressive spreading of which three stages have been suggested (7). From a staged sample of 887 brains from routine autopsies, the rate of progression of AD-related neurofibrillary (NF) changes was calculated: the earliest stages occur in comparatively young individuals, and positive correlation of more advanced stages with increasing age have been shown (30). In this study of 2661 brains obtained at autopsy from three German universities, Braak and Braak demonstrate that the proportion of brains without amyloid deposits and/or NF changes decreases with advancing age, although neither change necessarily accompanies old age. They confirm previous data that early stages of both types of lesion occur preferably in relatively young individuals, although the more advanced stages appear with increasing age, and that NF changes may precede the deposition of amyloid, suggesting that the latter is not a prerequisite for the development of NF changes. In general, initial NF stages I and II develop in the absence of amyloid deposits, whereas the terminal NF stages V and VI representing fully developed AD are usually associated with end