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Alzheimer Disease Pathology As a Host Response
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Abstract
Identification of amyloid-β and tau as the major protein components of senile plaques and neurofibrillary tangles, respectively, led to an exponential increase in investigations of these proteins and their corresponding metabolic pathways in Alzheimer disease (AD). The presumptions inherent in most studies and in the dogma of the amyloid cascade concept are that these hallmark lesions in AD brains contain molecules that drive the disease process, and that the proteinaceous accumulations are themselves toxic. On the other hand, the lesions of AD are, by definition, end-stage, and their relationship to the clinical disease is inconsistent; this has long been known but, generally, has not been acknowledged until relatively recently. Some recent attempts to address the etiology and pathogenesis of AD discard the pathology and focus on the interplay between invisible toxic intermediates, that is, amyloid-β oligomers and the synapse. The concept that the hallmark lesions may be nontoxic (something we have long suggested) is slowly gaining acceptance. We favor the interpretation that senile plaques and neurofibrillary tangles represent a host response to an upstream pathophysiologic process, and that the therapeutic target is the basic premise that proteinaceous accumulations are the consequences of the disease, rather than the cause, is in order and may be somewhat overdue (6).

Key Words: Alzheimer disease, Amyloid, Tau

INTRODUCTION
The discipline of neuropathology is principally concerned with morphologic alterations in neurologic disease and, in particular, structural alterations that can be visualized microscopically (Fig. 1). Because this is the case, the pathologic interpretation of neurodegenerative diseases necessarily focuses on cellular inclusions. The question we address is whether such lesions, in addition to being convenient for study by virtue of their ability to be detected, contain components or molecules that drive the disease or whether these lesions are better viewed as by-products of the basic pathobiologic processes that preceded the accumulation. Since the time of Alois Alzheimer and up to approximately 20 years ago, neuroscientists entertained a variety of mechanistic hypotheses to explain the neurodegeneration in this disease (1). Inclusions, however, tended to be viewed as “hallmark” lesions, rather than indicators of etiology. In more recent years, genetic analyses have linked the lesions to specific proteins and have led the field to pathogenic cascades that are presumed to be causal (2).

The expanded knowledge of lesion constituents and the accompanying presumption of etiology may have diverted attention toward processes that are, in essence, a host response to the underlying pathophysiology. Indeed, despite considerable time, expenditure, and repeated modifications, lesion-based therapies continue to be disappointing (3, 4), whereas simple enhancement of neurotransmission remains the only modestly useful therapy (5). In our opinion, a fundamental reorganization of the thought processes that reflect the basic premise that proteinaceous accumulations are the consequences of the disease, rather than the cause, is in order and may be somewhat overdue (6).

THE NEUROFIBRILLARY TANGLE

Historical Notes
Plaques were a known accompaniment of senile dementia in the late 1800s, but the first description of the neurofibrillary tangle (NFT) in 1907 can be attributed to Alzheimer (7). The lengthy description of “neurofibrils” by Fuller (8) several months prior to Alzheimer’s description of Auguste D. has been suggested as evidence that the NFT was also known prior to Alzheimer’s description. A careful review of Fuller’s article, however, indicates that he was most likely describing normal cytoskeletal elements and not genuine NFTs. It is also of interest to note that Alzheimer devoted 10 sentences and 2 paragraphs to his initial description of the NFT compared with only 2 sentences to the senile plaque (7, 9). This, and the fact that plaques were a known component of senile dementia at that time (10), suggests that the NFT was the more intriguing lesion, so much so that Alzheimer spent considerable time and effort illustrating NFTs and their variations (11). Nevertheless, despite copious literature by Alzheimer and his contemporaries, it is difficult to find firm allusions to the cause of the basic disease process (9–13). Rather, the importance and controversy rested for the most part in whether this condition affecting a relatively young patient represented a new disease or, instead, was a form of senile dementia with early onset (13).
The fact that NFTs stained intensely with the Bielschowsky silver technique, whereas unaffected neurons failed to stain, highlighted the use of the silver impregnation for diagnostic purposes. Moreover, Bielschowsky silver made extracellular NFTs, which were sometimes numerous, visible, and raised theories that date to Alzheimer’s description of Auguste D. regarding altered cytoskeletal elements that conferred their insolubility:

“Because these fibrils were stained differently from normal neurofibrils, a chemical conversion of the neurofibrils must have occurred. This may well explain why the fibrils survived the decay of cells...” (11)

The structure of the NFT was further elucidated by Terry (14) in 1963; the same year, Kidd (15) described paired helical filaments. Some ultrastructural details of NFTs were subsequently added to literature (16), but it was not until 1986 that NFTs were purified and the microtubule-associated protein tau determined as the major protein component (17). This finding initiated a substantial focus on tau pathophysiology; however, because the identification of tau in NFTs occurred approximately 2 years after the identification of amyloid-β (Aβ) in plaques, and because Down syndrome and familial Alzheimer disease (AD) had a genetic link to Aβ, it is not surprising that Aβ assumed primacy over tau as the important pathogenic, if not etiologic, factor in AD (2, 18, 19).

**Tau Protein**

We now know that the *tau* gene is composed of more than 100 kb and contains 16 exons (20). Upstream of the first exon are consensus-binding sites for transcription factors such as AP2 and SP1. Alternative splicing of tau nuclear RNA transcribed in the adult brain on Exons 2, 3, and 10 results in 6 tau isoforms. The isoforms differ in the presence of either 3 or 4 peptide repeats of 31 or 32 residues in the

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**FIGURE 1.** The hallmark histopathologic lesions of AD have shaped our views on the etiology and pathogenesis of the disease. **(A)** The neurofibrillary tangle is composed of hyperphosphorylated tau protein accumulated in paired helical filaments. **(B)** Senile plaques containing amyloid-β (Aβ) often exhibit extensive neuritic pathology (C) and accumulate in large numbers in the diseased brain (D). **(A, C)** Immunostained for phosphorylated tau. Scale bars = 25 μm. **(B, D)** Immunostained for Aβ protein. Scale bars = 25 and 100 μm, respectively.
C-terminal region encoded on Exon 10. This peptide repeat region comprises the microtubule-binding domain. Tau isoforms also differ in the expression of 0, 1, or 2 inserts encoded on Exons 2 and 3. The relative amounts of these tau isoforms and their phosphorylation status change during development; 3 repeat (3R) tau with no inserts is expressed in the fetus and early postnatal infant, whereas heterogeneous isoforms are expressed in the adult brain. This switch in RNA splicing also corresponds to a reduction in tau phosphorylation. Tau is relatively abundant in neurons, but it is present in all nucleated cells where it functions physiologically by binding microtubules and stabilizing microtubule assembly for polymerization.

It is interesting to note in this respect that the term “Alzheimer disease” of the early 1900s would be reserved for early-onset disease, whereas late-onset disease would be referred to as “senile dementia,” a condition already known to be associated with advanced age and accumulation of senile plaques. Given the association between early-onset disease and germline mutations (26, 27), one might also suggest that AD, or presenile dementia, is essentially familial early-onset AD, whereas an arguably different process, “senile dementia,” refers essentially to sporadic disease.

Similar to NFTs, senile plaques showed an affinity for silver with the Bielschowsky silver technique and were recognized as largely extracellular lesions since Marienescu’s (28) suggestion that plaques were derived from condensation of intercellular ground substance. This foreshadowed Divry’s (29), who reported in 1927 that plaques, like amyloid, were birefringent after Congo red staining. Little progress had been made into plaque pathogenesis aside from some ultrastructural details (30) until modern molecular techniques were applied to purified vascular amyloid and amyloid plaque cores (31, 32), and demonstrated a small protein, designated Aβ, later discovered to be a metabolic product of Aβ precursor protein (AβPP), transcribed on Chromosome 21. Not surprisingly, review of the literature from this period demonstrates a conspicuous shift in the notion that plaques are an accompaniment of disease to the assignment of plaques directly to etiology and pathogenesis (33–36). Identification of kindreds of familial AD linked to point mutations within and around the Aβ coding region, and the neuropathology of Down syndrome (early plaque pathology), reinforced this notion.

**THE SENILE PLACQUE**

### Historical Notes

Historical accounts indicate that senile plaques were described in 1892 by Blocq and Marinesco in the brain of an epileptic patient (10). Redlich also described plaques in 2 elderly epileptics in 1898 and termed them “miliar sclerosis.” Beljahow described plaques in association with senile dementia in 1887 (23), as did Redlich and Leri shortly thereafter (24). Alzheimer also acknowledged previous descriptions of plaques in the setting of senile dementia:

> “The patches in the cortex had in the meantime been observed in Presbyophrenia by Fischer who described them in detail in a number of papers and considered them as characteristic of that disorder. Redlich had also demonstrated them by different methods. I had myself already observed and described them in Dementia senilis using Nissl and Weigert staining...” (13, 25)

Nevertheless, like NFTs, senile plaques had not been previously described in association with early-onset or presenile dementia. It is also noteworthy that the second described case of AD, Johann F., was ostensibly a case of “plaque-only” AD, whereas pedigree analysis indicated that this was a case of familial AD (13).

Emil Kraepelin (12) was the first to use Alzheimer’s name in association with dementia in the eighth edition of his textbook of psychiatry. This was not because of the association of specific lesions with disease but because the disease affected a relatively young individual. Alzheimer was reticent to accept the new eponym but nevertheless acknowledged:

> “Even if the anatomical findings might suggest severe mental impairment, the early onset (one would have to assume a ‘senium praecox’), the profound language disturbance, spasticity, and seizures are very different from those of presbyophrenia which is usually associated with purely cortical senile changes...” (13, 25)

Amyloid-β

As with the expansion of knowledge related to tau, the discovery of Aβ was followed by an encyclopedic accumulation of data regarding the protein, its processing, and alterations in disease. It is now known that Aβ is the normal metabolic product of the AβPP via the action of 2 aspartyl proteases, β- and γ-secretase (2). β-Secretase first cleaves AβPP, which sheds a large C-terminal fragment. The remaining membrane-bound C-terminal stub is then cleaved by γ-secretase, producing an Aβ peptide of 38, 40, or 42 amino acids. The Aβ42 fragment is said to be more pathogenic, with a greater tendency to form fibrils and deposit in neural parenchyma (37). Indeed, according to the amyloid cascade hypothesis, increased Aβ42/Aβ40 ratio is considered a basic pathophysiologic process that drives AD pathogenesis (38).
AD ASSESSMENT AT AUTOPSY

A Diagnosis of Exclusion

The wealth of current knowledge of the molecular biology of tau and Aβ tends to distract from the basic human neuropathology. Several issues are important to keep in mind. Shortly after the initial description of AD, it was recognized that senile plaques and NFTs both occur with advanced age in nondemented individuals (13). The diagnosis of AD at autopsy therefore was, and still is, a quantitative exercise (6). In reality, the presence or absence of senile plaques and NFTs is diagnostically meaningless; clinical dementia is required to establish the diagnosis, as are numerous plaques and tangles. The diagnosis of AD is, therefore, a clinicopathologic correlation that requires lesion quantitation, rather than a pathologic diagnosis per se.

Among the various neurodegenerative diseases, AD is the only condition that overlaps substantially with “normal aging.” Cortical Lewy bodies and Lewy neurites, the various pathologic changes associated with frontotemporal dementia, and the various inclusions associated with subtypes of tauopathy, for example, are generally not encountered to the extent that plaques and tangles are in the cognitively intact elderly. Indeed, it may be stated that AD is the only neurodegenerative disease that is essentially a diagnosis of exclusion. Most neuropathologists who examine elderly brains at autopsy and who are compelled to provide a specific diagnosis in the absence of detailed neurologic data (particularly with the concurrence of confounding factors such as polypharmacy, hydrocephalus, and a host of metabolic derangements) appreciate the limitations of a histopathologic diagnosis and the often mythical concept of “autopsy-proven AD.” Indeed, in a recent study, the diagnosis of “dementia of unknown etiology” approached 50% in nonagenarians (39).

Moreover, AD is a chronic, nonneoplastic disease that is usually examined pathologically at the end point, that is, at autopsy. In other chronic, nonneoplastic diseases in which biopsy experience is available (e.g. chronic renal failure, chronic liver disease, interstitial lung disease, neuromuscular disease), the pathologic findings invariably become less specific with increased disease duration (6). Nevertheless, the task of the neuropathologist is to distinguish among clinicopathologic entities and provide a specific diagnosis. Because this is the case, it is not surprising that such terms as “possible,” “probable,” and “intermediate likelihood” are terms used diagnostically even after rigorous semiquantitative analysis of pathologic features and correlation with age.

Pathogenic Implications of Standard Diagnostic Criteria

The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) convened a Neuropathology Task Force with the expressed long-term goal “to produce more accurate and reliable neuropathologic criteria for AD, to determine the neuropathologic spectrum of AD, and to establish the types and frequencies of other disorders coexisting with AD or occurring alone.” (40). The criteria include sampling of 3 neocortical areas among other regions, impregnation with Bielschowsky silver, semiquantitation of senile plaques into categories (sparse, moderate, frequent), and comparing senile plaque frequency with age (younger than 50, 50–75, and older than 75 years), with the concept that the older the patient, the more plaques are required for the diagnosis of AD. The precursor Khachaturian criteria used a similar concept (41). The Braak method for neuropathologic staging described approximately the same time as, CERAD criteria (42) presumes that everyone with a lesion has some degree of AD regardless of clinical signs. Moreover, Braak staging relies on neurofibrillary pathology, rather than senile plaques, because of the stepwise progression from transentorhinal to limbic to neocortical of the former and wide intraindividual and interindividual variation of the latter. The National Institute of Aging–Reagan consensus criteria (published 6 years after CERAD and Braak) are a combination of the 2 methods (43).

A disconnect between lesion and pathogenesis is perhaps nowhere better illustrated than in these standard neuropathologic criteria for AD. The fact that the competing standardized methods for assessing AD (i.e. CERAD and Braak) quantitate different lesions composed of different proteins belonging to different metabolic pathways is prima facie evidence for a poor correlation between lesion and cause. It is also problematic that (according to CERAD, Khachaturian, and National Institute of Aging–Reagan) the older the patient, the more plaques are “forgiven,” and the more senile plaques are required to make the diagnosis of AD. It is a mathematical fact that there are instances in which the same number of senile plaques results in different diagnoses by application of the standard criteria. For example, a 49-year-old patient with a sparse number of senile plaques and dementia would have histologic findings that “indicate” the diagnosis of AD by CERAD criteria (definite AD), whereas a 76-year-old patient with the same number of senile plaques would have histologic findings that are uncertain of the diagnosis of AD (possible AD). By extension, if pathology presumes toxicity, it would become axiomatic that older patients tolerate senile plaques better than younger patients. Few, of course, would accept this conclusion, yet many accept the notion of toxicity of AD lesions.

EXTRAPOLATING GENETIC DATA TO SPORADIC DISEASE

Evidence that Aβ causes AD is largely genetic and is based on findings in Down syndrome (AβPP overexpression) and familial AD (inherited mutations that alter AβPP processing resulting in Aβ) (2, 6). Apolipoprotein E data are sometimes cited in support of a causative role of Aβ because apolipoprotein E facilitates Aβ fibrillogenesis as a function of polymorphisms (e.g. apolipoprotein E4) that predispose to late-onset AD; the data are, however, indirect. A host of transgenic mouse constructs and their experimental manipulations are also suggested as critical evidence that substantiate the Aβ hypothesis, although such models may suffer with respect to relevance (44). All things considered, the presence of AβPP-linked familial AD and changes in Down syndrome...
brains are still the most compelling pieces of evidence in favor of the amyloid cascade hypothesis, and without these, the hypothesis would not be credible.

Therefore, assuming the importance of AβPP overexpression in these genetic conditions, the question as to whether it is valid to extrapolate construct-based mutated proteins to sporadic disease should then be raised. In this respect, it is important to point out that the total identified familial early-onset AD kindreds with known mutations number only approximately 450 worldwide; of these, AβPP kindreds number less than 100, and PS2 mutation kindreds number less than 20 (Alzheimer’s Disease and Frontotemporal Dementia Mutation Database; http://www.molgen.ua.ac.be/ADMutations/default.cfm). This is in contrast to the denominator of dementia subjects who number at least 20 million. Moreover, in sporadic disease, specific risk factors come into play (e.g. head trauma, diet, sex hormones, educational background, aluminum exposure) (6). Many of these are either unaccounted for by the amyloid cascade hypothesis or accounted for only on an ad hoc basis. Clinical presentation in familial disease is also heterogeneous and often unrecognized as AD. Presentations such as cerebral hemorrhage without dementia, spastic paraparesis with delayed dementia, subcortical dementia with Parkinsonism, and seizures (6, 45, 46) clearly differ from sporadic AD. Pathologically, the extensive Aβ burden, including extensive white matter, deep gray matter, and cerebellar amyloid, and “cotton wool” plaques that lack fibrillar Aβ (e.g. PS1 mutation cases) differ from classical sporadic AD. Taken together, these data suggest that early-onset familial AD imperfectly mimics the far more common sporadic condition. By extension, transgenic models mimic familial early-onset cerebral amyloidosis far better than sporadic senile dementia, and treatment strategies based on AβPP mutation transgenics would likewise target familial early-onset cerebral amyloidosis far more precisely than sporadic senile dementia.

Whereas the Aβ1-42 species is commonly accepted as “pathogenic,” and the increased ratio of Aβ1-42/Aβ1-40 in familial AD is posited as a central piece of evidence (37, 47, 48), more recent studies show that the increased ratio is due to a marked decrease in Aβ1-40 (49, 50). As such, mutations that cause AD do so by producing less Aβ (51). Why this would be the case is a matter of investigation, but it raises the point that the primary role of Aβ in AD pathogenesis should be open to question.

TOXICITY OF AD LESIONS

All present knowledge with respect to the amyloid cascade and tau protein metabolism exists because senile plaques and NFTs are detectable by light microscopy. Amyloid-β was first purified and identified from visible microscopic lesions, namely, amyloid-laden blood vessels in Down syndrome brains and amyloid plaque cores of AD, whereas tau was first purified and identified from bulk isolation of NFTs. Had the respective lesions not been visible, neither would have been linked to Aβ or tau, and our copious knowledge of the amyloid cascade and tau metabolism would have been delayed or left uninvestigated.

Therefore, the microscopic pathology of AD is the foundation for the amyloid cascade and tau hypotheses (6).

The early models favored the straightforward notion that insoluble proteins (either Aβ or phosphorylated tau) were toxic to the brain. It was shown, for example, that toxicity of Aβ was linked to fibril formation (52). Amyloid-β has been shown to be toxic in vitro by a variety of mechanisms, including induction of apoptosis (53), promotion of inflammatory mediators (54), and an accelerator of oxidative stress (55). Toxicity of phosphorylated tau is also said to be linked to its aggregated state with similar properties in vitro (56).

Aβ as a “Toxic Intermediate”

 Widely recognized pitfalls, particularly with the amyloid cascade hypothesis, are the weak correlation between Aβ deposits and cognitive status (42, 57–61) and the lack of correlation between neural function observed by a given brain region (e.g. medial temporal lobe and memory) and the extent of Aβ deposits in that region (57–60). Similarly, large amounts of amyloid and varying plaque types may be found in the brains of the cognitively intact elderly (60, 62).

The amyloid cascade hypothesis, therefore, has been amended to accommodate this defect. The revised version suggests that synaptic damage mediated by low-n oligomeric, soluble (i.e. supernatant fraction after high-speed centrifugation), nonfibrillar Aβ is the fundamental pathogenic event (63, 64). Evidence for this mechanism is provided by correlations between soluble Aβ levels, synaptic loss, and cognitive deficits (2, 65–67). Experimentally, impairment in spatial memory in Tg2576 transgenic mice coincides with the appearance of nonameric and dodecameric Aβ, whereas decreased spine density of fascia dentata neurons and impairment in long-term potentiation (LTP) at ages prior to the appearance of dodecamers indirectly implicated smaller n-oligomers (68–70). Microinjection of low-n Aβ oligomers blocked LTP in another experimental study, whereas immunodepletion of the conditioned medium prevented the blocking of LTP. On the other hand, degradation of monomers did not alter the LTP effect, thereby again implicating low-n oligomers, rather than monomers or longer n-Aβ species. Structural damage to dendritic spines in organotypic hippocampal sections on exposure to Aβ oligomers has also been demonstrated.

These data are interesting, but a degree of circumspecation may be warranted. The study of LTP with various manipulations of tissue cultures and the testing of spatial memory in genetically altered mice and rats via water mazes and sequential pressing of levers as analogies to synaptic damage in human neurodegenerative disease that develops over decades are dubious, if not irrelevant, exercises compared with clinical trials. Moreover, synaptic degeneration is more a concept than an objective neuropathologic finding. Indeed, whereas Aβ studies now invariably cite synapse loss as the best correlate of clinical signs, synaptophysin immunohistochemistry and the counting of synapses by electron microscopy have no diagnostic value. Synaptophysin immunostaining is unreliable as an objective pathologic criterion, and electron microscopy, in addition to
being unreliable for strict quantitation for a host of reasons, is impractical.

It has also been shown experimentally that transgenic manipulation of A\(\beta\) mice to ablate production of A\(\beta\) (whether it be monomer, n-, or fibril) fails to rescue the cognitive deficit (71). Equally, other manipulations that leave A\(\beta\) levels stable can completely rescue the pathologic phenotype (72). Therefore, much as in their human counterparts, A\(\beta\), including “toxic intermediate A\(\beta\),” bears little relationship to cognition in transgenic animals (6).

**Tau as Toxic Intermediate**

In contrast to A\(\beta\), the correlation between the regional distribution of phosphorylated tau and clinical signs suggests a close relationship between tau and AD pathogenesis. The increased tau phosphorylation that accompanies AD is said to result in separation of tau from the microtubule, possibly aided by other factors (e.g. A\(\beta\), oxidative stress, inflammatory mediators) and sequestration in NFTs and neuropil threads. The loss of normal tau function (i.e. the stabilization and maintenance of microtubules) combined with a toxic gain of function can compromise axonal transport and contribute to the synaptic degeneration that is now a central theme (22, 73). Interestingly, the concept of NFT toxicity, like senile plaque toxicity, is increasingly being challenged. In one transgenic model, mice expressing a repressible human tau developed NFTs, neuronal loss, and behavioral impairments that stabilized after tau suppression. Nevertheless, NFTs continued to accumulate, suggesting that they are not sufficient to cause cognitive decline or neuronal death (44). In another AD-like model, axonal pathology with accumulation of tau preceded plaque deposition (74), and studies of a P301S tauopathy model demonstrated microglial activation and synapse loss prior to NFT formation (75). Thus, the proponents of tau phosphorylation seem to be headed toward an analogy of the updated A\(\beta\) cascade model by suggesting that toxicity of hyperphosphorylated tau relates to the presence of toxic tau intermediates. The fact that neurons with NFTs (and presumably tau oligomers) survive for decades (76) and show intact microtubules (77) argues against this notion.

**IS THE PATHOLOGY OF AD A HOST RESPONSE?**

With the mindset that the pathologic lesions and the complex biochemical cascades that accompany them are a response to more fundamental age-associated upstream processes such as oxidative stress (78) or inflammation (79), several problematic aspects of AD pathology become less so (Fig. 2). The difficulties in distinguishing AD from aging on the basis of neuropathology are no longer an issue because the pathology does not presume to address cause. Host responses across the spectrum of diseases differ from one disease to the next and from 1 patient to the next; they generally bear an imperfect relationship to the severity of the primary insult. The presence of such pathologies as hippocampal sclerosis, \(\alpha\)-synuclein pathology, achromatic neurons, variations in extent of cerebral amyloid angiopathy, differences among senile plaque types (cored, diffuse, neuritic, cotton wool, etc.), and differences among the various forms of tau pathology would be reserved for clinicopathologic correlation, rather than insight into causality. Clinical and demographic risk factors such as diabetes mellitus, atherosclerotic cardiovascular disease, steroid hormones, education level and cognitive reserve, diet, and exercise would be less relevant to lesion counts and more relevant to discovering upstream processes that lead to inherently variable lesions that occurred as a response. Modeling AD by genetically engineering animals may also be more focused on dementia and less focused on the production of lesions that require endless modification.

![FIGURE 2. Host response hypothesis. Age-related etiologic factors lead to multiple host responses, among which are the lesions of AD.](http://jnen.oxfordjournals.org/).
If the host response is directly deleterious, amelioration of pathology by binding of toxic intermediates such as with Aβ vaccination will make some progress toward treatment. On the other hand, if this construct removes a neutral or beneficial host response and does not address an upstream cause, dementia would persist or even worsen. With removal of Aβ, classic AD would become, in effect, tangle-only dementia, the Lewy body variant of AD would become diffuse Lewy body disease, and plaque-only AD would become dementia lacking distinctive histology.

CONCLUSIONS

The following thought experiment might be considered. Chronic renal failure, like AD, is a common medical illness associated with advanced age, atherosclerosis, and diabetes mellitus (80, 81). For the sake of argument, consider chronic renal failure the analog to senile dementia. If such cases were examined at autopsy (i.e. end-stage), there would be extensive glomerulosclerosis, deposits of which include collagen and other extracellular matrix proteins. If the extent of glomerulosclerosis was quantitated into sparse, moderate, and frequent, one might find increased diagnostic certainty with higher numbers of sclerotic glomeruli. One might also find that higher numbers are required in older age groups because sclerotic glomeruli (analogous to senile plaques or NFTs) normally increase with advanced age. Therefore, the criteria would have to take this into account (analogous to CERAD or Khachaturian). On the other hand, one can look at the kidney irrespective of clinical disease and stage the changes (analogous to Braak) with the idea that fewer numbers of lesions are simply preclinical disease. Furthermore, one might isolate and purify glomeruli and find specific cellular proteins that are products of dysfunctional cellular metabolism, one of which is Type IV collagen, deposited as a poorly soluble aggregate. We might then, in turn, note that rare cases of early-onset familial glomerulosclerosis exist, some of which have mutations in Type IV collagen (82). Would it then be scientifically sound to produce transgenic models with Type IV collagen mutations, subject the models to therapeutic intervention, and then treat patients with age-related sporadic chronic renal failure based on those data?

Alzheimer disease pathology, and its irregular association with disease, has remained essentially unchanged since the original description of Auguste D. by Alois Alzheimer in 1907. In the last 20-plus years, however, knowledge of lesion constituents and pathophysiologic cascades has expanded exponentially. Approaches that seek to ameliorate lesions will continue. If current efforts continue to fail, however, a fundamental reorganization of the concept of AD pathogenesis (i.e. that AD lesions represent effect, rather than cause) may serve a useful purpose. Likewise, the advice of Max Bielschowsky to students of neuropathology in 1932 is nonetheless apropos:

“Such observations demonstrate to us that we may employ the conception of specificity in the histopathology of ganglion cells only with the greatest caution. It must be emphasized once again that pathological cell types give us no direct indications for a precise diagnosis, but only reveal that in the nervous system pathological processes have been taking place. They indicate whether these processes are progressing more or less rapidly and whether they tend to destroy the cell life or only exert a passing influence. Consequently cell pictures are of value as indicators of pathological reactions only in the general sense. Moreover, it must be remembered that they may be considered only partial manifestations of processes involving the whole tissue complex. The changes of neuroglia, of the circulatory apparatus and connective tissue are of equal importance in the formation of our judgments of the etiological relationship between occasional anatomical findings and the associated clinical picture.” (83)

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